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Neural remodeling in retinal degeneration

Robert E. Marc[a,*], Bryan W. Jones[a], Carl B. Watt[a], Enrica Strettoi[b]

[a] *John A. Moran Eye Center, Department of Ophthalmology, University of Utah School of Medicine, 50 N Medical Center, Salt Lake City, UT 84132, USA*

[b] *Istituto di Neuroscienze, del Consiglio Nazionale delle Ricerche, 56100 Pisa, Italy*

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Abstract

Mammalian retinal degenerations initiated by gene defects in rods, cones or the retinal pigmented epithelium (RPE) often trigger loss of the *sensory* retina, effectively leaving the *neural* retina deafferented. The neural retina responds to this challenge by remodeling, first by subtle changes in neuronal structure and later by large-scale reorganization. Retinal degenerations in the mammalian retina generally progress through three phases. Phase 1 initiates with expression of a primary insult, followed by phase 2 photoreceptor death that ablates the sensory retina via initial photoreceptor stress, phenotype deconstruction, irreversible stress and cell death, including bystander effects or loss of trophic support. The loss of cones heralds phase 3: a protracted period of global remodeling of the remnant neural retina. Remodeling resembles the responses of many CNS assemblies to deafferentation or trauma, and includes neuronal cell death, neuronal and glial migration, elaboration of new neurites and synapses, rewiring of retinal circuits, glial hypertrophy and the evolution of a fibrotic glial seal that isolates the remnant neural retina from the surviving RPE and choroid.

In early phase 2, stressed photoreceptors sprout anomalous neurites that often reach the inner plexiform and ganglion cell layers. As death of rods and cones progresses, bipolar and horizontal cells are deafferented and retract most of their dendrites. Horizontal cells develop anomalous axonal processes and dendritic stalks that enter the inner plexiform layer. Dendrite truncation in rod bipolar cells is accompanied by revision of their macromolecular phenotype, including the loss of functioning mGluR6 transduction. After ablation of the sensory retina, Müller cells increase intermediate filament synthesis, forming a dense fibrotic layer in the remnant subretinal space. This layer invests the remnant retina and seals it from access via the choroidal route. Evidence of bipolar cell death begins in phase 1 or 2 in some animal models, but depletion of all neuronal classes is evident in phase 3. As remodeling progresses over months and years, more neurons are lost and patches of the ganglion cell layer can become depleted. Some survivor neurons of all classes elaborate new neurites, many of which form fascicles that travel hundreds of microns through the retina, often beneath the distal glial seal. These and other processes form new synaptic *microneuromas* in the remnant inner nuclear layer as well as cryptic connections throughout the retina. Remodeling activity peaks at mid-phase 3, where neuronal somas actively migrate on glial surfaces. Some amacrine and bipolar cells move into the former ganglion cell layer while other amacrine cells are everted through the inner nuclear layer to the glial seal. Remodeled retinas engage in anomalous self-signaling via rewired circuits that might not support vision even if they could be driven anew by cellular or bionic agents. We propose that survivor neurons actively seek excitation as sources of homeostatic Ca^{2+} fluxes. In late phase 3, neuron loss continues and the retina becomes increasingly glial in composition.

Retinal remodeling is not plasticity, but represents the invocation of mechanisms resembling developmental and CNS plasticities. Together, neuronal remodeling and the formation of the glial seal may abrogate many cellular and bionic rescue strategies. However, survivor neurons appear to be stable, healthy, active cells and given the evidence of their reactivity to deafferentation, it may be possible to influence their emergent rewiring and migration habits.

Keywords: Retinitis pigmentosa; Remodeling; Plasticity; Cell death; Retina

*Corresponding author.

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Contents

1. Introduction

1.1. Retinal remodeling starts early and is progressive

The vertebrate retina is a tandem device: the photoreceptive, glutamatergic *sensory* retina drives the signal processing *neural* retina. Most retinal degenerations initially afflict the sensory retina and/or the RPE and many forms produce photoreceptor-depleted foci that expand and fuse, leading to extreme visual impairment or total blindness. Diverse sources of emerging data reveal negative plasticity in the remnant neural retina

following loss of the sensory retina. The goal of this review is to draw together the lines of evidence; to detail the essential features of remodeling in retinal degenerations; to evaluate these processes in the context of known CNS plasticity and remodeling in response to challenges such as deafferentation. As a prototypical CNS assembly, the retina should be expected to remodel extensively in response to pathological stimuli. Alterations should be expected in the neural retina when photoreceptors degenerate. We will endeavour to show these expectations valid.

Though the notion of negative retinal remodeling induced by retinal degenerations is not new, it has not received much prior attention and certainly has not been integrated into schemata for retinal rescues. It can be argued that neural remodeling has been passively and actively neglected. A recent Medline search on "retinal degeneration" yielded ≈300 papers containing the words *bipolar, horizontal, amacrine* or *Müller* cells out of >13,000 articles retrieved. Less than 3% of relevant literature addresses the destinies of retinal neurons and glia after the death of their photoreceptor partners. This is partly due to the essential transparency of remodeling. In the absence of photoreceptor drive, remodeling is undetectable in vivo and histological methods such as routine light microscopy are insensitive to the early responses of neurons to photoreceptor stress and death. The vast majority of scientific papers dealing with the fate of the neural retina during and after photoreceptor degeneration have focused on numerical cell survival, largely neglecting classical and advanced methods for neuronal visualization. Given our current knowledge regarding the molecular deconstruction of photoreceptors during challenge or degeneration (John et al., 2000; Rex et al., 2002), we might profitably inquire of the morphological and biochemical integrities of the ≈55–60 classes of neurons that form a mammalian retina. Confocal microscopy, advanced immunocytochemical techniques, and quantitative molecular phenotyping have opened new windows on remodeling. Its pervasiveness emerges as irrefutable. Even so, various recent media still present the view that the neural retina is either refractory to photoreceptor loss or that changes may be minimal (Scarlatis, 2000; Chow et al., 2002; Gekeler and Zrenner, 2002; Margalit et al., 2002; Zrenner, 2002).

Degeneration of the sensory retina is often accompanied by early changes in circuitry of the neural retina (Wong, 1997; Banin et al., 1999; Peng et al., 2000; Strettoi and Pignatelli, 2000; Aleman et al., 2001; Strettoi et al., 2002, 2003). These changes do not abate, but rather devolve to a protracted phase of negative *remodeling* of neuronal and glial elements in the remnant neural retina (Marc et al., 2001; Ren et al., 2001; Jones et al., 2002, 2003a; Sullivan et al., 2003). The key trigger seems to be the loss of cone photoreceptors. Remodeling involves three levels of restructuring in the neural retina: (1) neuronal death; (2) migration of cells; (3) rewiring. These are not trivial or collectively rare events, though visualizing them requires selective detection technologies. Remodeling potentially corrupts spatial processing and may even transform retinas into self-signaling neuronal assemblies with little ability to provide "proper" signal throughput as gauged by normal assemblies of visual circuits. Such changes may render many cell and bionic implant rescue strategies unfeasible. Beyond this, remodeling may constrain windows of opportunity for genetic rescues or molecular retinal maintenance. The mechanisms triggering remodeling are unknown, but it is a general feature of mammalian neural retinas challenged by sensory deafferentation effected by a range of photoreceptor degenerations. Our theme is that the mammalian retina is similar to other areas of the central nervous system (CNS) in its response to deafferentation on molecular, cellular and systems levels. Both retina and CNS display atrophy, apoptosis, reshaping of axonal and dendritic fields, revision of synaptic connectivity and efficacy that alter the signal processing attributes of entire pathways, alterations in gene expression, and glial transformations. Remodeling in the CNS is often guided by remnant synaptic inputs, while the retina becomes a system unto itself. Retinal remodeling has three implications we wish to emphasize. 1. Remodeling exposes the cryptic, incipient plasticity of the normal mammalian retina. 2. Remodeling challenges cellular and implant rescue strategies. 3. Remodeling may enable experimental revision of the remnant retina.

1.2. The remodeling scenario

Neural remodeling in the degenerating mammalian retina follows a stereotyped sequence of events after photoreceptor degeneration. As this review will examine many of these events in some detail, it is profitable to start with an overview of remodeling. The remodeling scenario is outlined in Fig. 1, using the human retina as an exemplar, recalling that mammalian retinas used as experimental surrogates are virtually identical to >90% the human retina in terms of cone density, circuitry, and the molecular signatures of individual cell types. Retinal degenerations are of three basic forms: rod-initiated, cone-initiated, and debris initiated. We will use the common rod-initiated RP-like process for an outline and note key deviations in certain models where necessary.

Phase 0: *The normal retina*. The retina represents separate transport compartments bounded by cellular seals. The *sensory retina* is composed of photoreceptor cells and is internally compartmentalized by high-resistance tight junction arrays formed distally at the basolateral RPE margins and high-resistance intermediate junctions arrays formed proximally by Müller cell

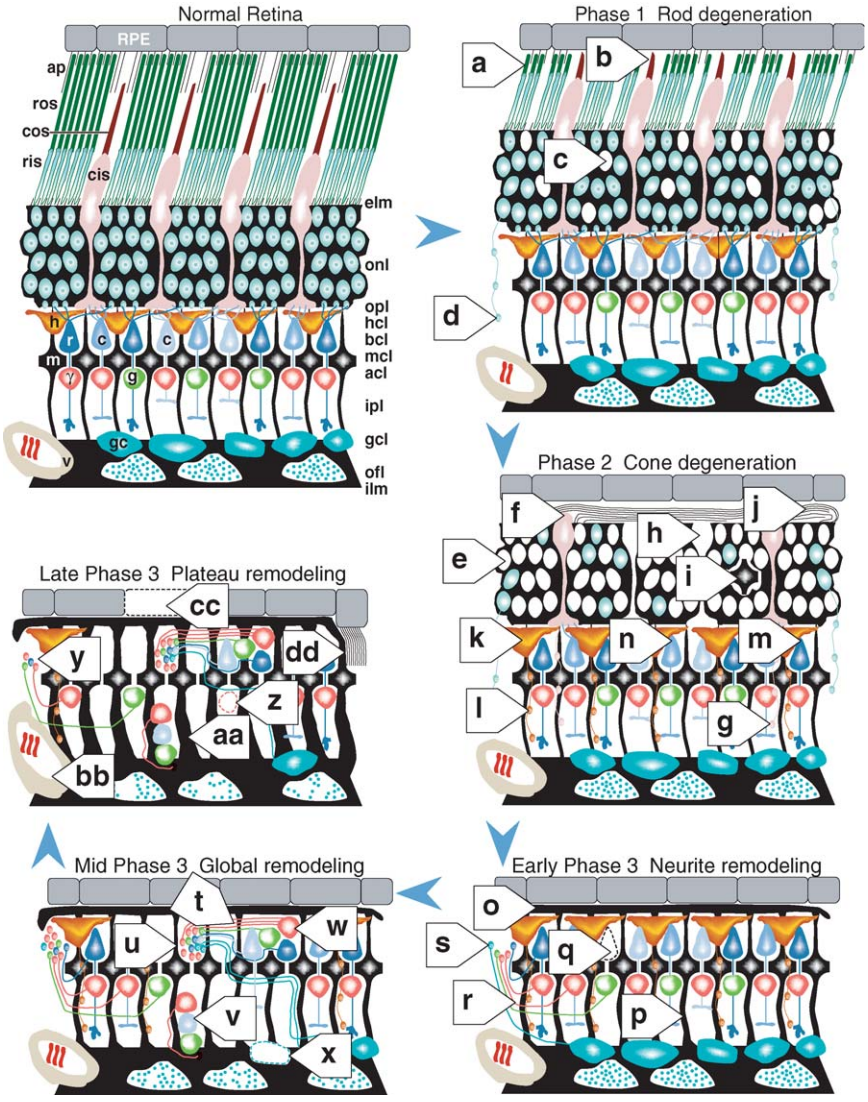


Fig. 1. Remodeling of the mammalian retina in retinal degenerations. *Normal retina*. The human retina and its basic cell types are used as a general guide to the transformation of retinal structure. The 30 basic remodeling events illustrated are likely common to all mammalian retinas, but timings may vary with models. *Phase 1—Rod degeneration*: (a) rod outer segment truncation, (b) cone outer segment truncation, (c) rod cell death, (d) rod neurite extension. *Phase 2—Cone degeneration*: (e) massive rod death, (f) cone truncation, (g) cone neurite extension, (h) progressive cone cell death, (i) Müller cell somatic translocation to the outer nuclear layer, (j) subretinal fibrosis, the early stages of the glia seal, (k) horizontal cell somatic hypertrophy, (l) horizontal cell neurite extension, (m) rod bipolar cell dendrite retraction, (n) cone bipolar cell dendrite retraction. *Early phase 3—Neurite remodeling*: (o) consolidation of the fibrotic layer into the glial seal, (p) Müller cell hypertrophy, (q) initial neuronal cell death, (r) initial fascicle formation, (s) initial microneuroma formation. *Mid-phase 3—Global remodeling*: (t) extensive multicellular fascicles, (u) extensive microneuroma growth, (v) inversion of amacrine and bipolar cells into the inner plexiform and ganglion cell layers, (w) eversion of amacrine cells and some ganglion cells to the glial seal, (x) progressive neuronal cell death. *Late phase 3—Plateau remodeling*: (y) regression of microneuromas due to cell death, (z) continued cell death. (aa) compensatory hypertrophy of Müller cells, (bb) hypertrophy and invasion of vessels, (cc) retinal pigmented epithelium cell loss, (dd) invasion of retinal pigmented epithelium apical processes. Abbreviations: acl, amacrine cell layer; ap, retinal pigmented epithelium apical processes; bcl, bipolar cell layer; c, cone bipolar cells (dark cells = ON center, light cells = OFF center), cis, cone inner segments; cos, cone outer segments; elm, external limiting membrane; g, glycinergic amacrine cells, γ, GABAergic amacrine cells; gcl, ganglion cell layer; h, horizontal cells; hcl, horizontal cell layer; ilm, inner limiting membrane; ipl, inner plexiform layer; m, Müller cells; mcl, Müller cell layer; onl, outer nuclear layer; opl, outer plexiform layer; r, rod bipolar cells; ris, rod inner segments; ros, rod outer segments; RPE, retinal pigmented epithelium; v, vascular cells.

apical microvilli. The latter constitutes a diffusion barrier perforated by photoreceptor inner limbs: the perinuclear soma, nucleus, axon and synaptic terminal. The RPE is the blood retinal barrier for the outer limbs of photoreceptors: myoids, ellipsoids and outer segments. The *neural retina* is a bounded entirely by high-resistance intermediate junction seals of the Müller cells: distally at the apical microvilli, proximally at the Müller

cell foot pieces and internally at vessels invested by Müller cell processes. This scheme functionally isolates the extracellular sensory transduction compartment of photoreceptors from their extracellular neural synaptic compartment, similar to hair cells and other sensory cell arrays. Within the sensory retina, the RPE and Müller cells regulate ionic transport, metabolite transport, fluid transport, retinoid transport, and outer segment turnover. Within the neural retina, Müller cells specifically regulate extracellular K^+, GABA and glutamate levels; provide glutamine for glutamate synthesis; regulate extracellular volume (likely via anion flux and taurine transport); and provide for carbon skeleton recycling and redistribution.

Phase 1: *Rod degeneration*. Whether triggered by malfunction or insufficiency of specific proteins, degenerating rods display progressive decreases their ability to produce outer segments. The rate of synthesis lags RPE phagocytosis and outer segments shorten. Though the mechanisms of photoreceptor stress and forms of apoptosis may be debated, rods with shortened outer segments are at risk. Most rods are fated to die and move through stressed, deconstructed, irreversibly stressed, and apoptotic stages. Some rods may escape stress and enter the neural retina as *survivor* rods, but this appears to be rare. The details of cone stress during this phase are not clear, but the subretinal space is compressed and cone outer segments are truncated. Initial changes in the neural retina are dramatic but transparent to simple histological examinations. During initial stress and rod deconstruction, rod neurites sprout and enter the inner retina, extending to the ganglion cell layer in some cases and expressing rhodopsin. In late phase 1 or early phase 2, rods may retract neurites and remnant presynaptic terminals prior to death.

Phase 2: *Cone degeneration*. When rod outer segments are lost, plasma membrane rhodopsin levels in rod inner segments rise and the rate of rod death increases. Collapse of the subretinal space parallels the ablation of cone outer segments and remodeling of the inner segment. Cone deconstruction includes redistribution of cone opsins to inner segments, changes in expression of key proteins, and perhaps transient extension of axons into the neural retina. Cones begin to die, likely due to multiple stressors, but death may be accelerated by migration of activated microglia into the sensory retina. Elaboration of a fibrotic distal seal by Müller cells, some of which show nuclear translocation into the outer nuclear layer, entombs the remaining cones. Initial remodeling of the neural retina begins as rod and cone bipolar cells retract their dendrites and revise their expression of synaptic signaling receptor proteins. The rod-targeted axon terminal fields of horizontal cells undergo retraction and the cone-targeted horizontal cell somas hypertrophy and extend new neurites into the inner plexiform layer. Every bipolar and horizontal cell appears to be remodeled. Though a fraction of bipolar cells dies at this stage, the changes are quantitatively invisible by routine histological analysis.

Early phase 3: *Progressive neurite remodeling.* The loss of the sensory retina completes the deafferentation of the neural retina and the Müller cell seal becomes compacted. The seal is irreversibly bound to and invests the neural retina. Müller cell hypertrophy, in part due to up-regulation of intermediate filament synthesis, forms large columns that segment the retina. Neurons of the inner plexiform layer begin to remodel, with new neurites from all cell types appearing in the inner nuclear layer, forming patchy foci in the remnant outer plexiform layer. Global neuronal cell death is statistically detectable.

Middle phase 3: *Global remodeling*. Global remodeling includes concurrent neuronal death, cell migration, and rewiring via ectopic fascicle evolution and formation of ectopic synaptic *microneuromas*. Neuronal death shows no bias; all cell types are vulnerable. The rate is also variable and appears partially dependent on the speed and coherence of cone loss in phase 2. Neuronal migration includes eversion of amacrine cells to the distal margin of the retina and inversion of bipolar and amacrine cells to the ganglion cell layer, perhaps guided by Müller cell surfaces. Bundles of mixed neurites from all cell types course through the retina at all levels, most graphically in the remnant outer plexiform layer just proximal to the glial seal. Microneuromas contain synaptic terminals of all types of neurons, including bipolar cell ribbon synapses and conventional synapses of GABAergic and glycinergic amacrine cells. All neurons appear to preserve their normal basic molecular signatures. New synaptic connections are abundant.

Late phase 3: *Plateau remodeling*. Basic remodeling processes persist. Neuronal death continues and can significantly deplete the inner nuclear and ganglion cell layers, with Müller cells partially filling the space. Neurite fascicles and microneuromas may regress as neuronal cell death depletes the retina. The inner plexiform layer becomes thinner. The optic fiber layer can become thinned and ganglion cell layer vessels migrate into the retina. Preretinal membranes and new extracellular matrices are formed. In some diseases, progressive RPE alterations are evident, including cell death, elaboration of columns of apical processes extending deep into the remnant neural retina, and migration of some survivor RPE cells into the retina, lining retinal vessels.

Different initial scenarios for cone- and debris-initiated retinal degenerations. Cone-initiated diseases may simply reverse the order of photoreceptor loss. Phase 1 would encompass cone stress and apoptosis, followed by phase 2 ablation of the outer nuclear layer via bystander-effect loss of rods. This excludes those cone dystrophies in which rods are spared. Cone–rod dystrophies and

debris-initiated diseases may display overlapping phases 1 and 2. Debris-initiated retinal degenerations are largely those in which RPE function is directly or secondarily compromised, resulting in an inability to internalize outer segments and accumulation of debris in the subretinal space. Cumulative stresses such as lipid oxidation, metabolite deprivation, microglia/macrophage activation may lead to a relatively coherent loss of rods and cones. However, after sensory deafferentation, neural remodeling appears to follow the same phase 3 profiles.

2. Human retinal degenerations and animal models

2.1. Human retinal degenerations initiated by rod, cone and RPE defects

Human retinal degenerations largely originate in the sensory retina and its adjacent transport tissues, the RPE and choroid. They are diversely sorted by clinical phenotypes, affected gene, protein function and malfunction, and cellular association (Daiger and Sullivan, 2003). With respect to ultimate photoreceptor loss, inherited disorders form a continuum (Deutman and Hoyng, 2001; Rivolta et al., 2002). Some cone dystrophies (COD) exist as isolated photopic dysfunction, with preservation of scotopic vision, while others initiate with or rapidly progress to involve both cone and rod loss (CORD). Rods are a primary site of gene defects, ultimately devolving in dual scotopic and photopic vision impairment. Different mutations of a single gene, e.g. the rhodopsin gene *Rho* (Sung et al., 1994), can yield varied initial patterns, progressions and final stages. Even the same mutation of a single gene (e.g. the peripherin gene) can result in disease variants. A large number of defects grouped in the clinical entity *retinitis pigmentosa* (RP) arise from defects in structural and transduction genes expressed in rods (Milam et al., 1999; Phelan and Bok, 2000; Weleber and Gregory-Evans, 2001). Different *Rho* mutations leading to expression of rhodopsin with C-terminal truncations or N-terminal modifications can have varied dominant negative effects, leading to slow, severe scotopic and photopic vision loss, likely triggered by different distal pathways converging on rod death (Berson et al., 1991; Olsson et al., 1992; Sung et al., 1994). Homozygous null mutations producing non-functional protein can yield progressive severe vision impairment over decades (Rosenfeld et al., 1992). Alternatively, homozygous mutations can be aggressive, such as *Pde6b* non-sense mutations that prevent expression of functional PDE6 β subunits, leading to high rod cGMP levels and early rod death.

Retinal degenerations can initiate in cones with varied outcomes. Cone (COD) and cone–rod (CORD) dystrophies can emerge from central (autosomal dominant COD/CORD) or peripheral loci (e.g. X-linked CORD), either sparing scotopic vision in some cases or resulting in severe blindness. The disk rim protein peripherin (Prph2) is expressed in both rods and cones (Arikawa et al., 1992) and individual mutations can emerge as RP or AMD-like diseases, with macular loss and sparing of rods (Wells et al., 1993), in contrast to digenic peripherin/ROM1 defects. AMD, COD/CORD and Leber Congenital Amaurosis (LCA) represent a range of disease presentations, many initiated by defects in some of the same genes (Zack et al., 1999). The key point is that cone loss can be primary (e.g. COD), concurrent with rod loss (LCA, CORD) or secondary, as in many forms of RP.

Other forms of apparent retinal degeneration arise from gene expression defects in the RPE. As the RPE must theoretically service both rods and cones via (1) the visual cycle (but see Mata et al., 2002), (2) outer segment phagocytosis, (3) subretinal space volume regulation and (4) metabolite transport, the initial presentation of retinal disease as rod-biased or cone-biased may indicate regional differentiation in defect expression (macular versus peripheral RPE) or cellular partitioning, such as a complete dependence of rods on the RPE for retinaldehyde reisomerization, but only partial dependence by cones. Severe defects impacting both scotopic and photopic vision include LCA Type II caused in part by defects in retinoid processing pathway elements such as RPE65 (Marlhens et al., 1997). Many of these diseases appear to lead to focal, spreading loss of RPE cells after which both rods and cones are compromised and it is common to find retinal regions lacking in RPE and photoreceptors altogether.

A significant amount of research has focused on defining the initial molecular defects of these diverse diseases, especially in terms of the impacts of gene defects on photoreceptor structure, protein trafficking, photoreceptor performance, and photoreceptor survival. However, the transition from nominal normal photoreceptor function through progressive impairment at near-death, with final activation of apoptosis-like events clearly impacts all facets of photoreceptor structure and function, including its role as the first synaptic element in the afferent visual pathway.

2.2. Animal models

Natural and designed mutations of eye and photoreceptor-specific genes in mammals have proven to be potent tools in vision research and many of these have been reviewed thoroughly with respect to photoreceptor degeneration (Baehr and Frederick, 2000; Menon et al., 2001; Chang et al., 2002). Table 1 summarizes some of the key models that have proven useful or may yet be useful in tracking retinal remodeling. Most null mutations in natural populations manifest as visually

Table 1
Representative animal models for analysis of neural remodeling

Natural	Gene	Cellular phenotype	Human disease phenotype
Mouse *rd1*	*PDE6B*^{rd1}	Rod cGMP elevation	arRP
Mouse *rd2*	*Prph2*^{Rd2}	Outer segment malformation	RP, AMD (haploinsufficiency)
Mouse *sh-1*	*Myo7a*	Rhodopsin trafficking defect	Usher syndrome Type 1B
Mouse *or*^{J}	*Chx10*	Retinal hypocellularity	Microphthalmia
Rat RCS	*Mertk*	Subretinal space debris stress	arRP
Chicken *rd*	*Gucy1*	Rod/cone cGMP depression	rLCA type I
Briard Dog	*RPE65*	Retinoid metabolism failures	LCA type II
Transgenic	**Gene**	**Cellular phenotype**	**Human disease phenotype**
Mouse P23H	*Rho*	Rhodopsin aggregation defect	adRP
Mouse VPP→GHL	*Rho*	Rhodopsin aggregation defect?	adRP
Mouse rhoΔCTA	*Rho*	Rhodopsin inactivation defect	adRP
Mouse TG9N	*RGS9*	Unknown effector coupling	CORD
Mouse *rdcl*	*Rho, LCR*	*PDE6b* defect + LCR-gated toxin	adRP, CORD
Rat P23H	*Rho*	Rhodopsin aggregation defect	adRP
Rat S334ter	*Rho*	Rhodopsin inactivation defect	adRP
Pig P347L	*Rho*	Rhodopsin trafficking defect?	adRP
Knockout	**Gene**	**Cellular phenotype**	**Human disease phenotype**
Mouse RKO	*Rho*	Rod outer segment stunting	arRP
Mouse *Crx*$^{-/-}$	*Crx*	Attenuated rod phenotype	adRP, adCORD, LCA
Induced	**Gene**	**Cellular phenotype**	**Human disease phenotype**
Rat LD	None	Debris stress and phototoxicity	RP, AMD, CORD

Abbreviations: ad, autosomal dominant; AMD, age-related macular dystrophy; ar, autosomal recessive; LCA, Leber congenital amaurosis; RP, retinitis pigmentosa; LCR, locus control region upstream of cone pigment genes.

impaired homozygous individuals and are generally similar to human recessive disease. The mouse retinal dystrophy *rd1* defect arises from a non-sense mutation in the *Pde6b* subunit gene that truncates about half the PDE6 β protein, rendering it inactive (Bowes et al., 1990). The human version of the same mutation is an established cause of arRP. Some retinal degenerations arising from null mutations also present as heterozygous haploinsufficiency defects, e.g. the *Prph2* null mutations (Meins et al., 1993; Apfelstedt-Sylla et al., 1995; Lam et al., 1995). Dominant-negative effects of altered proteins are manifested as dominant disease and are reasonably (though not accurately) simulated in transgenic models where altered and normal proteins are co-expressed. Lack of control over transgene integration sites and copy number accounts for the diversity of phenotypes in retinal degeneration models. Mechanisms underlying phenotype diversity in human disease are more complex and different in nature (Badano and Katsanis, 2002). Though the precise details of various mechanisms leading to early stress, irreversible stress and apoptosis of photoreceptors may be different in various models and bona fide human autosomal dominant disease, it is also likely that the mechanisms devolve to common end processes. Since mutations in the rhodopsin gene are extremely common in RP and account for the bulk of known genetic forms of adRP, considerable effort has been expended to produce models that express defective rhodopsin. C-terminal truncation of rhodopsin leads to ineffective turn-off of transducin activation by rhodopsin (Chen et al., 1995) and slow outer segment degeneration as in adRP. Other forms such as the N-terminal P23H and related rhodopsins that mimic adRP defects (Naash et al., 1993; Petters et al., 1997) transit the endoplasmic reticulum to the rod outer segment inefficiently (Sung et al., 1994; Frederick et al., 2001). These two groups of rhodopsin mutations have been grouped by Sung et al. (1991) as class I and II defects, respectively, which might correspond to different disease phenotypes in terms of the coherence and timing of rod cell death. The human P23H adRP phenotype also seems particularly variable and may involve additional environmental stresses such as enhanced susceptibility to phototoxicity (Heckenlively et al., 1991) or may prove to have oligogenic components. Other models do not yet correspond to known clinical defects but provide a platform for exploring the retinal sequelae of concurrent cone and rod death. A recent transgenic model developed by C.-K. Chen (University of Utah) over-expresses the N-terminal domain of RGS9, a retina-specific GTPase accelerator protein and this leads to rapid and complete

rod and cone photoreceptor death by postnatal day (pnd) 60, mimicking CORD-like diseases. The albino rat has long been known to be susceptible to environmental light damage (LD) and, since LD can be initiated in a mature retina, offers the distinct advantage of decoupling development of both sensory and neural retina from the consequences of photoreceptor death (Noell et al., 1966).

2.3. Space and time

The clinical differentiators of human cone- and rod-initiated degenerations arise from the presence of a cone-rich fovea in the midst of an otherwise unremarkable mammalian retina. Rod diseases appear to initiate in the periphery and cone diseases in macular/perimacular loci. However, cone densities of rodents, though nominally nocturnal, are not different from the peripheral primate retina. Cone densities (cells/mm^2) for varied species are similar: 10–12,000 in mouse (Jeon et al., 1998); 5–6000 in rat (Euler and Wässle, 1995); 5000 in peripheral macaque >5 mm (20°) eccentricity (Grunert et al., 1994); 6000 in peripheral human beyond 4 mm (13°) eccentricity (Curcio et al., 1990). Even more critical is the fact that much of the circuitry of rodent retinas is virtually identical to peripheral primate retina (Euler and Wässle, 1995), making analysis of the consequences of remodeling in rodent model systems germane to the human condition. The central 1° half-angle of high-resolution primate vision subtends but 0.3 mm of retinal extent and the remaining retina mimics most other mammals. Thus diseases like RP that appear to encroach upon central vision from the periphery will appear pan-retinal in rodents. A whole mouse retina equals $\approx$1% of a human retina and finding significant spatial gradients is difficult. Similarly, diseases initiating in the human macula have no clear murine *spatial* counterparts. Thus it is difficult but not impossible to investigate geographical degeneration progressions that are so obvious in humans, including degeneration processes are inhomogeneous on submillimeter scales. Larger animals such as dogs may offer better opportunities to investigate these patterns of degeneration. The LD albino rat exhibits an unexplained patterned degeneration, with photoreceptor loss initiating in the central dorsal retina and spreading with a very discrete border to encompass much of the eye. This border offers unique opportunities to spatially map phenomena that otherwise develop over time at one locus (Jones et al., 2003b).

Equating time across models is difficult. Setting aside human diseases such as recessive LCA and murine models such as the natural *rd1* mouse that display perinatal onsets, even fast human diseases such as Stargardt's Disease take years to present and many adRPs take decades. Even considering the tremendous variability in expression (especially of dominant diseases), onsets are successively later for X-linked RP, arRP, and adRP, suggesting that the coherence of the initial defect plays a key role in disease progression. Even after clear onset, different genetic or phenotypic forms of a disease can progress at different rates. It is difficult to deconvolve spatial and temporal progressions of disease in patients, as the cellular scales of degeneration processes escape monitoring except in the most graphic cases. Histology of human retinal degenerations, however, suggests that most disease progression can be heterogeneous on a submillimeter scale, especially in terms of cone survival after rod photoreceptor loss. Bouquets of cones can persist as islands surrounded by rivers of cone death (Marc et al., 2001). Unlike the apparent uniform, regimental shortening of rod outer segments in primary rod diseases, secondary cone loss involves spatially heterogeneous processes, implying focal sources of stress. Numerous candidates are possible, and may differ across disease types, but recruitment and activation of microglia into cell-killing foci is one very plausible secondary process (Gupta et al., 2003).

Vision impairing rod-initiated retinal degenerations in humans can take decades to progress to the point where central vision is challenged. Conversely, a mouse lives but 1000 days, yet retinal degenerations are expressed rapidly. The mechanisms controlling lifespan are still a matter of debate and involve environmental and pleiotropic genomic effects, but there are simple geometric factors that might be considered. Assuming photoreceptor degeneration initiates inhomogeneously in larger retinas, the rate of vision loss will scale with affected area, which will depend on the number of initial foci, their sizes and growth rates. If this focal model is valid, we can consider constraints on disease progression in rodent retinas. A mild light-damage insult in albino rats takes some 60–200 days to spread from central dorsal retina to the retinal margins. Similarly, many models of dominant disease in rodents also take 100–200 days or longer) to effect complete loss of photoreceptors in the outer nuclear layer. In a simplistic view, a human retina represents $\approx$30–100 $\times$ the surface area of a rodent retina. Foci of cone degeneration loss in the periphery may thus take over 15–50 years to fuse and encompass the entire human retina if degeneration spread at the same rate as photoreceptor loss in the LD rat. More acute damage spread has been described by Stone et al. (1999), with full coverage occurring in 2 weeks. Even with this faster model, a focal injury would take 1–4 years to cover a human retina. Taking into consideration the great variability of disease progression rates, the impact of oligogenic disease inheritance (Badano and Katsanis, 2002), and the possibility that some cone islands may resist stress (perhaps via glial shielding), it is reasonable to hypothesize that rodent and primate

neuronal remodeling rates are not very different once we correct for retinal area. While we have no quantitative evidence that cone clusters or apparent islands of resistance similar to human retinas occur in rodents, the *rd1* mouse does, in fact, display prolonged survival of a small populations of cones in dorsal retina (Jiménez et al., 1996; Ogilvie et al., 1997).

3. Rod and cone death patterns in retinal degenerations

Significant effort is now being expended to determine why and how photoreceptors die in retinal degenerations and what environmental factors might impact the speed and scope of cell death (Remé et al., 1998; Hao et al., 2002). Many of these details clearly lie outside the scope of this review, but the initiators, secondary stressors, and durations of stress prior to photoreceptor death likely shape the natures and extents of early remodeling defects.

3.1. Subretinal space debris models involve relatively coherent rod and cone death

Diseases or insults that lead to failure of RPE phagocytosis result in the accumulation of debris in the subretinal space. The prime model of this phenomenon is the RCS rat with a deletion mutation in the *mertk* receptor tyrosine kinase gene (D'Cruz et al., 2000). This defect leads to reduced or absent outer segment-specific phagocytosis and rapid accumulation of outer segment debris in the subretinal space. Such debris is clearly a potential generator of lipid peroxidation-derived cytotoxic and genotoxic aldehydes (Blair, 2001), and the rate and toxicities of lipid aldehydes will depend on many factors, including the thickness of the debris, free radical sources, changes in photoreceptor metabolism, oxygenation, RPE glutathione levels, light history, circadian status, etc. Even defining qualitative models for expected photoreceptor death patterns in debris models is difficult, but the acceleration of the damage spread in hyperoxia and its attenuation in hypoxia (Stone et al., 1999) suggests, in part, that ongoing lipid peroxidation in the debris zone is a likely stressor. Initial loss of rods and cones appears to be rather coherent and differentials in rod and cone death rates (Cicerone, 1976) are likely due to relative stress resistance. While the effects of light damage in rodents clearly involve the compromise of RPE function, both in terms of molecular signatures (Jones et al., 2003b) and potential susceptibility conferred by RPE65 gene polymorphisms (Danciger et al., 2000; Grimm et al., 2000), there is also the likelihood that any light-induced RPE malfunction is conflated with direct photoreceptor phototoxicity, leading to a fairly rapid and complete ablation in the central zone. The growth of damage, however, moves as a diffusive wave and suggests that the wave front of debris may be a source of genotoxic aldehydes that induce adjacent waves of DNA damage. In any case, early damage in debris models involves substantial overlap in rod and cone death, blurring phases 1 and 2 (Fig. 1).

3.2. Rod degenerations elicit secondary cone stress and death

Most of what we know about retinal degeneration sequelae has emerged from models in which rod photoreceptor transduction elements are impacted by null or dominant negative proteins. The *rd1* mouse natural rod degeneration mutant lacks a functional PDE β subunit and is unable form a function PDE$\alpha\beta$ heteromer. As guanyl cyclase expression begins in photoreceptors early in development, cGMP levels rise without attenuation and this induces apoptotic rod photoreceptor death (Lolley, 1994). The toxicity of high cGMP levels may be gated by developmental expression of cGMP-gated channels in rods, consistent with evidence that the Ca channel blocker D-cis-diltiazem delays rod death in *rd1* mice (Frasson et al., 1999). However, Pawlyk et al. (2002) argue that D-cis-diltiazem is ineffective. Multiple sites of cGMP-induced stress might operate in the *rd1* mouse. The progression of photoreceptor degeneration was examined in detail by Jiménez et al. (1996) using mapping of opsins. Though mouse retinas are small, gradients of cell loss can be detected, with pnd 25 losses of both rods and cones concentrated centrally and later losses progressing more rapidly ventrally than dorsally, with greater cone preservation dorsally. By pnd 100, the ventral retina lacked opsin expression altogether. Importantly, and consistent with the concept that some cones survive the stress of surrounding cell death, about 2000–2800 cones persist in the dorsal retina at an advanced age of pnd 600. Considering that the average mouse retina contains about 189,500 cones (Jeon et al., 1998), this is a 1.5% survival rate and indicates that over 98% of the neural retina has become deafferented. Even if one presumes all survivor cones are packed into an area of about 1 mm^2, the cone density in that region has nevertheless dropped 83%. In mouse, 1° of visual angle subtends 31 μm (Remtulla and Hallett, 1985) or a patch of about 9 cones in the normal mouse retina, and this decreases to 1 or 2 in the small cohort of survivor cones in the *rd1* mouse. In primates, 1° subtends much of the rod-free central area of highest visual acuity, with cone densities of 65,000–200,000 depending on species. While sparse remnant cones could mediate light sensing in the *rd1* mouse, spatial vision could only arise from the convolution of eye aperture and head movements. On balance, rod degenerations are of great risk to cones. The mechanisms of cone loss in these and related models

remain a matter of debate. It has been argued that rods may provide survival factors for cones (Mohand-Said et al., 1998), but the variability in cone survival patterns in different rod-initiated degenerations (e.g. *Pde6B*^{rd1} vs *Prph2*^{rd2}) suggests this cannot be completely true. Some rod death is apparently non-cell autonomous in slow adRP mimics such as P347S rhodopsin transgene bearing mice and transgenic/normal chimeras (Huang et al., 1993), leading to speculation that trophic factors are involved. Modes of cell death in other models (*Pde6B*^{rd1} and *Prph2*^{rd2}) do appear largely cell autonomous, arguing that a trophic model must have a limited space constant and efficacy; that survival factors cannot be a general explanation for cone death. As rods die, they also stimulate the recruitment of resident retinal microglia to the outer nuclear layer and apparently enable their activation, resulting in generalized cell killing (Gupta et al., 2003). However, the slow loss of cones that survive killing episodes might reflect persistent, basal survival factor dependencies. An in-depth discussion of these issues has been provided by Adler et al. (1999). Cones may also produce their own survival factors, e.g. in cone rich squirrel retinas, the primate macula and in pure-cone foveas of lizards and birds. This may explain focal clusters of resistant cones in advanced RP, especially in foveolar regions (Marc et al., 2001). The rare survivor cones of the *rd1* mouse argue that rod survival factors must not be an absolute requirement.

Little is known of the dynamics of photoreceptor demise in COD/CORD. In some forms central cone vision precedes rod loss, leading to severe visual impairment, where other forms are relatively mild, with scattered or marginal rod loss. Progression is slow in many forms, with adult onset marked by color vision and acuity deficits. Cone loss seems absolutely required for activation of phase 3 remodeling. Models that produce coherent or closely overlapping rod and cone loss, e.g. the *rdcl* and TG9N transgenic mouse systems, may serve as CORD mimics and these systems remodel most aggressively. There is evidence that some forms of CORD involve mechanisms of cone pathology that differ substantially from cone stress in common forms of RP (Gregory-Evans et al., 1998), but comparable animal models have not been validated.

3.3. Photoreceptor near-death experiences

Molecular homeostasis in the near-death epochs of retinal photoreceptors may become radically challenged in a process termed photoreceptor *deconstruction* (Mervin et al., 1999; Rex et al., 2002). Rex et al. (2002) conceived of deconstruction as changes in protein expression by photoreceptors in a challenged but not necessarily irreversibly stressed state, but the same logic applies to near-death states of photoreceptors. In particular, detached cones eliminate expression of opsins, the Ca^{2+} binding protein GCAP1 and calbindin, while phosducin levels double. Cone degeneration in rod-initiated disease is likely a slower, less concrete insult than detachment. Cones in various stages of deconstruction in human RP show changes in cytosolic macromolecule expression, notably decreased calbindin and arrestin signals, while many transmembrane proteins such as opsins seem well-expressed even in cones with severely altered forms (John et al., 2000). Metabolic, protein and transcriptional networks likely function far from thermodynamic equilibrium, and stress may force cells down paths of malfunction from which they can never recover. For simplicity, we will refer to photoreceptors as progressing through normal → stressed → *deconstructed* (not yet committed to apoptosis) → irreversibly stressed → apoptotic phases.

The photoreceptors are the first elements to display remodeling. Two symptoms of photoreceptor malfunction occur in stressed photoreceptors: (1) anomalous redirection of opsins into inner segment plasmalemmas; (2) anomalous restructuring of photoreceptor axons by sprouting and/or retraction. Immunocytochemistry of human retinal degenerations suggests that photoreceptor inner segments begin to malfunction in their roles as presynaptic elements early in stress (Li et al., 1995a; Milam et al., 1999; Fariss et al., 2000; Marc et al., 2001). The period preceding rod death is often associated with a progressive shortening of rod outer segments and slow changes in the distribution of rhodopsin. Normal rod inner segments contain immunocytochemically detectable rhodopsin, but at levels 10–100 × lower than outer segments (Hicks and Molday, 1986). Elevations of inner segment rhodopsin have been observed in human RP (Li et al., 1995a; Fariss et al., 2000), mouse retinal degenerations (e.g. Nir and Papermaster, 1986; Usukura and Bok, 1987), LD rats (Jones et al., 2003b), and experimental retinal detachment (Lewis et al., 1991; Fariss et al., 1997). It thus appears that any significant diminution in the rate of rhodopsin acceptance by the outer segment leads to rhodopsin redistribution in the inner segment. Arguably, defects in post-golgi rhodopsin transport (Deretic et al., 1995) or ciliary gate-keeping may be key sites of rod stress, and outer segment shortening reflects that defect. The effects of anomalous rhodopsin levels on inner segment function are not known and may not always be deleterious. However, Illing et al. (2002) have shown that P23H rhodopsin forms oligomers, accumulates in cytoplasmic aggresomes, and ultimately limits throughput of the critical ubiquitin-dependent proteasome pathway. Thus P23H rhodopsin is a potential cytotoxin mimicking CNS neurodegenerations based on anomalous protein aggregations.

The second major near-death defect of photoreceptors involves the activation of neurite growth. Fig. 2 shows these phase 1–2 anomalies in human and experimental systems. In normal rods, rhodopsin is localized mainly to outer segments (Fig. 2A). In human RP, areas containing surviving rods can display rhodopsin positive neurites extending into the inner nuclear and inner plexiform layers (Fig. 2B), even into the ganglion cell layer (Li et al., 1995a; Fariss et al., 2000). Using anti-rhodopsin Rho 1D4 monoclonal IgG (developed by Molday and MacKenzie, 1983) on thin sections with quantitative silver–streptavidin–gold visualization, it can be seen that inner segment rhodopsin levels do not become significant until late in the process of outer segment truncation (Fig. 2D and E) and that fine rhodopsin positive processes course into the inner nuclear layer. Some rod cells even escape the massive ablation of the outer nuclear layer in retinitis pigmentosa by assimilation into the remnant inner nuclear layer (Fig. 2E). This demonstrates that plasma membrane rhodopsin is not implicitly cytotoxic and some cells, even after significant stress, can escape death. It is also important to note that sprouting rods display SV-2 immunoreactivity in terminal boutons (Fariss et al., 2000), implying accumulation of vesicles that could be functional. Rod neurite sprouting is also evident in AMD (Gupta et al., 2003) with some processes traversing the entire inner nuclear and inner plexiform layers (Fig. 2F). Rhodopsin redistribution and neurite extension also occurs in the LD rat model (Jones et al., 2003b). As the photoreceptor outer segments approach a small fraction of their original length, rhodopsin signals appear in both the inner segment plasma membrane and the cytosol, likely as accumulations of transport vesicles. Rods in regions where rod cell death is already advanced show neurite extension into the inner plexiform layer along with evidence of rod cell migration. Cone photoreceptors also display neurite sprouting in the *rd1* mouse (Fei, 2002) and in human RP (Milam et al., 1996), with some neurites reaching the inner plexiform layer in the latter. This phenomenon was not previously described for other animal models. Other anomalies such as cone terminal hypertrophy in CORD (Gregory-Evans et al., 1998) have been noted. It would not be surprising if cone photoreceptors in many retinal degenerations were found to transiently grow neurites as irreversible stress and cell death approach.

Two mechanisms may underlie pathologic rod neurite sprouting. First, it may represent an unmasked plasticity and it would not be surprising if transcriptions of genes involved in developmental growth cone elaboration were unmasked in an epoch prior to cell death. Photoreceptor neurite sprouting may not be a "normal" or reparative response, as rods neurites bypass their normal targets. A second mechanism may simply be failure of homeostasis and not plasticity at all. A rod maintains its dimensions through balanced protein production and turnover. The appearance of opsin in rod inner segments suggests that the balance is altered and neurite growth may simply represent loss of control over cell size. It is intriguing that both rod and cone photoreceptors display coherent, massive extension of neurites into the inner plexiform layer during development that are retracted as the outer plexiform layer matures (Johnson et al., 1999). Neurite extension also involves global expression of rhodopsin and recoverin in rod inner segments (Fig. 3), and synaptic proteins. Unlike the stressed photoreceptors in RP or AMD, developing rods and cones merely retract processes and do not die. Remarkably, rods in reattached retinas, after first retracting their axons and spherules in detachment, extend them anew but overshoot the outer plexiform layer, entering the inner retina (Fisher and Lewis, 2003). It does not appear that rods in retinas afflicted with inherited degenerations show as coherent a response as in development, which suggests that neurite extension is enabled briefly, as a near-death experience, but some RP retinas express very high numbers of neurites (Fig. 2). Some persist long enough to form fascicles in the outer plexiform layer, some of which reach the ganglion cell layer (Milam et al., 1996). Regardless of the mechanism leading to neurite extension in photoreceptors, photoreceptor death constitutes deafferentation of the neural retina.

4. Plasticity in the mammalian retina

4.1. Developmental plasticity

Prior to exploring reactions of the mature neural retina to sensory deafferentation, it is useful to review evidences of plasticity in the retina. Circuit assembly in the mammalian retina involves significant postnatal refinement, including improved high spatial frequency cutoffs of retinal ganglion cells at about pnd 30 in cats (Rusoff and Dubin, 1977). There is increasing evidence that light history impacts maturation. In a remarkable study, Ikeda and Wright (1976) demonstrated that the spatial resolutions of sustained LGN neurons driven by an amblyopic eye were poorer than those cells driven by the normal eye. They concluded that such effect was likely distal to visual cortex and represented reorganization of pathways in the LGN or, provocatively, the retina. The dominant model of amblyopia was then and today remains focused on cortical reorganization, and it is not surprising that this hypothesis was criticized and then ignored. However, recent analyses of the effects of light deprivation on the properties of mouse retinal ganglion cells (Tian and Copenhagen, 2001) provides strong evidence that the maturation of retinal circuitry is potentially shaped by modulated photoreceptor drive.

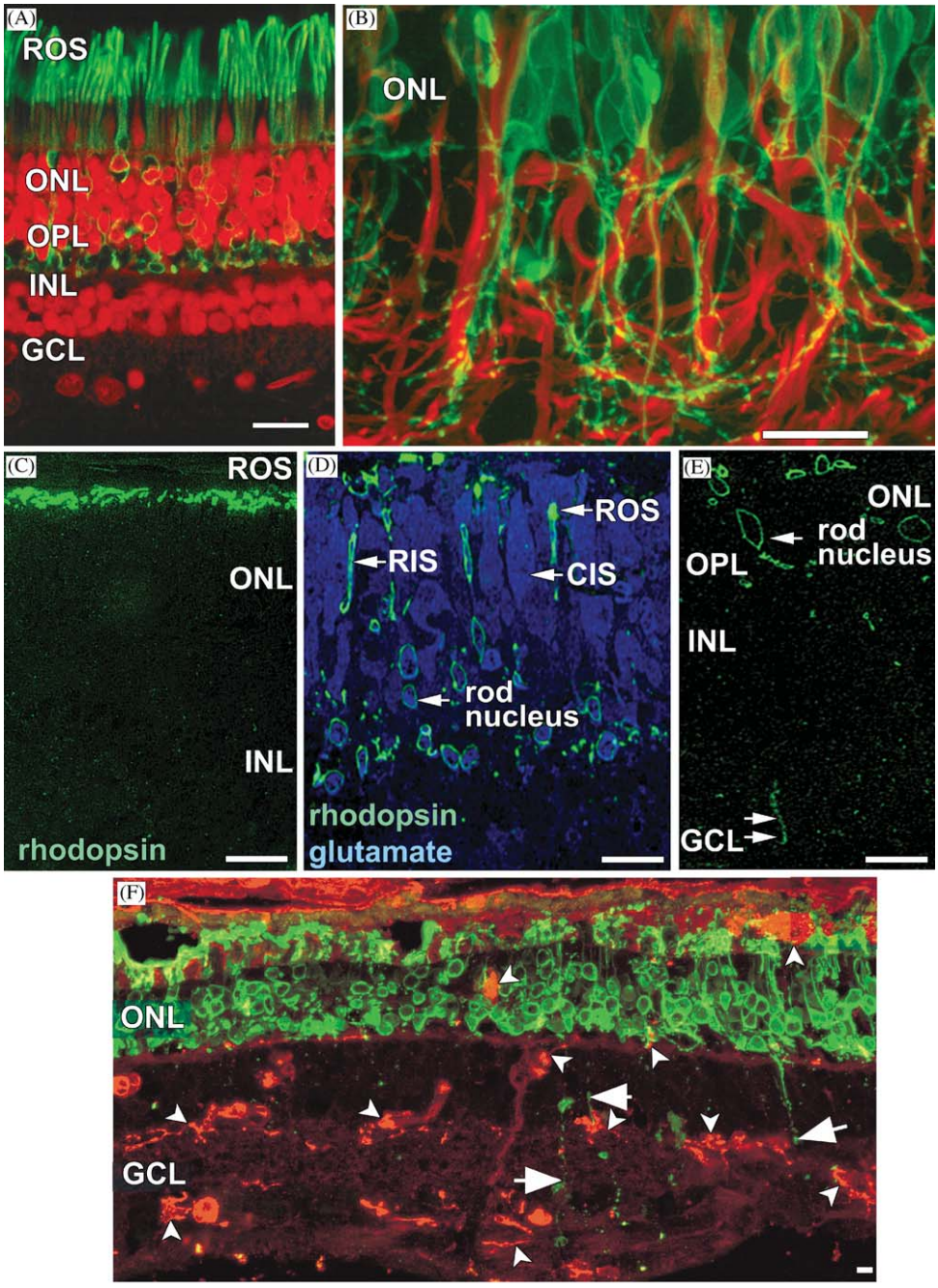


Fig. 2. Rhodopsin redistribution and rod neurite sprouting in retinal degenerations. (A) Confocal fluorescence imaging of rhodopsin signals (green, anti-rhodopsin monoclonal antibody 4D2 from R. Molday) in normal human retina (accession UW-0802-95). Nuclear layers are visualized with propidium iodide (red confocal channel). (B) Confocal fluorescence imaging of rhodopsin signals (green) and glial fibrillary acidic protein signals (red) in phase 1–2 human retinitis pigmentosa (Foundation Fighting Blindness [FFB] accession #340) showing massive extensions of rod neurites into the inner nuclear layer, closely associated with Müller cell processes. (C) Optical thin (250 nm) section imaging of rhodopsin signals (anti-rhodopsin monoclonal antibody 1D4 courtesy of R. Molday; visualized with silver-intensified 1 nm streptavidin-gold detection of biotinylated 2° IgGs) in phase 1 human retinitis pigmentosa (FFB accession #552). Only the truncated outer segments express significant rhodopsin signals, estimated at ≈ 5 mM, inner segment signals $< 100\,\mu$M. (D) Optical thin section imaging of rhodopsin (green) and glutamate (blue) signals in phase 2 human retinitis pigmentosa (FFB accession #524) showing significant redistribution of rhodopsin into rod inner segments. Rhodopsin signal ≈ 1 mM. Rod outer segments are largely ablated, with a few remaining stubs proximal to the former external limiting membrane. (E) Optical thin section imaging of rhodopsin (green) in late phase 3 remodeling of the retina in human retinitis pigmentosa (FFB accession #378; no light perception). Thin sectioning captures membrane-associated rhodopsin in sparse neurites in the inner nuclear and ganglion cell layers, after all photoreceptor outer segments have been ablated. (F) Confocal fluorescence imaging of human AMD with geographic atrophy (FFB accession #614) displaying rhodopsin signals (green channel) in rods, rod inner segments and neurites invading the neural retina (large arrows). Microglial cells (arrowheads) in the subretinal space, the outer nuclear layer and near rhodopsin positive rod neurites are labeled with biotinylated RCA-I lectin (red channel) selective for terminal D-galactose or *N*-acetyl-galactosamine residues. All abbreviations as in Fig. 1. All scale markers = 25 μm. Figures A and B reproduced from Farris et al. (2000), by copyright permission of the authors and Elsevier Science, Inc. Figures C–E from Marc et al. (2001). Figure F from Gupta et al. (2003), by copyright permission of the authors and Elsevier Science, Inc.

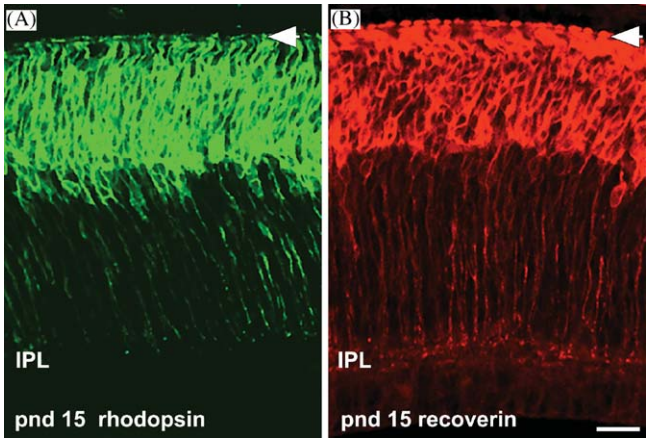


Fig. 3. Coherent rod neurite extension into the pnd 15 ferret inner plexiform layer visualized by immunocytochemistry for rhodopsin (green) and recoverin signals. Recoverin positive cells significantly outnumber rods as many of them are cones. Arrows, external limiting membrane. Scale: 10 μm. Reproduced from Johnson et al. (1999) by copyright permission of the authors and Wiley Interscience.

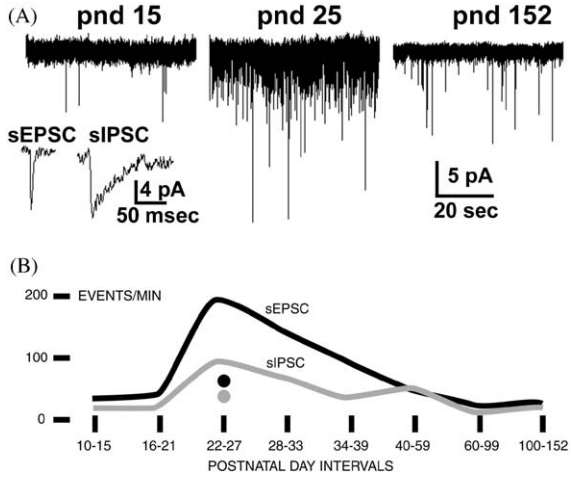


Fig. 4. Increased frequency of spontaneous excitatory (sEPSC) and inhibitory (sIPSC) postsynaptic currents following eye opening in mice and its suppression by dark-rearing. (A) Representative records of spontaneous retinal ganglion cell postsynaptic currents recorded from voltage-clamped ganglion cells at pnd 15, 25, 152. A massive increase in spontaneous activity occurs around pnd 25. (B) Envelopes of mean sEPSC (black) and sIPSC (grey) activity over the first 100–150 days of life and the mean pnd 24 sEPSC (black dot) and sIPSC (grey dot) activity after dark-rearing. The suppression of spontaneous sEPSCs was significant. Figure A reproduced from Tian and Copenhagen (2001), by copyright permission of the authors and Cell Press. Figure B replotted from Tian and Copenhagen (2001).

In particular, a wave of spontaneous EPSPs and IPSPs emerges around pnd 25 (Fig. 4A), increasing retinal ganglion cell activity over 4-fold and subsiding by pnd 60, even though light-driven responses are also maturing (Fig. 4B). This suggests the invocation of a maturation epoch that may tune presynaptic efficacy or circuitry itself. However, the maturation is not an automaton and is partly gated by endogenous light-driven activity as dark-rearing abolishes the wave of spontaneous activity. Taken together with observations from Fisher (1979) and Sosula and Glow (1971) that postnatal light-deprivation statistically increases the number of amacrine cell synapses in the inner plexiform layer, one might conclude that refinement of retinal circuitry, like that of virtually all other mammalian CNS networks, requires some level of activity modulation to achieve normal status; that stimulus deprivation constitutes a form of deafferentation. Detecting such endogenous maturational plasticities is problematic for they may be delicately concealed as subtle changes in expression of key synaptic proteins, changes in local wiring, or refinement of dendritic form. Most anatomical and physiological surveys might fail to detect significant changes in retinal organization in response to developmental light deprivation, and as such changes might have dynamic components, the discovery of a specific epoch for changes is especially important (Tian and Copenhagen, 2001).

Intrinsic, light-independent processes also may participate in shaping the retina and ganglion cell arbors in particular. The work of Feller, Wong, Shatz and colleagues on the propagation of excitation waves across the mammalian retina prior to and during the emergence of mature retinal circuitry demonstrates that multiple endogenous sources of focal and global excitation are activated. In particular, large waves of Ca^{2+} influx are mediated by cholinergic signaling at pnd 0–14 in mouse, precede the maturation of glutamatergic synaptic drive in the inner plexiform layer, but are not required for it (Bansal et al., 2000). However, the absence of acetylcholine-gated waves in mice lacking $\alpha 2$ or $\beta 3$ nicotinic receptors does lead to a delay in both the pruning of ganglion cell dendrites and their refined lamination into narrow sublayers of the inner plexiform layer. It has long been suspected that pruning of retinal ganglion cell arbors is a key process in the refinement of function (Rusoff and Dubin, 1977; Rusoff and Dubin, 1978) and these data suggest that cholinergic waves play a role in that refinement.

Further insights into the developmental plasticity of retinal ganglion cells were provided by an elegant experiment by Perry and Linden (1982). A small optic fiber layer lesion at birth led to loss of a strip of ganglion cells by 3–6 months of age. Axotomy is fatal to mammalian retinal ganglion cells. However, surviving ganglion cells surrounding the lesion sent the majority of their dendrites to one side of the soma *into the depopulated zone*, unlike normal ganglion cells that have a roughly elliptical dendritic convex hull centered around the soma (Fig. 5). The orientation distribution of the longest dendrite from each cell's arbor was nearly random in cells far from the lesion, while cells near the

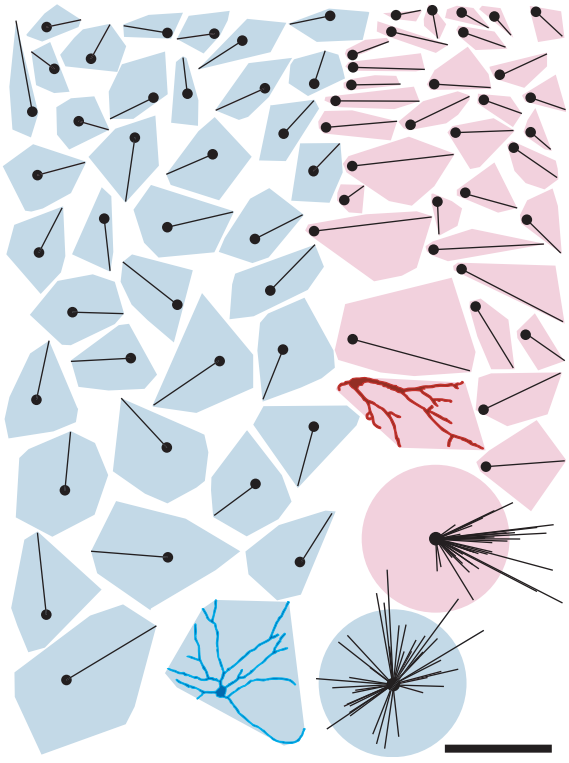


Fig. 5. Plasticity of retinal ganglion cells in development. Convex hulls of mature rat retinal ganglion cells visualized by retrograde HRP cytochemistry in regions distant (blue) and near (red) to a pnd1 optic fiber layer lesion that depleted linear patches of retinal ganglion cells, replotted from the data of Perry and Linden (1982). In each hull, the dot represents the soma and the line indicates the direction and length of the most distant filled dendrite. Even though retrograde HRP visualization reveals only part of the dendritic arbor, the orientation of the most distant point shows no preference (blue polar plot) in ganglion cells far from the lesion. Conversely, ganglion cells adjacent to a depopulated done preferentially invade it (red polar plot), even though they reside in effectively normal environs. Selected large cells for each group are shown. Scale: 250 μm.

depopulated zone excluded 235° of orientation. The authors proposed that the phenomenon arose from imbalanced dendritic competition among ganglion cells, with those bordering the depopulated zone having preferential access to inputs from the inner plexiform layer. The accumulated evidence suggests that development of normal mammalian retinal circuitry invokes neuronal plasticity that subtly transforms retinas when either appropriate stimuli or cellular neighborhoods are altered.

4.2. Plasticity in mature neural retina

Little is known of structural plasticities in the mature mammalian retina. Light adaptation is an archetypal plasticity that effects a functional transition from scotopic to photopic vision. In fishes and amphibians, both graphic structural and subtle molecular events attend light adaptation, including photomechanical movements of the RPE and photoreceptors, neurite extension and retraction by horizontal cells, and alterations in bipolar cell synaptic terminal structure. More subtly, but perhaps more physiologically evident, several molecular switches are invoked by light-adaptation, e.g. reduction of homologous coupling between horizontal cells (reviewed in Witkovsky and Dearry, 1991; Weiler et al., 2000) and reduction of spike firing frequency and truncation of firing episodes in ganglion cells (Vaquero et al., 2001). Many adaptive processes are apparently gated by dopamine, presumably released by amacrine-like cells driven by cone-dominated circuits (Marc, 1995, 2003). Light adaptation attenuates coupling between cone horizontal cells, gated at least by dopamine in most vertebrates, including mammals (He et al., 2000; Weiler et al., 2000) and is presumed effected through a D1-type PKA-dependent pathway. Other adaptive mechanisms are gated by nitric oxide signaling, which is more complex, but nevertheless potent (Blute et al., 2000). Both dopamine and nitric oxide appear involved in mammalian network adaptation of glycinergic AII amacrine cells. Dopamine selectively attenuates homologous AII–AII gap junctional coupling while exogenous nitric oxide donors attenuate heterologous AII–cone bipolar cell coupling (Mills and Massey, 1995). These network plasticities will become unregulated when photoreceptor drive is removed in retinal degenerations and, glossing the details, retinal degenerations should effectively convert the retina to a perpetually or at least sporadically photopic network. This presumes, of course, that essential retinal circuitry does not change, and that may not be true. Taken together with our knowledge of dopamine receptor distributions in retina, network adaptation in the mammalian retina likely involves several forms of molecular plasticity, but there is no evidence of structural modulation such as synaptic remodeling or neurite movements.

A remarkable report (Pinaud et al., 2002) suggests that enriched, complex visual environments in young adult rats can significantly increase expression of immediate early gene products NGFI-A (nerve growth factor-induced gene A) and Arc (a synaptic cytoskeleton-associated protein), as well as the late gene products synapsin and GAP-43, implying significant synaptic reorganization, if not outright synaptogenesis. This is extremely surprising for vision researchers who hold pretty strongly to the belief that the mature retina is a largely static synaptic assembly of cells. Given that the visual environments of two control groups in the study were likely different only in the behavioral salience of the visual scenes they experienced, this finding might suggest important roles for retinal efferents (Drager et al., 1984; Gastinger et al., 1999; Gastinger et al., 2001) as signaling elements in adult retinal plasticity.

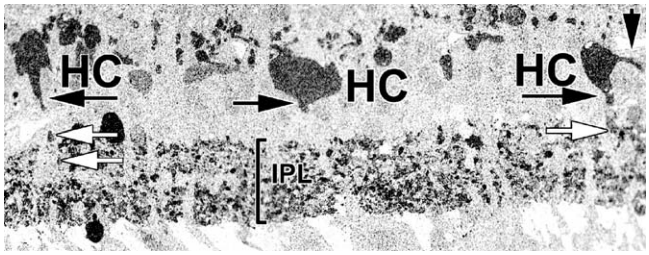


Fig. 6. Cat retinal horizontal cell hypertrophy and neurite extension after 83 days of acute detachment visualized by GABA immunoreactivity. Three hypertrophic horizontal cell somas exhibit abnormal stout processes arising from their proximal surfaces (horizontal black arrows) and extending fully into the inner plexiform layer (horizontal white arrows). An additional process extending from the lateral surface of a horizontal cell arcs into the inner nuclear layer (downward arrow). Scale: 25 μm. Reproduced from Marc et al. (1998b) by copyright permission of the authors and the Association for Research in Vision and Ophthalmology.

The adult mammalian retina also activates neurite sprouting and structural remodeling when challenged. Peichl and Bolz (1984) induced neurite extension from cat horizontal cells by intravitreal injection of kainic acid and some of these processes reached the inner plexiform layer. S.K. Fisher, G.L. Lewis, K. Linberg and their colleagues have produced a large body of work documenting the remodeling of retinal neurons in adult cat retinas triggered by retinal detachment. Again, horizontal cells are among the most obvious participants and, early in detachment, send dendrites into the outer nuclear layer, pursuing or being dragged by retracting photoreceptor synaptic terminals, but following Müller cell surfaces (Lewis et al., 1998; Fisher and Lewis, 2003). Rod bipolar cell dendrites react similarly. In addition, horizontal cells in the chronically detached cat retina also extend anomalous large neurites towards the inner plexiform layer (Marc et al., 1998). Many horizontal cells in the detached region elaborate these proximal neurites (Fig. 6), implying that the remodeling response may be extensive. Given the varied circumstances in which horizontal cell neurite extension can be induced, it is perhaps remarkable that the normal retina is held in such structural stasis. In addition, retinal detachment can induce ganglion cells to remodel, sprouting neurites that can even penetrate the internal limiting membrane and invade epiretinal membranes (Coblentz et al., 2003; Fisher and Lewis, 2003).

5. Deprivation and deafferentation-induced remodeling in the CNS

As we are about to consider remodeling in the retina, as brief review of CNS remodeling is in order. The mammalian CNS remodels during development and learning, as well as in response to injury or disease. Plastic responses produced by CNS neurons in association with learning and memory, e.g. changes in the numbers of dendritic spines (Sorra and Harris, 2000), are compelling examples of the flexibility of neuronal circuits. Altered visual experience can induce compensatory axonal sprouting associated with functional remodeling (DeBello et al., 2001). However, the CNS displays reactive impairment after loss of sensory drive, with structural and molecular reorganizations that propagate throughout the afferent synaptic stream (Wall et al., 2002). Amblyopia arises, in part, from interocular mismatches in retinal ganglion cell activity, and negative circuit remodeling impairs the afferent visual pathway (Von Noorden and Crawford, 1978; Levitt et al., 2001). A paradigmatic example of remodeling caused by deafferentation occurs in the auditory system, detailed in the now-classic work of Rubel and colleagues (Deitch and Rubel, 1984; Rubel and Fritzsch, 2002). The removal of the cochlea in avians and mammals produces the retraction of dendritic arbors in cells of second order nuclei innervating the cochlea, followed by atrophy of neuronal cell bodies and, ultimately, by transneuronal degeneration (Hashisaki and Rubel, 1989). Though first discovered as developmental "critical periods", deafferentation-induced remodeling is not constrained to development. Neural assemblies in the mature CNS display extensive deafferentation-induced apoptosis (Capurso et al., 1997) and synaptic reorganization (Baekelandt et al., 1994; Salin et al., 1995). Massive retrograde transneuronal loss of retinal β ganglion cells occurs after adult cortical ablation (Cowey et al., 1989; Stoerig and Cowey, 1997). Remodeling is common in CNS pathways, triggered by inner hair cell death (Dodson, 1997; Dodson et al., 1997), spinal injury (Sugimoto et al., 1990), or neurodegenerative diseases (Anderton et al., 1998). Not all central pathways remain susceptible past the critical period (Mostafapour et al., 2000), but impairment of signaling to the lateral geniculate nucleus (Levitt et al., 2001), somatosensory cortex (Buonomano and Merzenich, 1998), and other mature neural arrays evoke varied forms of negative remodeling, including atrophy (Globus, 1975; Pasic et al., 1994; Ginsberg and Martin, 2002), apoptosis (Ginsberg and Martin, 2002), axonal arbor restructuring (Kaas and Florence, 1997) and dendritic re-patterning (Anderton et al., 1998; Fiala et al., 2002). One common hypothesis is that dendritic arbor remodeling arises from loss of afferent excitatory input (Turrigiano and Nelson, 2000). Myriad molecular effects are associated with deafferentation including changes in expression of extracellular matrix proteins (Levitt et al., 2001), glutamate receptors (Gazzaley et al., 1997), and early immediate genes (Byers et al., 2000). If the neural retina displays retrograde remodeling after cortical lesions, why would it not show anterograde remodeling? As we shall see, it does.

6. Early remodeling in retinal degenerations

6.1. Systems expressing early remodeling of neural retina

Only a few model systems have been carefully examined for evidence of early remodeling, but the data are unequivocal: even at early stages of photoreceptor stress and deconstruction, the neural retina reacts with bipolar and horizontal cell remodeling. The most extensive analysis has been carried out in the *rd1* mouse, but similar phenomena have been observed in the *rd10* mouse, $Crx^{-/-}$ mouse, FVB/N mouse, RCS rat, and P347L transgenic pig. Early remodeling is transparent to conventional visualization, especially those concerned only with documenting cell loss. Figs. 7 and 8 show wild type and *rd1* eccentricity-matched pnd 90 retinas visualized with the nuclear intercalating dye ethidium bromide and phase contrast toluidine blue staining respectively. Each documents the total loss of photoreceptors from the sensory retina and the illusory patency of the neural retina. Apparent integrity by light microscopy is not a test of phenotypic preservation. Selective visualization methods reveal that photoreceptor loss triggers three sets of fast transformations in the outer plexiform layer and neurons of the distal inner nuclear layer: the fast structural remodeling of rod-driven pathways, the fast deconstruction of rod bipolar cell gene expression, and early remodeling of cone-driven pathways.

6.2. Fast structural remodeling of rod pathways

Two structures in the in the outer plexiform layer are directly driven by rods: rod bipolar cells and the axon terminals of horizontal cells. The axons of mammalian horizontal cells are thought to be too long to mediate passive current spread and there is no evidence of physiologically activated spiking in horizontal cell somas. The axon terminals, rich in mitochondria, ribosomes and neurofilaments are electrically isolated and functionally autonomous to a great extent. They are, in this view, equivalent to rod horizontal cells.

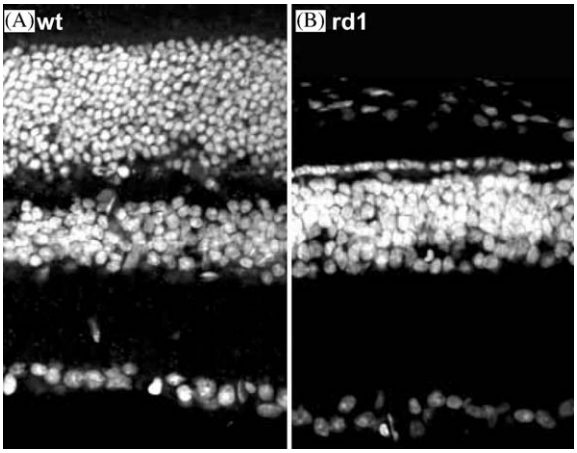


Fig. 7. Eccentricity-matched retinal layering in pnd 90 (A) wild type and (B) *rd1* mouse retinas visualized with ethidium bromide fluorescence, showing complete ablation of the outer nuclear layer.

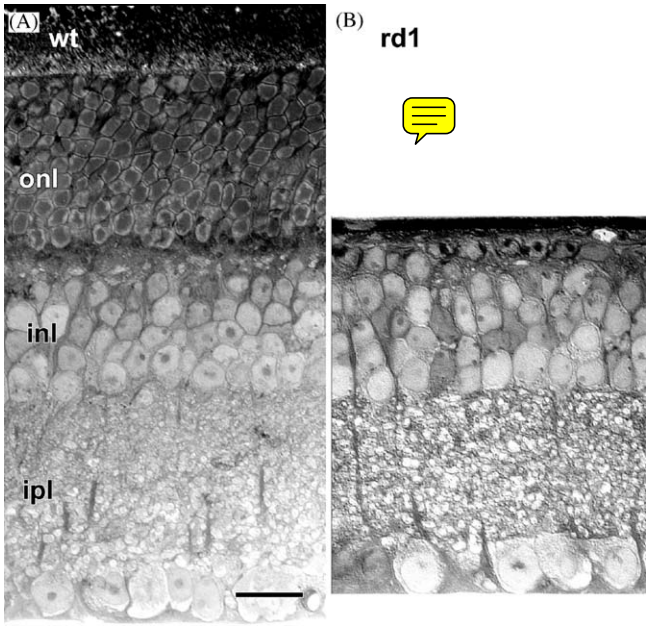


Fig. 8. Eccentricity-matched retinal morphology in pnd 90 (A) wild type and (B) *rd1* mouse retinas visualized with semi-thin section phase imaging of toluidine blue staining. Though the outer nuclear layer is ablated, the neural retina appears unaffected. Scale: 20 μm.

The first strong evidence that retinal neurons react to the death of rods, and perhaps react to stressed or irreversibly stressed rods, is the failure of rod bipolar cells to maintain proper dendritic arbors ((Strettoi and Pignatelli, 2000; Strettoi et al., 2002, 2003). The stress, deconstruction and apoptosis of rods in the *rd1* mouse begins extremely quickly and ≈97% are lost by pnd 17 (Carter-Dawson et al., 1978; Jiménez et al., 1996). Rods are dying while rod bipolar cells are forming their dendrites and attempting synaptic contact with them and this truncates dendrite development in *rd1* rod bipolar cells. Fig. 9 shows mouse rod bipolar cells visualized with protein kinase Cα (PKCα) immunoreactivity in wild-type and *rd1* retinas at pnd 90, after all rods are lost. The *rd1* bipolar cells lack dendrites and, although a few are transiently formed at earlier times, e.g. pnd 30 (Strettoi et al., 2002), it is clear that the absence of rod spherule targets represses the initial development of rod bipolar cell dendrites (Strettoi and Pignatelli, 2000). Visualization of single rod bipolar cells via ballistic DiI labeling more graphically illustrates the loss (Fig. 10), with most fine dendrites disappearing altogether and a few truncated processes emerging from a remnant proximal dendrite. It would not be surprising

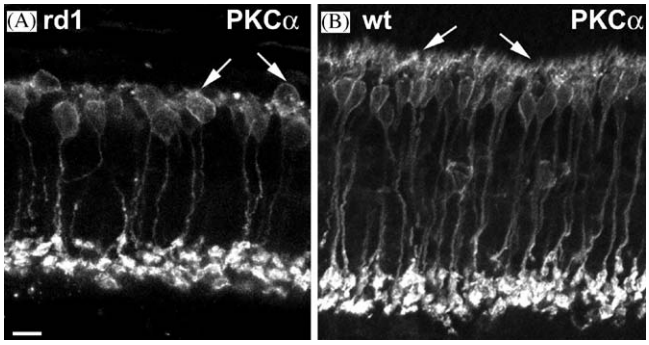


Fig. 9. Rod bipolar cell PKCα immunoreactivity in (A) *rd1* and (B) wild-type mouse retinas at pnd 60–90. Arrows indicate the position expected for rod bipolar cell dendrites in the outer plexiform layer. Scale: 10 μm.

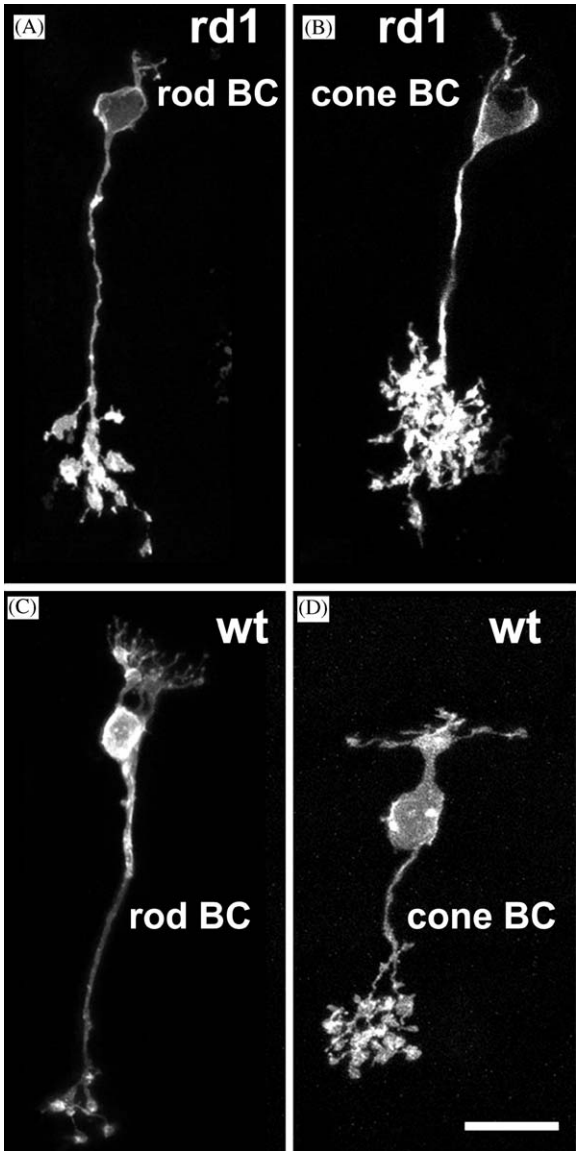


Fig. 10. Single rod and cone bipolar cells visualized by 'gene-gun' ballistic DiI labeling in *rd1* (A, B) and (C, D) wild-type mouse retinas. Dendrites are sparse and truncated in all bipolar cell types from the *rd1* mouse retina. Scale: 10 μm.

if these "straggler' dendrites in the outer plexiform layer contacted rare surviving cones (see below). By pnd 90, ≈30% of rod bipolar cells are lost from the central retina, following the pattern of rod degeneration in general (Strettoi and Pignatelli, 2000) and presaging the slow, but cumulative death of neurons at advanced ages in retinal degenerations. However, this cell death is only obvious and statistically detectable by isolating the rod bipolar cell population with the PKCα phenotype and performing careful counts at all retinal loci. Simple histological methods, such as toluidine blue staining, will miss this early cell death.

The cone–rod transcription factor *Crx* regulates the expression of key phenotype-defining proteins in rod photoreceptors, including rhodopsin, the rod transducin α subunit and PDE γ (Livesey et al., 2000). Its inactivation in $Crx^{-/-}$ mice leads to aberrant development, i.e. the rod is already stressed and deconstructed by pnd 10, with photoreceptor degeneration ensuing at ≈pnd 21 and nearly complete by pnd 180 (Furukawa et al., 1999). Thus the rods survive for an extended period compared to the *rd1* model. Rod bipolar cells do develop perfect dendrites early in life but, as rod degeneration advances, they progressively retract until, at 7 months of age, rod bipolar cells of a $Crx^{-/-}$ retina resemble those of the *rd1* retina: unipolar neurons, with scant if any dendrites (Fig. 11). Cone bipolar cells eventually lose their dendrites at a slower rate. Similarly the *rd10* mouse, with a missense mutation the *Pde6b* gene (Chang et al., 2002) and a much slower retinal degeneration than *rd1*, shows the same pattern of neurite retraction, even though rod death does not overlap with rod bipolar cell neurite development. Loss of rods provokes loss of bipolar cell dendrites.

The behavior of rod bipolar cells in the transgenic pig P347L defect seems different, at first, with the most graphic change being the formation of ectopic synaptic complexes between rod bipolar cells and cones (Peng et al., 2000). However, the *rd1* and $Crx^{-/-}$ models involve loss of cones as well as rods. Though cone survival exceeds rods in the *rd1* mouse, almost half are lost by pnd 26, and 98% are lost by pnd 100–120 (Carter-Dawson et al., 1978; Jiménez et al., 1996). Cones and cone-specific genes have not been as carefully mapped in the $Crx^{-/-}$ mouse, but ERG data suggest that much of the cone signal is also attenuated along with rods (Furukawa et al., 1999) and *Crx* expression is likely a key determinant of the cone phenotype. This differs dramatically from the transgenic pig P347L rhodopsin mutant, a model of human adRP, with rod photoreceptor loss spanning a year and significant cone survival at pnd 600 (Petters et al., 1997), even though the

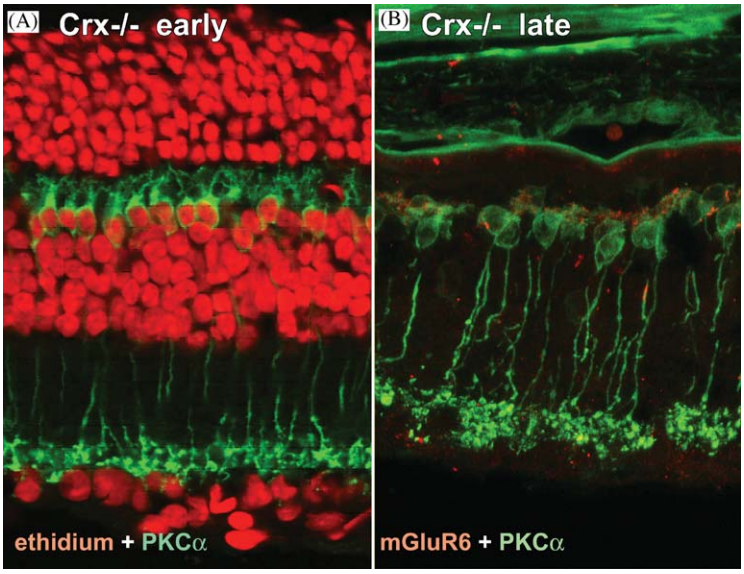


Fig. 11. Rod bipolar cell PKCα immunoreactivity (green) visualized in $Crx^{-/-}$ mouse retinas prior to (A) and after (B) rod cell death. Before rod cell death, evidenced by the complete layer of rod nuclei (red, ethidium bromide fluorescence), rod bipolar cells (green) develop profuse dendrites similar to wild-type rod bipolar cells. After rod death, rod bipolar cells retract their dendrites as in the *rd1* model.

cones begin phenotype deconstruction by pnd 30, with loss of PDEγ, arrestin and recoverin signals (Li et al., 1998). In view of our understanding of late remodeling, it is not surprising that the rod bipolar cells would redirect dendrites to available surviving cones: an opportunity absent in *rd1* and $Crx^{-/-}$ mice. Furthermore, rods in the transgenic pig appear to lack both presynaptic ribbons and vesicles (Li et al., 1998), even though they make neurites that extend into the neural retina, past the rod bipolar cells (Milam et al., 1999). So P347L pig bipolar cells may have had only cones to contact from the outset. However, Peng et al. (2000) also report switching of neurites from rods to cones in the pnd 18 *rd1* mouse, based on confocal concordance of rod bipolar cell PKCα and cone terminal synaptophysin signals. While this seems to conflict with the observations of Strettoi and colleagues, remnant erroneous contacts might be associated with the few surviving dendrites of rod bipolar cells for a brief epoch. Nearly 65% of cones are still present in the pnd 18 *rd1* retina, dropping to ≈40% by pnd 30 and 6% by pnd 90 (interpolated from Carter-Dawson et al., 1978). Thus, early pruning as well as maldevelopment of rod bipolar cell neurites is not inconsistent with short, remnant dendrites contacting cones. Loss of cones makes ectopic cone contacts of ephemeral significance, however. As cones should already be preoccupied with the dendrites of cone bipolar cells, acceptance of new rod bipolar cell dendrites suggests some reactive remodeling by the cones as well, consistent with the observations of Fei (2002) in the *rd1* mouse retina. Previous reports suggest that the cones of the P347L pig had shrunken synaptic terminals early in development (Li et al., 1998), but whether this is sustained until cone death is unclear.

The rod-driven axon terminals of horizontal cells are also altered in the *rd1* mouse as their fine processes retract and the remaining primary arbor appears to hypertrophy (Strettoi et al., 2002), suggesting a process similar to the pruning of bipolar cell dendrites. The coverage of retinal space is now less effective, with large gaps and loss of fine terminal processes. This occurs very rapidly and, in the *rd1* mouse at least, likely represents a combined failure of maturation and loss of afferent signaling. Some fine processes remain and it is not yet known whether they find new targets within the remnant outer plexiform layer. As about 30% of horizontal cells will die in the central retina by pnd 90, rod-driven axon terminals will also disappear.

6.3. Deconstruction of the rod bipolar cell molecular phenotype

The group C GPCR mGluR6 is a phenotype marker for ON center bipolar cells in general. Given dendritic retraction, what might be the fate of a transmembrane GPCR? Upon dissolution of the outer segment, rods continue to insert their GPCR rhodopsin into the plasma membrane. While this seems to happen to some extent in rod bipolar cells, it is clear that mGluR6 immunoreactivity is significantly diminished in truncated rod bipolar cells of the *rd1* mouse retina as early as pnd 10, long before the onset of phase 3 remodeling (Strettoi and Pignatelli, 2000; Strettoi et al., 2002, 2003). Some mGluR6 protein appears to be redirected into the

axon, though it is difficult to tell whether this signal is in the axonal membrane or in accumulated transport vesicles. The $Crx^{-/-}$ and *rd10* models display a similar loss of mGluR6 immunoreactivity. Is the remnant protein functional? Recent assessments of the physiological competence of ON center bipolar cells in the *rd1* mouse indicate that, by pnd 28–56, they have lost the ability respond to glutamate application (Varela et al., 2003). The mGluR6 protein may still be expressed at low levels and fail to insert into the membrane or other components of the mGluR6 signaling pathway, such as $G_o\alpha$ (Dhingra et al., 2000, 2002) may be lost as well. Goα signals are lost from the outer plexiform layer due to dendritic retraction, but there is no evidence of aberrant repositioning of $G_o\alpha$ in the *rd1* mouse (Strettoi et al., 2002). Even the mGluR6-inhibited cation channel could be lost. In the absence of photoreceptor-derived glutamate signaling, rod bipolar cells should be intrinsically *depolarized* if the channel is still present and activated. As we shall see below, there is more to the story than that. In addition, Varela et al. (2003) found that $GABA_A$ receptor mediated signaling was enhanced several fold in the same bipolar cells that lacked glutamate responses. This suggests that deconstruction of the rod bipolar cell phenotype is more extensive than dendritic loss alone.

6.4. Remodeling of cone pathways

Even at early stages of rod loss in the *rd1* mouse retina, cone-driven bipolar and horizontal cells display structural and molecular anomalies that parallel those of rod-driven cells. By p90, cone loss reaches ≈98% in the *rd1* mouse (Carter-Dawson et al., 1978) and both ON and OFF center cone bipolar cells display the same degree of dendritic revision as rod bipolar cells when visualized by caldrendrin and neurokinin-3 immunoreactivity (Strettoi et al., 2002). Cone-driven horizontal cells appear to be similarly impacted and undergo structural changes very quickly. By pnd 15, extensive neurite sprouting has occurred (Strettoi et al., 2002) and many of these axon-like processes descend into the proximal inner nuclear layer and inner plexiform layer (Fig. 12A). By pnd 90 the horizontal cell somas have undergone significant hypertrophy, though they have lost their fine terminal dendrites. Similar horizontal cell hypertrophy and dendrite depletion, as well as less precise somatic layering in the distal inner nuclear layer has been described in RCS rat (Chu et al., 1993). The FVB/N (Friend virus B-trophic/NIH general purpose Swiss) mouse (Taketo et al., 1991) displays a phenotype resembling *rd1* and, as shown in Fig. 12C–E, phenotyping with calbindin D-28K shows that ectopic horizontal cell neurites enter the inner plexiform layer as early as pnd 14, becoming extensive by pnd 65 (Park et al., 2001). The high incidence of neurites in these and other

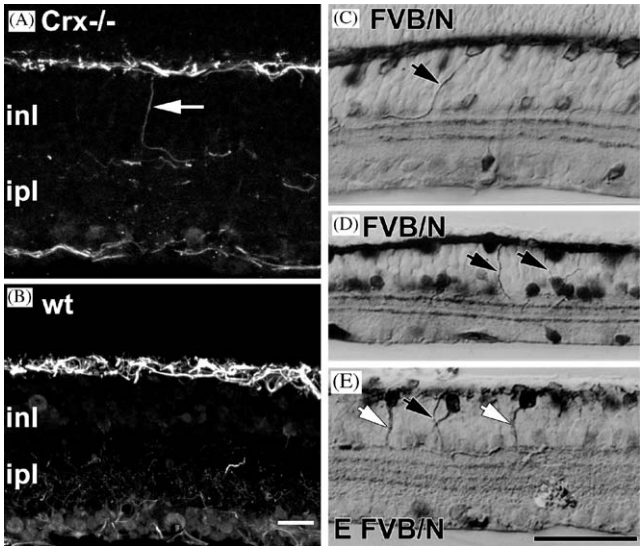


Fig. 12. Horizontal cell neurite sprouting in mouse retinas expressing photoreceptor degenerations. (A) After rod cell death in the $Crx^{-/-}$ retina, horizontal cell axon terminal fields visualized with 200 kDa neurofilament immunoreactivity appear to generate fine axon-like processes that enter the inner plexiform layer. (B) Neurofilament immunoreactivity reveals no such axons in the wild-type mouse retina. Scale for A and B, 10 μm. (C–E) In the FB/N mouse, visualization of the entire horizontal cell somatic and axonal field with calbindin D-28K immunoreactivity reveals both axon-like (black arrows) and large caliber dendrite-process from the proximal surfaces of the horizontal cell somas (white arrows). Scale for C–E, 50 μm. Figures C–E reproduced from Park et al. (2001) by copyright permission of the authors and Springer-Verlag. Relabeled by RM.

models gives the very strong impression that all horizontal cells are remodeling, not just a rare few. This is consistent with the data showing that all rod and cone bipolar cells retract dendrites. Loss of photoreceptor input thus appears to invoke similar, coherent reactions in postsynaptic cells.

The propensity of horizontal cells to sprout ectopic neurites that course through proximal retina is well known from many different types of preparations. What are these neurites? Are they functional? Two different kinds of process might arise: slender, axon-like processes that may be remnants of axon terminals (e.g. Fig. 12) and stout processes emerging from the proximal faces of horizontal cell somas, resembling primary dendrites (Figs. 6 and 12). While no evidence of synaptic connections exists for these new processes, horizontal cell dendrites and terminal axonal fields are legendary for lacking distinctive presynaptic specializations in spite of their known physiological roles as feedback elements (reviewed in Marc, 2003). If the processes do make synapses and are truly axonal in nature, it would seem unlikely that they involve long range signaling since horizontal cell axons are traditionally non-spiking. Normal horizontal cell somas and axon terminals are functionally driven by AMPA receptors (Blanco and de

la Villa, 1999; Marc, 1999b) and the extent to which this expression persists in new horizontal cell neurites may determine the persistence and efficacy of any new horizontal cell-mediated circuitry in the inner plexiform layer.

6.5. Remodeling of synaptic molecular architecture

Photoreceptor degeneration would obviously include deconstruction of the inner segment and synaptic terminal. Even though rods in the *rd1* retina do form distinctive presynaptic spherules, Blanks et al. (1974) demonstrated that rod bipolar cells did not successfully form the central element of the postsynaptic triad, implying that the intercellular signaling necessary for successful contact, synapse formation and synapse consolidation was already impaired in the *rd1* mouse. The developmental failure thus appears to be molecular and not merely structural. The sustained elevation of cGMP in rods, implicated in their cell death, may also impair inner segment cGMP-gated processes. Intracellular Ca^{2+} regulation and signaling (Schlossmann et al., 2000) and cerebellar long-term synaptic depression (Lev-Ram et al., 1997) act through cGMP-dependent kinases. Altered presynaptic mechanisms may thus prevent bipolar cells from making contacts. Evidence that altered behavior of the rod presynaptic terminal impacts rod survival has been provided by Read et al. (2002), who show that a combined *rd1* and L-type Ca channel mutant exhibits delayed rod death. Since L-type Ca channels are restricted to the inner segment and synaptic terminal in particular, this makes the synaptic compartment another candidate for the mechanisms of rod death. Rod bipolar cell dendrites may fail to approach spherules that lack vesicle release, in processes analogous to synaptic long-term depression, even though the photoreceptor experiences Ca^{2+} load challenges. That rod bipolar cell dendrites might preferentially seek active terminals is supported by data from the P347L pig and chimeric wild type + *rd1* mice that have a mosaic of degenerating and normal retina. These mice display some hypertrophied rod spherules with multiple synaptic ribbons and excessive numbers of invaginating contacts (Sanyal et al., 1992). Mature mammalian rod spherules are small (1–2 μm), roughly spheroidal, with two synaptic ribbons (Migdale et al., 2003) and a postsynaptic triad composed of a few processes arising from either horizontal cell axon terminals or rod bipolar cells. However, amphibian rods have multiple ribbons and contact many types of bipolar cells in addition to horizontal cells. The study of Sanyal et al. (1992) presumably reflects the responses of *normal* wild-type rods to a surfeit of target rod bipolar cells and horizontal cell axon terminals, and is evidence of bona fide plasticity rather than the effects of phenotype deconstruction. Some postsynaptic processes might be altered even in dendrites that still contact rods. Aleman et al. (2001) concluded that a post-receptoral mechanisms might underlie an increase in rod→rod bipolar cell gain in P23H rats during phase 1–2 degeneration, when rod loss is partial. As the bipolar cells will eventually retract dendrites and may deconstruct their mGluR6 signaling as in the *rd1* model, this evidence suggests that unusual intermediate states might exist, depending on the speed of rod loss. If rods drop out, bereft dendrites are left with cation channel pathways that should be open, decreasing the fraction of a rod bipolar cell's impedance that can be controlled by light. This should diminish gain. But if those dendrites retract and that conductance path is lost, the fractional impedance control might increase. The apparent change in functional drive is further evidence of neuronal responses to a changing environment, but is epiphenomenal to the ultimate fate of this retina: remodeling.

Both the *rd1* mouse and P347L transgenic pig display anomalous and presumably ephemeral synapses between rod bipolar cells and cones, making superficial flat and mildly invaginating contacts at cone pedicles (Peng et al., 2000). However, mammalian rod bipolar cells make connective errors in the normal retina, occasionally contacting cones (Dacheux and Raviola, 1986) and some ON center cone bipolar cells in the primate retina also make flat contacts, especially near central retina where space is limited (Chun et al., 1996). Given that any erroneous contacts made by rod bipolar cells during development are likely to be late (bipolar cells are born long after cones), it might not be surprising if most of the contacts observe in the transgenic pig model are a mixture of remnant and new contacts.

The synaptic terminals of rod bipolar cells in the *rd1* mouse also appear to be frozen in an early developmental stage (Fig. 13), as their varicosities normally are considerably smaller than normal; the long presynaptic bipolar cell ribbons of dyad synapses are replaced by small, ball-shaped ribbons (Strettoi et al., 2002, 2003), reminiscent of immature ribbon synapses of the developing retina and those displayed in the inner plexiform layer of cultured rat retinal slices (Sassoè-Pognetto et al., 1996). While such dot-like ribbon synapses are common in the normal rat retina (Watt, Jones, Yang, and Marc, unpublished data), they are not found in mature rod bipolar cells. The size of the synaptic ribbon is associated with the ability of the cell to provide sustained glutamate release and rod cone bipolar cells in the *rd1* retina appear severely compromised.

At early stages of retinal degeneration, there appears to be little obvious change in the numbers, phenotypes or dendritic architectures of amacrine cell or ganglion cells (Peng et al., 2000; Strettoi et al., 2002, 2003). This includes one of the primary targets of rod bipolar cells, the AII glycinergic amacrine cell. But it is important to recall the time scales on which these analyses are carried

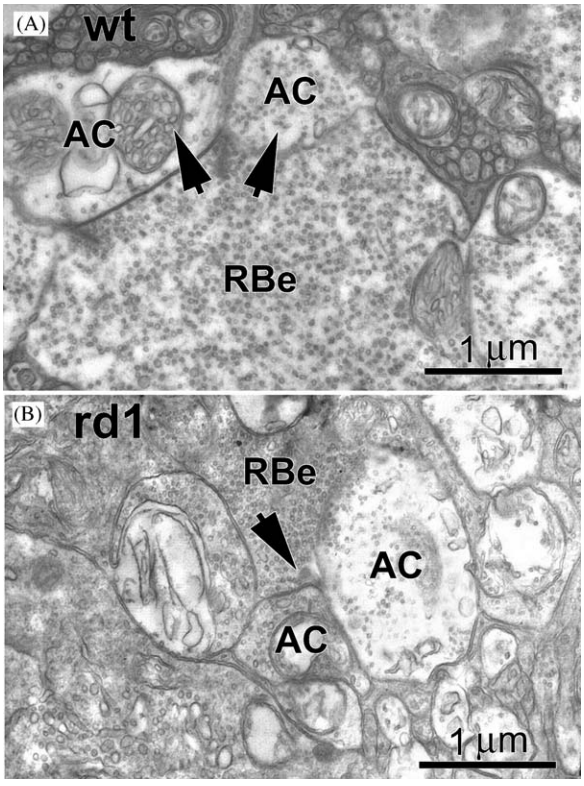


Fig. 13. Ultrastructural visualization of rod bipolar cell synaptic endings (RBe) in the proximal inner plexiform layer of (A) wild type and (B) *rd1* mouse retinas. (A) Rod bipolar cells normally target amacrine cells (arrows, AC) at ribbon synapses. The presynaptic ribbon is usually plate-like and, in cross-section, appears as a stripe about 5–6 vesicles long. (B) In the *rd1* mouse and early in retinal development, rod bipolar cell synaptic ribbons (arrow) appear small and spherical.

out. The *rd1* model in particular is very fast, with active photoreceptor loss occurring in parallel with the development of the neural retina. Since basic retinal circuitry, especially that of the inner plexiform layer, appears to develop without much photic guidance, loss of photoreceptor drive is not expected to change amacrine cell connectivity in the early days or weeks of retinal degeneration. But brain pathways demonstrate transneuronal anterograde or retrograde reactions operating on scales of months and years. We will therefore need to consider the effects of retinal degenerations on the inner plexiform layer on a similar time scale.

6.6. Remodeling of the Müller cell phenotype

Normal retinal Müller cells seal the transduction compartment of the sensory retina from its synaptic part, and seal the neural retina from the vitreous. Quantitative immunocytochemistry demonstrates one of the presumed phenotype proteins for the archetypal CNS astrocyte lineage, the intermediate filament glial fibrillary acidic protein (GFAP), is restricted to the filament-rich end feet of the Müller cells near the inner limiting membrane (Lewis et al., 1988). Müller cells in many challenge models including retinal detachment (Lewis et al., 1989), ischemia (Barnett and Osborne, 1995; Osborne and Larsen, 1996), experimental proliferative vascular retinopathy (McGillem and Dacheux, 1999), and attempted retinal bionic implants (Pardue et al., 2001), display increases in intermediate filament expression, later associated with the extension of processes into the subretinal space or damaged retinal zones. Retinal Müller cells display GFAP and vimentin upregulation and glutamine synthetase downregulation in response to retinal detachment (Lewis et al., 1989). Changes in intermediate filament expression appear to be the earliest evidence of Müller cell responses to retinal degeneration as GFAP signals increase during the acute phase of rod death in the *rd1* mouse (Strettoi et al., 2002, 2003).

No cell is better positioned to sense rod death than the Müller cell: every rod inner limb is completely encased in a sheath of glial processes and every rod death may be detected. This is consistent with the observations of Fletcher and Kalloniatis (1996) that the early postnatal RCS rat displays anomalous increases in Müller cell glutamine content long before photoreceptor death is complete. The light damage (LD) Sprague–Dawley rat model expresses a similar, perhaps even more dramatic phenomenon as the temporal sequence of photoreceptor death is conveniently remapped into anatomical space (Jones et al., 2003b). Photoreceptor damage and death appears as a stereotyped gradient with three zones. The outer zone, though perhaps stressed, remains normal in terms of RPE, rod, cone and Müller cell molecular phenotypes. In the transitional zone, RPE cells are compromised by an internal propagation of stress or signals through homocellular coupling or a progressive bystander effect. In the transitional zone, RPE cells alter their signatures, expressing losses in glutamine and glutathione, and become incapable of outer segment phagocytosis. A debris layer develops and rods photoreceptors display extremely lengthened outer segments, which buckles the retina. Within 100 µm of this zone, rod cell death is massive and, just at this junction, glutamine levels of Müller cells increase $\approx 10\times$ and the initial fibrotic layer is elaborated (Jones et al., 2003b). Though rod cell death releases a pulse of glutamate, the entire glutamate content of the retina is not much of a challenge for Müller cells and cannot significantly and cannot significantly raise glial glutamine levels. Perhaps other changes in the Müller cell phenotype, such as down-regulation in the expression of the SN1 glutamine export mechanism (Varoqui et al., 2000), is part of the Müller cell response to photoreceptor cell death. This delicate Müller cell phenotype revision or

deconstruction will be difficult to analyze, as any disturbance appears to invoke at least the GFAP response. Even isolated Müller cells display GFAP expression early in cell culture and then spontaneously display loss in glutamine synthetase and GFAP expression (McGillem et al., 1998). Furthermore, Müller cells express sensitive, stretch-activated Ca^{2+}-permeant cation channels (Puro, 1991; Marc, 1999b), and any disturbance, such as rod death, retinal detachment, and certainly culturing, will activate these sensors. Once these changes are activated, can a normal Müller cell phenotype be restored? A stable baseline for the normal Müller cell macromolecular phenotype may be difficult to obtain in any manner other than quantitative immunocytochemistry. The loss of the outer nuclear layer and the onset of Müller cell hypertrophy signals the transition of phase 3 remodeling of the neural retina.

7. Late remodeling in retinal degenerations

7.1. Anatomical evidence for late remodeling in human retinal degenerations

The earliest data suggesting that advanced retinal degenerations triggered more severe defects than merely the loss of part or all of the sensory retina arose from standard histological surveys of retinitis pigmentosa tissue. The advent of animal models has driven many of these studies from recent memory, leaving many with the impression that loss of the sensory retina is the only significant defect arising in retinal degenerations. The true status of the neural retina has not been better summarized than by Kolb and Gouras (1974) in their analysis of advanced human RP:

> Outside the fovea the retina became atrophic with disorganization of the cellular layers, gliosis and pigment-containing cells scattered about.... Most of the cones in this retina have degenerated.... What impressed us with these electron microscopic observations was how rapidly the pathology changed from totally degenerate cones on the foveal slope to those near the foveola whose pathology was too subtle to appreciate by light microscopy (from: Kolb H, Gouras P. 1974. Electron microscopic observations of human retinitis pigmentosa dominantly inherited. Invest Ophthalmol Vis Sci 13:487–498).

To a great extent, the atrophy of the neural retina in RP has long been appreciated (Marshall and Heckenlively, 1988). The emerging transformation of the neural retina in RP can even be seen in the beautiful illustrations of Fuchs' *Diseases of the Fundus Oculi With Atlas* (1949). Wolff (1935) describes the apparent loss of the ganglion cell layer in RP, but it is likely that glial proliferation and development of preretinal membranes confounded this interpretation. Milam et al. (1999) provides an extensive summary of early and late transformations of neurons and non-neural elements in human RP. Some histopathology of retinitis pigmentosa has focused on numerical evidence of cell loss, without immunocytochemical segmentation of populations. Even so, it is clear that retinal areas distant from surviving photoreceptors bear little resemblance to normal retinas; that even a trained anatomist could not, in many cases, identify the tissue as ocular in origin. Anatomical surveys of the macula in human RP (Stone et al., 1992; Santos et al., 1997; Humayun et al., 1999) document variable ganglion cell loss, from mild to severe, but well-preserved regions of the neural retina appear to possess surviving sensory retina harboring cones, albeit altered ones. Taken together, the three anatomical studies of human RP document ganglion cells losses in the macula and periphery, with more severe loss in the periphery. Using computational visualization methods, regions of cone depletion can be shown to express both neuronal loss and remodeling (Marc et al., 2001), suggesting that cone loss and subsequent remodeling are intimately related.

One of the most powerful methods for delineating the state of the neural retina in general is computational molecular phenotyping, which fuses array methods in immunocytochemistry and computational visualization to scan small molecule signals in all cells of a sample (Marc et al., 1995; Kalloniatis et al., 1996; Marc and Cameron, 2002; Marc and Jones, 2002; Jones et al., 2003a). Using these methods to screen RP retinas proved a powerful method to identify the origins of nearly all of the cells in a sample, despite significant remodeling. Fig. 14 displays peripheral retina from advanced human retinitis pigmentosa using concurrent visualization of taurine, glycine and glutathione signals. Several essential features of late phase 3 retinas are obvious. Many neuronal cells are lost and the vacated space is partly filled by Müller cells. In particular, the ganglion cell layer is devoid of neurons and filled by hypertrophic Müller cell endfeet. Other neurons, e.g. glycinergic amacrine cells visualized as a green channel, display both hypertrophy and some are displaced to the distal margin of the remnant retina. Along with this reorganization, clusters of ectopic neuropil are present. It is not possible to tell from pathology material whether these are new clusters of neurites or remnant processes dragged about by moving neurons or pushed about by glial hypertrophy. Animal models provide the answer (see below). The invasion of RPE cells to surround retinal vessels has long been established as the pathologic process that forms so-called bone spicule pigment in human RP. Continued elaboration of extracellular matrix by the relocated RPE cells occludes the vessel lumina, causing death of inner nuclear layer and

ganglion cell layer neurons (Li et al., 1995b). Given the great difference between the appearances of such retinas and the common claims that the neural retinal remains sufficiently normal to warrant rescue, even in advanced retinal degenerations, it is fair to ask: Is late-stage human pathology representative? The solution, as evidenced for early remodeling, is to apply advanced visualization methods to both animal models of retinal degeneration and human RP samples.

7.2. Mammalian systems expressing late remodeling of neural retina

Most rodents have short lives in vision research laboratories. When their outer nuclear layers have been ablated, investigators historically lose interest in them. Though photoreceptor cell death (phase 1 and 2) may be complete by pnd 30–150 in various models, the emergence of easily detectable features of phase 3

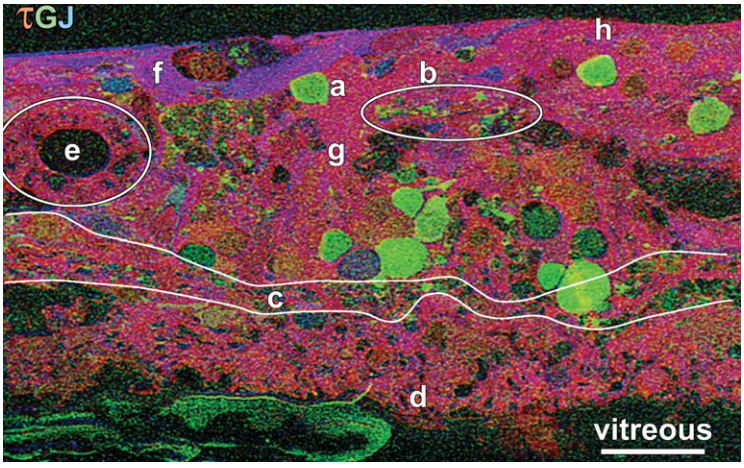


Fig. 14. Taurine–glycine–glutathione (τGJ)→rgb mapping of late phase 3 remodeling in human retinitis pigmentosa (FFB 133, 76 year old female, 2 h post-mortem). This vertical image demonstrates massive cell loss typical of late stage RP, with complete loss of the ganglion cell layer and severe depletion and disruption of the inner nuclear layer. Key defects are indicated. (a) Migration of glycinergic amacrine cells to the distal margin of the remnant neural retina. (b) Formation of ectopic amacrine cell neurite clusters. (c) Severe thinning of the inner plexiform layer. (d) Completely acellular ganglion cell layer (but for Müller cell processes). (e) Rings of remnant RPE cells in the remnant neural retina. (f) High glutathione processes of unknown provenance. (g) Hypertrophic Müller cells (high taurine 'red' signal). (h) Distal glial fibrotic seal. Scale: 25 μm.

Table 2
Remodeling in retinal degenerations

Gene	Model	Type	*n*	Onset	d	st	nm	f	*μ*	gm	gc	gs	v	r
Mixed	Human RP	Natural	20	?	×	×	2	×	×	×	×	×	?	×
rho	Rat S344ter	Transgenic	9	340	×	×	4	×	×	×	×	×	×	×
rho	Rat P23H	Transgenic	12	372	×	×	6	×	×	×	×	×	×	×
mertk	Rat RCS	Natural	7	270	×	×	12	×	×	×	×	×	×	×
——-	Rat LD	Induced	90	120	×	×	2	×	×	×	×	×	×	?
pde6β	Mouse *rd1*	Natural	9	610	×	×	2	×	×	×	×	×	×	×
pde6β	Mouse *rdcl*	Transgenic	20	180	×	×	2	×	×	×	×	×	×	
RGS9	Mouse TG9N	Transgenic	19	160	×	×	35	×	×	×	×	×	×	×
rho	Mouse GHL	Transgenic	12	555	×	×	6	×	×	×	×	×	×	×
rho	Mouse *rho−/−*	Knockout	4	365	○	○	○	○	×	○	○	×	○	○
rho	Mouse rhoΔCTA	Transgenic	8	541	○	○	○	○	×	○	○	×	○	○
?	Mouse *nr*	Natural	3	300	×	×	2	×	×	×	×	×	×	×
agtpbp1	Mouse *pcd*	Natural	2	321	○	○	○	○	○	○	×	×	○	○
prph2	Mouse *rd2*	Natural	1	>151	○	○	○	○	○	○	○	×	○	○
elovl4	Mouse *elovl4−/−*	Knockout	3	>180	○	○	○	○	○	○	○	×	×	○
chx10	Mouse or^{J}	Natural	3	<0	×	×	[a]	×	×	×	×	○	×	×
$p27^{Kip1}$	Mouse $p27^{Kip1}/or^{b}$	Knockout	1	<63	×	×	5	×	×	×	×	○	○	○

Abbreviations: ×, present; ○, absent; ?, undetermined; d, cell death in the neuronal retina; st, strictures of the inner plexiform layer; nm, neuronal migration expressed as the maximum number of glycinergic amacrine cells/mm observed; f, fascicles; *μ*, microneuromas; gm, glial migration; gc, glial columns; gs, glial seals; onset, in pnd; v, vascular invasion; r, RPE invasion.

[a] Only isolated retinal patches survive in *chx10*.

[b] The $p27^{Kip1}$ ko rescues hypocellularity in *chx10* but also exhibits neuronal remodeling.

typically occurs ≈pnd 200–600, depending on the aggressiveness and coherence of the initial degeneration. Fortunately, some have invested in long-term archives of certain models, notably Matthew LaVail and Wolfgang Baehr/Jeanne Frederick. These archives, augmented by samples from various colleagues, have permitted screening of a range of retinal degenerations arising from different initial molecular defects. The models and their remodeling defects, so far as they are known, are summarized in Table 2. Four classes of retinal degeneration models have been analyzed: naturally occurring, transgenic, knockout and induced. Different initial defects appear to devolve to a common process of phase 3 remodeling. The RCS rat and, to some extent, the LD rat are debris-based defects that lead to fairly rapid loss of both rod and cones, and both express stereotyped phase 3 remodeling. Transduction pathway defects expressed as a dominant negative (transgenic rhodopsin and RGS9 defects) or the classical recessive defect of the *rd1* mouse all lead to remodeling. Some models, such as the *rho*−/− knockout mouse and the transgenic rhoΔCTA rhodopsin C-terminal truncation mutant represent extremely "gentle" defects that appear to trigger cone loss very slowly. Remodeling onset is first seen in these models as microneuromas (see below) in the remnant inner nuclear layer. The gene defect in the nervous *nr* mouse is not known, but has been classified as a relatively slow photoreceptor degeneration model. Even so, it remodels quite vigorously, suggesting that there is a relatively coherent phase of rod stress, deconstruction and death that triggers coherent cone loss. Finally, the or^J mouse is a hypocellularity mutant characterized by failure to express the Chx10 transcription factor and severe depletion of bipolar cells, at least, during early retinal development. These retinas are deranged at birth, but by pnd 365 they are left with essentially no retina, merely focal patches of a few neurons forming tiny neuropil clusters. The emergence of this anomalous retina may have no direct bearing on remodeling in retinal degenerations, but does emphasize the fact that loss of any major cell cohort leads to atrophy, apoptosis, and remodeling among survivors. Indeed, the numerical rescue of the or^J defect by knockout of the $p27^{Kip1}$ cyclin-dependent kinase inhibitor (Green et al., 2003) still produces a severely remodeled retina, with numerous migration defects (Jones et al., 2003a).

In summary, phase 3 remodeling involves ten major types of retinal restructuring after ablation of the photoreceptor layer. (1) Progressive death of retinal neurons as evidenced by focal or global cell depletion, resembling late stage human RP. (2) Migration of all types of neurons, including eversions of amacrine cells to the distal margin and inversions of amacrine and bipolar cells to the ganglion cell layer. (3) Segmentation of the inner plexiform layer. (4) Global emergence of neurite fascicles containing many different cell classes. (5) Development of synaptic microneuroma clusters in the remnant distal retina and formation of new synapses throughout the retina. (6) Migration of Müller cell somas to distal and proximal borders of the retina. (7) Formation of hypertrophic columns of Müller cells. (8) Formation of a thick seal of Müller cell processes at the distal margin of the retina, as the end stage of subretinal fibrosis. (9) Invasion of blood vessels from both the vitreal and perhaps even choroidal margins of the retina. (10) Invasion of RPE cells or apical processes deep into the retina.

Typical molecular phenotyping of a representative slow model is summarized in Figs. 15–17. The GHL transgenic mouse was developed by Naash et al. (1993) as a mimic of human adRP. The mutant rhodopsin likely induces a primary ER stress and is not transported to rod outer segments (Frederick et al., 2001). However, as the GHL mutation is intended to mimic the same

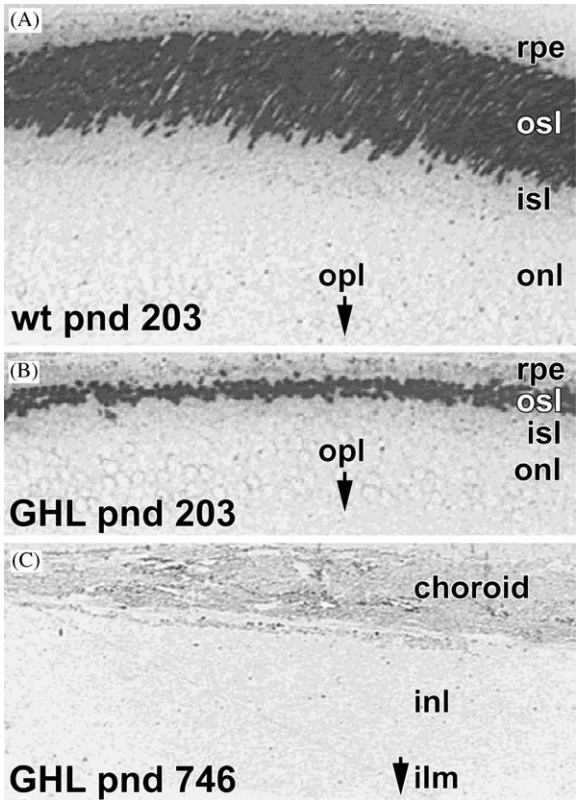
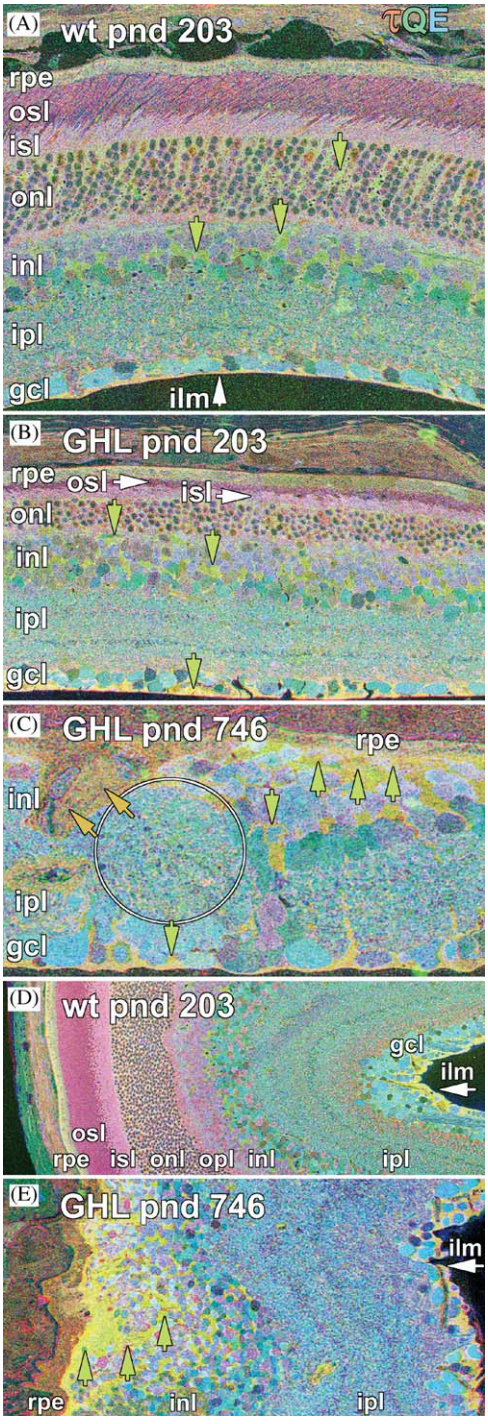


Fig. 15. Rhodopsin signals (monoclonal antibody rho 1D4, courtesy of R. Molday) in transgenic littermate wild-type and GHL mice visualized in 250 nm sections with streptavidin 1 nm-gold and silver intensification. (A) Wild-type pnd 203 day littermate with strong outer segment layer (osl) signals, weak inner segment signals and no perinuclear signals. Some rhodopsin immunoreactivity in phagosomes can be detected in the RPE. (B) Phase 2 GHL littermate of the animal in panel A, pnd 203. Rod outer segments are attenuated to about 10% of their original length with little or no immunoreactivity in the perinuclear region. (C) Phase 3 GHL mouse, pnd 746 lacks any photoreceptors.

adRP defect as the P23H model, a similar mutant rhodopsin oligomerization and inhibition of proteasome function is likely (Illing et al., 2002). On a wild-type background, photoreceptor cells shorten and rods die over the first year of life. Even at about 10% of their original length, GHL rods do not display significant redistribution of wild-type rhodopsin into the inner segment (Fig. 15A and B) when visualized with quantitative thin section immunocytochemistry, unlike



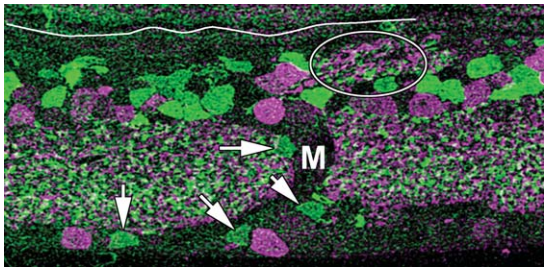


Fig. 17. Advanced phase 3 remodeling in the GHL mouse. Dual channel GABA-glycine (γG)→magenta-green mapping in a thin sections of a pnd 746 GHL transgenic mouse. A hypertrophic Müller cell corridor (M) is flanked by amacrine cells, many of them glycinergic (arrows) that are apparently migrating into the ganglion cell layer. The border between the remnant RPE and the glial seal is indicated by the wavy line. A dense microneuroma of new neuropil is forming in the distal retina (ellipse).

redistribution commonly seen in LD rats or certain human RP retinas (e.g. Fig. 2). Wild-type rhodopsin is still transported to the rod outer segment base and rods may not display significant inner segment rhodopsin immunoreactivity until the outer segment is gone. But by this time, few live rods will be left. Eventually, all rod and cone photoreceptors die, leaving the GHL retina completely deafferented (Fig. 15C). Viewing the retina as a τQE map (taurine, glutamine, glutamate) is a powerful way to visualize all cells (Marc et al., 1995; Kalloniatis et al., 1996) including neurons, vascular cells and glia (Fig. 16A and D). In particular, normal Müller cells in all vertebrates display a unique high τQ signature shared by no other retinal cells. This signature can be seen around the rod nuclei in the outer nuclear layer, as polygonal somas usually positioned between the amacrine and bipolar cell layers within the inner nuclear layer, and as a continuous border at the proximal margin of the retina, forming the internal limiting

Fig. 16. Taurine–glutamine–glutamate (τQE)→ rgb mapping in thin (250 nm) sections of normal and GHL littermate transgenic mice. Standard τQE mapping discriminates photoreceptors (magenta), neurons (various colors), and Müller cells (yellow-green) due to the high taurine and glutamine contents of the latter (yellow-green arrows). (A) Wild-type pnd 203 day littermate with normal lamination and Müller cell signals (downward arrows). (B) Phase 2 GHL pnd 203 littermate shows normal neural retinal signatures despite photoreceptor outer segment layer truncation. (C) Mid-phase 3 GHL pnd 746 littermate displays extensive retinal remodeling, including evolution of a thick glial seal (upward arrows), invasion of the neural retina by RPE cells (oblique orange arrows), and eruption of the inner plexiform layer into the distal retina (circle). Severe neuronal depletion is also occurring. (D) Oblique section of a wild-type pnd 203 littermate showing normal retinal lamination and precise Müller cell process distributions in the outer nuclear layer and forming the inner limiting membrane. (E) Oblique section of a mid-phase 3 GHL pnd 746 littermate displaying the thick glial seal (upward arrows) that invests the remnant inner nuclear layer and separates it from the RPE.

membrane. By pnd 203, over half of the rods have died and the outer segments of the surviving rods are <10% of their normal length. Even so, the signatures and positions of all retinal neurons and glia appear indistinguishable from normal retina. But by the end of the second year of life, all photoreceptors have been gone for about a year, and the retina is severely transformed (Fig. 16C and E). Most evident from the τQE signatures is the emergence of a dense fibrotic layer between the neural retina and the remnant RPE. Masses of RPE cells also move into the retina, displacing inner nuclear layer cells, which are also depleted in number some regions of the inner plexiform layer bulge upwards. At the same time, visualization of individual classes of neurons displays the inversion of glycinergic amacrine cells to the ganglion cell layer and the evolution of new neurites in the remnant inner nuclear layer (Fig. 17). The inner nuclear layer is significantly thinned.

While is not possible to detail the results from all the models listed in Table 2 (see Jones et al., 2003a), the basic features of phase 3 remodeling are summarized in the *theme maps* of Fig. 18. Theme maps are formal classification maps derived from all of the signatures in a dataset. The methods for classification, statistical verification and theme map generation/exploration have evolved since we first introduced them (Marc et al., 1995), but the principles remain constant: a theme map color is a cell class defined by its molecular signature. In such maps, all structures get classified: nothing gets left out. In a normal Sprague–Dawley rat retina, the

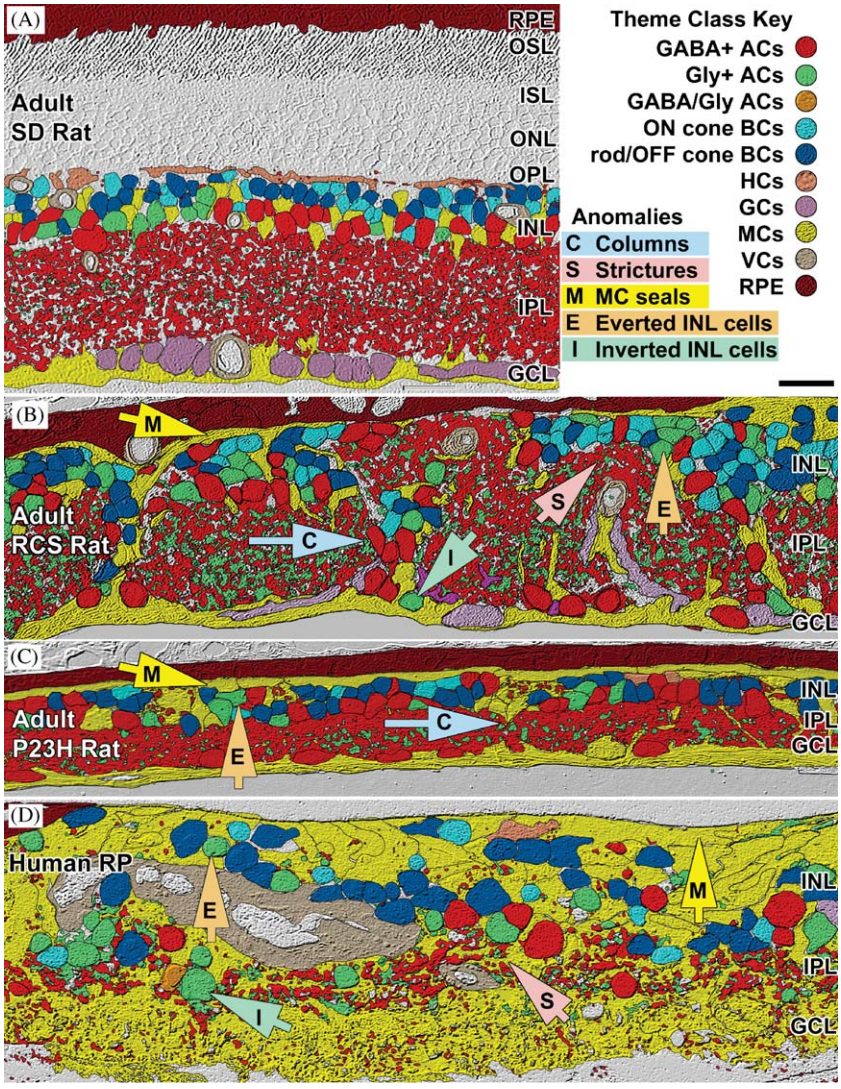


Fig. 18. Theme maps of (A) normal pnd 700 Sprague–Dawley (SD) rat, (B) pnd 900 RCS rat, (C) P372 P23H line 1 transgenic rat, and (D) human RP (FFB accession #133-OD, 67 year-old, female, advanced RP, simplex, fixed 2.5 h post mortem). In normal retina, cell layers are precisely defined. Remodeling clearly disrupts lamination via migration on Müller glia columns (C), yielding eversion (E) of GABAergic and glycinergic amacrine cells to the distal Müller glial seal (M) and inversion of amacrine and bipolar cells (I) to the ganglion cell layer. Glial hypertrophy and neuronal movement can be so extensive that the inner plexiform layer is segmented, distorted and forced through strictures (S) as small as 10 μm. Reproduced from Jones et al. (2003a), by copyright permission of the authors and Wiley Interscience.

lamination of nuclear and plexiform layers is precise (Fig. 18A). In an adult RCS rat of pnd 900, the retina is highly transformed, displaying the glial seal, bidirectional migrations of neurons, neuronal loss, and segmentation of the inner plexiform layer (Fig. 18B). These zones of transformations are distributed across the entire retina and presage the ultrastructural alterations described below. Some transgenes lead to more rapid and severe alterations than others. While most result in fairly slow photoreceptor loss, mimicking adRP, some can result in near total ablation of the retina and the ganglion cell layer in particular. Line 3 of the P23 H transgenic rat displays extensive phase 3 remodeling, with loss of most neurons and a severely depleted ganglion cell layer (Fig. 18C). The few remaining neurons in the ganglion cell layer appear to be GABAergic amacrine cells or ganglion cells coupled to amacrine cells. Late stage human RP resembles the P23H rat retina to a great degree, especially in terms of neuronal loss and Müller cell hypertrophy (Fig. 18D).

7.3. The onset of phase 3 remodeling

It is clear that near-total loss of the photoreceptor layer is a prerequisite for initiating phase 3 remodeling. There is no single time point that holds true for all models, nor a single spatial progression, as far as we can discern. Some models are extremely aggressive, such as the transgenic TG9N mouse (from C-K Chen, University of Utah), the dual transgenic *rdcl* mouse, and the rat LD model, all of which display nearly complete ablation of the photoreceptor layer in 30–60 days (pnd or post-LD) and show advanced remodeling by 120–180 days. These models mimic some forms of CORD in the coherence of rod and cone loss. The *rdcl* model explicitly targets both for cell death (Freedman et al., 1999; Lucas et al., 1999, 2001a). The RGS transgenic mouse expresses an N-terminal fragment of the GTPase accelerator RGS9, required for rapid transduction inactivation in both rods and cones (Lyubarsky et al., 2001a, b), though the nature of the dominant negative effect is unknown. Finally, the LD model effects a coherent damage to the RPE which, when combined with potential direct phototoxicity, ablates rods and cones concurrently. These models provide three very different initial conditions that all lead to cone loss and fast remodeling onset. Models that initiate in rods alone uniformly require 2–5 × longer (pnd 300–600) to display remodeling, presumably due to the survival of cones. In all retinas showing significant cone survival, remodeling is either absent or minimal, except for the pervasive glial seal. The seal emerges when the outer nuclear layer is largely, but not completely gone, and it entombs any surviving cones. Even though such cones are structurally modified and likely express deconstructed macromolecular phenotypes, they still may have access to essential chromophore recycling through the Müller cells (Mata et al., 2002), provided the Müller cells have not lost this function.

7.4. Glial remodeling

The remodeling of Müller cells involves transformation of the Müller cell phenotype, hypertrophy, evolution of the distal fibrotic seal and displacement of patches of intermediate junctions (zonula adherentes) into the neural retina. We have only a fragmentary view of the Müller cell transcriptome and proteome in retinal degenerations, but it appears likely that some of the common features of glial stress, such as increases in intermediate filament expression, indicate a general transformation associated with process extension. Müller cell processes appear to preferentially self-associate in bundles, surround new neurite fascicles, support neuronal migration and seal off invading RPE cells from the neural retina, much like normal adhesion processes at the external limiting membrane. The large elevations of glutamine levels in the Müller cells of LD (Jones et al., 2003b) and RCS rats (Fletcher and Kalloniatis, 1996) has no simple explanation. Our current hypothesis is that glutamine export is impaired.

The formation of the distal glial seal is common to human (Milam et al., 1996) and animal (Jones et al., 2003a) retinal degenerations, and occurs in every instance where the sensory retina becomes significantly depleted of rods. It may be the single most difficult barrier to retinal rescue. For example, Radner et al. (2001), reported that only 3 of 10 *rd1* mice sustained photoresponses after photoreceptor transplants at pnd 13, and *zero of 10* at pnd 56. This is the onset time for seal development. It is difficult to prove that the seal represents completely new processes, since the collapse of the outer nuclear layer leaves behind a great mass of Müller cell distal processes. Retinal detachment provides evidence that Müller cells can elaborate new processes that move into the subretinal space (summarized in Fisher and Lewis, 2003). Furthermore, using the aged ambient-light model of retinal degeneration, Sullivan et al. (2003) show unambiguous novel process evolution by Müller cells, including eruption of the distal arbor into the choroid. In any event, the glial seal accompanies all degenerations of the sensory retina (Table 2), arises from within the neural retina and entombs it, obliterating the subretinal space. The seal can be apposed to remnant RPE cells or the choroid in cases where RPE cell dropout has occurred due to cell death or depletion by invasion. However, the seal is not perfect and is interrupted by foci of direct neural retina-RPE or neural retina-choroid contact and these seem to be sites of aggressive cell invasion or inner plexiform layer remodeling. Where RPE cells or extensions of their apical processes are found deep within the neural retina

of the RCS rat, they are surrounded by small 200–500 nm diameter Müller cell processes that are self-linked by homocellular intermediate junctions, identical to findings in human RP (Li et al., 1995b; Milam et al., 1996). Remodeled Müller cells still seem able to form compartments to regulate fluid and metabolite flow. Late in remodeling, Müller cells can occupy much of the retina (Fig. 18), consistent with hypertrophy and perhaps even hyperplasia. There is no concrete evidence for the latter in retinal degenerations but Müller cell proliferation does occur in response to retinal detachment (Fisher et al., 1991; Lewis et al., 1999).

7.5. Invasions of the retina

The focus of this review is the neural retina, but the behaviors of non-neural elements may be as significant as those of neurons and Müller cells with respect to initialing or supporting remodeling. Many forms of advanced RP involve the focal loss of RPE cells, trans- or de-differentiation of RPE cells, or invasion of the retina by RPE cells. The preferential accumulation of RPE cells around vessels in advanced RP and patchy denuding of the RPE layer is particularly striking even early retinal histology (Fuchs, 1949). The RPE can enter the retina in toto, usually along with or towards vessels or send columns of apical processes (apical folds transformed into tubules) deep into the retina, even approaching the ganglion cell layer (Watt and Marc, unpublished observations). Fine, tubular Müller cell processes interconnected by intermediate junctions always surround these RPE processes. As RPE cells can apparently transform into fibroblast-like cells, many unidentified fusiform cells in advanced RP specimens and animal retinal degeneration models may be remnant survivor RPE cells. The key effects of RPE invasion are likely: (1) loss of the blood-retinal barrier, permitting protein permeation in areas where glial seals are incomplete and allowing invasion of immune system cells; and (2) attenuation of retinal vessels by "cuffing" and extracellular matrix production (Milam et al., 1999; Weleber and Gregory-Evans, 2001). The reverse process, retinal invasion of the choroid, is dramatic evidence that loss of RPE cells can trigger vigorous remodeling on an unprecedented scale (Sullivan et al., 2003).

In many phase 3 animal models, we have observed occasional invasion of the distal retina by vascular elements. Whether this follows or leads excavation of the retina is not certain, but Müller cell processes always circumscribe the invasion and, if they are available, RPE cells. But similar findings have not been reported in human retinal degenerations, RP in particular. The incidence of such events is probably associated with the speed and confluence of the Müller cell seal formation. An incomplete seal may allow either sporadic entry of RPE cells and occasional choroidal vascular endothelium or, in the opposite case, eruption of the Müller cells and the retina into the choroid (Sullivan et al., 2003). Both human and rodent retinas occasionally display large, anomalous vascular tracts that pierce the inner plexiform layer, apparently arising from vessels in the ganglion cell layer. This phenomenon was first described in RCS rats (Villegas-Perez et al., 1998), but may be present in many retinal degenerations.

Though little is known of astrocyte behavior in retinal degenerations, hypertrophied or hyperplastic astrocytes spanning the entire retina can occur in human RP (Jones and Marc, unpublished observations). Retinal astrocytes proliferate in experimental detachments, and it would not be surprising if they also proliferated in retinal degenerations. Astrocytes have been found mixed within epiretinal membranes along with Müller and RPE cells (summarized in Milam et al., 1999; Weleber and Gregory-Evans, 2001), and are reasonably abundant in vascularized regions of mammalian optic fiber layers (Karschin et al., 1986; Schnitzer, 1988). They may play an unrecognized role in remodeling.

The invasion of the retina by ectopic immune cells or the activation of resident microglia (Schnitzer, 1989; Provis et al., 1996) is a topic far beyond the scope of this review and has been considered thoroughly with respect to AMD (Hageman et al., 2001; Penfold et al., 2001). Recent histopathology has demonstrated the apparent recruitment of activated endogenous microglia into the degenerating outer nuclear layer in human RP and AMD (Gupta et al., 2003). While microglia may play a role in secondary death of cones, there is no evidence that their activities end there. We have no explanation for the neuronal death that begins in phase 2, peaks in phase 3 and can continue throughout life. Since debris-filled amoeboid cells can be found in the RCS rat retina at pnd 900 (Watt and Marc, unpublished data), microglia appear to remain active throughout the remodeling process. Monocytes are also occasionally found near gaps in the glial seal in the RCS rat. The extent and significance of immune cell invasion for phase 3 remodeling is unknown, but the cells certainly have access to the degenerating retina in these models. That said, there is no compelling evidence for immune cell invasion of the retina or autoimmune responses in the vast majority of human RP cases. Heckenlively et al. (2000) found eight instances of serum anti-recoverin immunoglobulins (IgG + IgM) in a sample of 521 RP cases, arguing that autoimmune processes are rare in RP. By extension, neither humoral nor cellular processes likely play major roles in remodeling. Though serum proteins can gain access to the retina through fenestrations formed by retinal endothelial cells in response to relocated RPE cells (Li et al., 1995b), the zonulae adherentes between adjacent Müller processes seem to limit extravasated protein to the space around the endothelial cells.

7.6. Neuronal remodeling

7.6.1. Neuronal death

It is evident from late-stage human and animal retinal degeneration systems that neurons slowly die after deafferentation and that most previous studies simply stopped too soon to detect cumulative effects. Depletion of the ganglion cell layer can be dramatic and often complete in some areas (Figs. 14 and 18), and some RP patients report no induced phosphene percepts upon transocular current stimulation (Delbeke et al., 2001). Bipolar and amacrine cells are also potentially lost in great numbers by late stages. It is going to be difficult to visualize neurons in the process of apoptosis via TUNEL or immunocytochemistry for apoptotic markers. Depletion of 50% of all neurons in the inner nuclear layer over 150 days would yield ≈3 in 1000 cells in apoptosis at any one time, assuming a constant death rate. This number would be smaller for slower remodeling systems and, therefore negative results from apoptosis assays mean little. If there were a single pulse of intense death or multiple episodes of death, the probability of finding apoptotic neurons outside those episodes would be vanishingly small. That said, neurons begin to die early, perhaps even in phase 2 in some models, and death continues throughout phase 3.

Tracking the specific cell classes that die is critical. It appears that rod bipolar cells can become stressed and about 30% die in the central retina of the *rd1* mouse by pnd 60–90 (Strettoi and Pignatelli, 2000). This is not a trivial loss. However, rod bipolar cells make up only 40–50% of the bipolar cells in mammals and bipolar cells are only ≈40% of the inner nuclear layer proper. This cell loss in the rod bipolar cell population represents but a 6% total cell loss in the inner nuclear layer, which is statistically undetectable in most preparations. Since the Müller cells may proliferate (extrapolating from studies of retinal detchment by Fisher et al., 1991; Lewis et al., 1999, 2002), cell counting alone using non-discriminating stains will reveal only gross losses and will necessarily underestimate them, leading to a perhaps mistaken view that inner nuclear layer cells could be "spared disproportionately" (Santos et al., 1997). Cell survival should be re-examined in view of quantitative segmentations of cell populations in the retina (Kalloniatis et al., 1996; Jeon et al., 1998). Santos et al. (1997) report a loss of 20% of inner nuclear layer cells based on analyses of samples from human RP donors and concluded that such a limited death rate does not hamper retinal rescue. But Müller cells can comprise from one-third to half of the mass of the inner nuclear layer in primate retina and there is no evidence that any Müller cells die. Thus, the reported loss must be completely neuronal and is thus ≈40%. And the consequences might be very severe if cell loss was biased for certain cell classes. The inner nuclear layer of the mammalian retina, including that of humans, is 20% cone bipolar cells. Besides carrying cone-driven signals to the inner plexiform layer, *these cells carry all rod-driven signals to the ganglion cells*: i.e. AII amacrine cells "piggy back" on the cone pathway by establishing specialized contacts with the axonal endings of cone bipolar cells in the inner plexiform layer (see below). A retina without cone bipolar cells would look almost normal by standard light microscopy, but it would be impossible to restore vision through photoreceptor intervention because the new transplanted sensory retina would be functionally disconnected from the ganglion cell layer output. Thus even losses of 10–20% of the inner nuclear layer represent potentially massive depletion.

Similarly the loss of ganglion cells in severe RP can approach 70% (Santos et al., 1997), but since no estimates can be made of the extent of astrocyte proliferation, invasion of amacrine cell and bipolar cell somas, or selective loss of certain ganglion cell types, even milder losses cannot be viewed as insignificant. Many analyses of ganglion cell loss in retinal degenerations focus on regions where cones still survive, even if deconstructed. Stone et al. (1992) concluded that macular ganglion cell retention was 50–75% in advanced RP, even with considerable photoreceptor loss. Astrocytes should not be present in the macula, so proliferation should not corrupt these counts. But it was clear from the histology that truncated cone bouquets and even rows of cone synaptic pedicles were still present, implying an intact synaptic pathway to some cones. We believe that is the essential key to long- term ganglion cell survival.

No cell types appear immune to cell death, but no cell types are yet known to be uniquely sensitive either. Survivor neurons can include rod bipolar cells, both ON center and OFF center bipolar cells, GABAergic amacrine cells, glycinergic amacrine cell, apparent horizontal cells and ganglion cells. But losses can be extremely focal, depleting zones 100–300 μm in diameter, surrounding by clusters of apparently normal retina (Marc et al., 2001; Jones et al., 2003a). Thus, at this stage in our knowledge, neuronal death seems slow, progressive and non-specific. Detailed examination of individual animal models will substantially improve our knowledge of neuronal depletion patterns in retinal degenerations.

7.6.2. Neuronal migration

As the inner nuclear layer begins to change structure via neuronal loss and Müller cell hypertrophy, neurons appear in anomalous locations. In the normal mammalian retina, GABAergic amacrine cells never appear at the distal margin of the inner nuclear layer, but do in remodeling retinas (e.g. Figs. 17 and 18). Similarly, bipolar cells and glycinergic amacrine cells never appear

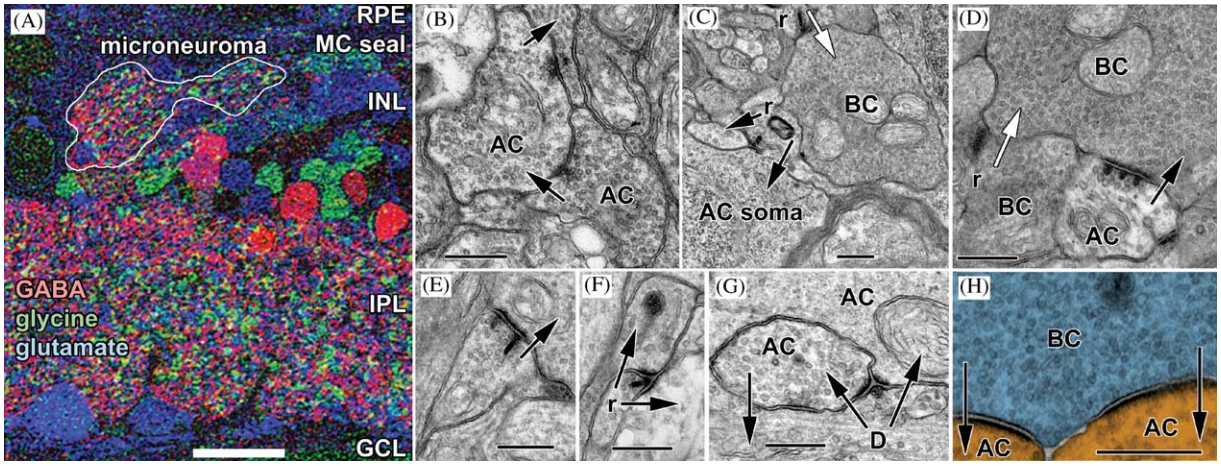


Fig. 19. Microneuromas and apparent retinal rewiring. (A) γGE→rgb mapping of RCS rat retina showing the emergence of new neuropil beneath the distal Müller cell (MC) seal. Microneuromas are tangles of GABAergic (red), glycinergic (green) and glutamate + (blue) neurites. Scale: 20 μm. (B) Microneuroma amacrine→amacrine→target synapse chains. (C) Anomalous bipolar→amacrine cell soma and bipolar→bipolar synapses. (D) Presynaptic multiprojection amacrine→bipolar and bipolar→bipolar cell contacts. (E) Multi-ribbon synapses. (F) Classic bipolar cell presynaptic dyad element in a process ≈100 nm diameter, with few vesicles. (G) Anomalous dyad-like synapse (D) with amacrine cell feedback. The presynaptic element contains few vesicles and resembles an amacrine cell dendrite. (H) Theme map of a large bipolar cell terminal lacking ribbons but making large conventional contacts onto amacrine cell dendrites. The blue overlay denotes the signature of an ON-center cone bipolar cell; orange denotes GABAergic amacrine cells. Synaptic directions are indicated by arrows; white arrows, bipolar→bipolar cell contacts; scales for B–H, 200 nm. Reproduced from Jones et al. (2003), by copyright permission of the authors and Wiley Interscience.

in the normal ganglion cell layer, but do in remodeling retinas in zones near columns of glial hypertrophy (Figs. 17, 18 and 20). Additional GABAergic neurons are almost certainly inserted into the ganglion cell layer, but since there are abundant GABAergic starburst amacrine cells and ganglion cells coupled to GABAergic amacrine cells, it is only by visualizing GABAergic amacrine cells near columns in the inner plexiform layer (Fig. 18B) that we infer repositioning. The presence of glycinergic amacrine cell somas in the ganglion cell layer is a semi-quantitative index of remodeling, as such cells do not normally occur therein. Some retinal ganglion cells that display glycine signals as a result of heterocellular coupling (Marc and Liu, 1985; Marc and Jones, 2002), but they have distinctive signatures: they are not amacrine cells. Misplaced glycinergic amacrine cells in the normal mammalian retina are extremely rare (<0.001/mm), and become >1000× more common in remodeled retinas (Jones et al., 2003a). In severely advanced model degenerations where the retina itself has become largely atrophic and lacking in neurons, it is even possible for neurons to follow glial processes into the remnant choroid (Sullivan et al., 2003).

There are three possible mechanisms for the appearance of anomalous signatures at the proximal and distal margins of the retina: (1) migration, (2) displacement, (3) signature change in situ. The latter is most unlikely, for the characteristic signatures of bipolar, amacrine and ganglion cells appear to be stable in retinal degenerations. We find no intermediate signatures, though absolute glutamate levels may drop in all cells. Further, the clusters of neurons that appear within the inner plexiform layer are an anomaly. Finally, all signature types remain associated with their unique size cohorts: bipolar cells are always the smallest cells and ganglion cells the largest in normal and remodeling retinas. Neuronal repositioning may occur by active cell migration and passive displacement by glial hypertrophy. We favor migration for several reasons. (1) Neurons are commonly found lining vertical or oblique hypertrophic Müller cell columns, but we see no evidence that hypertrophic glial masses displace the neurons downward. (2) Migration is clearly bidirectional: amacrine cells can go up or down in the same region. (3) New neurite fascicles are always associated with Müller cell surfaces (e.g. Fig. 21). (4) Migrating photoreceptor neurites in phase 1 retinal degenerations are often closely apposed to Müller cells (Fariss et al., 2000). (5) Migrating Müller cell apical processes prefer to follow cone surfaces (Fisher and Lewis, 2003).

While we do not know the mechanisms of neuron and neurite guidance in remodeling, there are reasonable candidates that might profitably be explored. Neuronal-glial cell adhesion, migration and growth systems involve integrins (Meyer et al., 2000; Biran et al., 2001), IgCAM superfamily members (NCAM, L1), cadherins and protocadherins (Murase and Schuman, 1999; Wu and Maniatis, 2000; Kam et al., 2002; Tasic et al., 2002), semaphorins, eph/ephrins, neureglins, etc. Integrins are particularly interesting candidates. Integrin subunits of many types are expressed throughout the mature retina and RPE (Brem et al., 1994; Chen et al.,

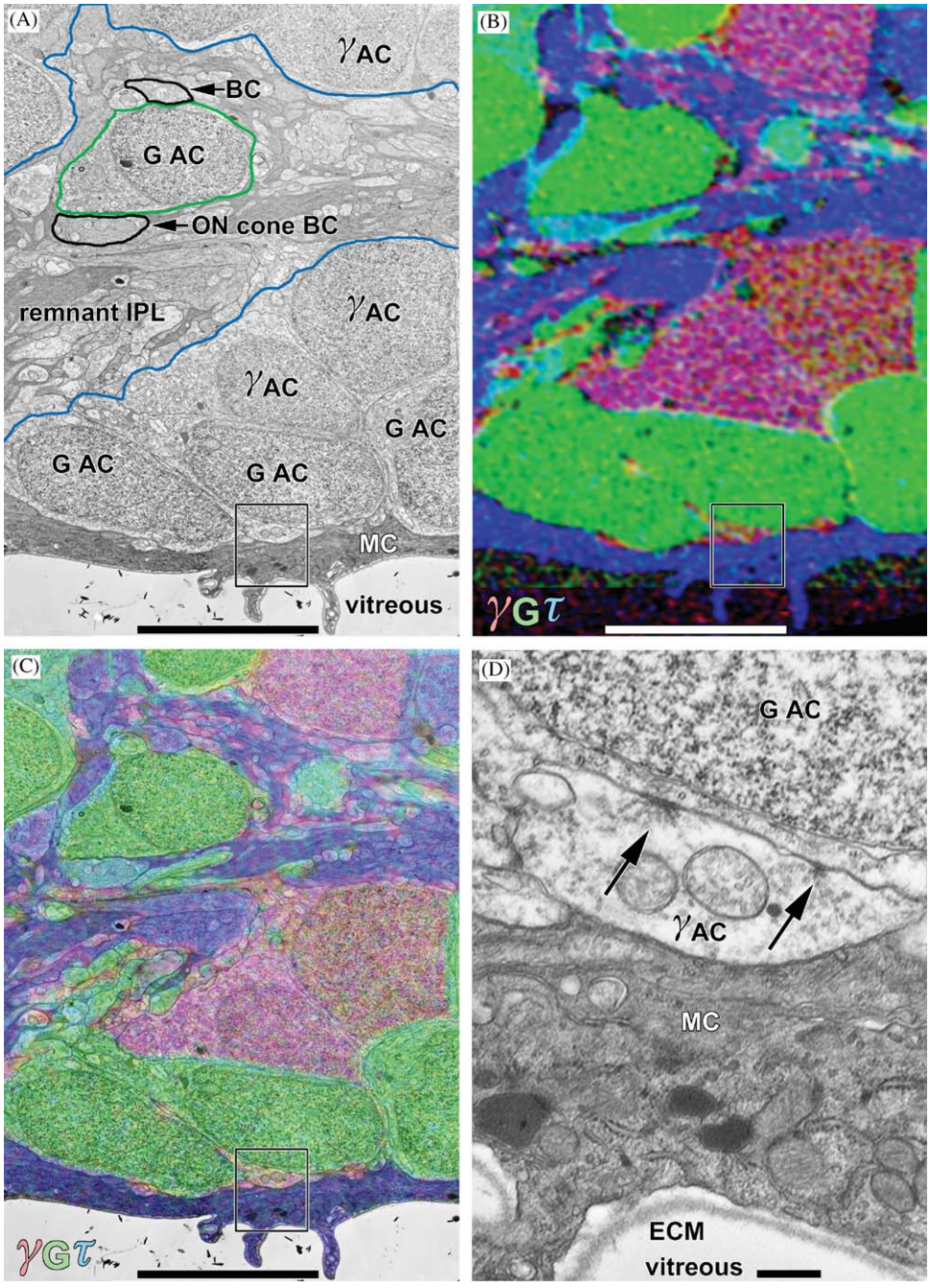


Fig. 20. Repositioned glycine+ and GABA+amacrine cells in the former ganglion cell layer. (A) Monochrome digital montage of glycine+ and GABA+amacrine cells after migration into the ganglion cell layer, bordered proximally by Müller cell processes and the vitreous and distally by a strip of remnant inner plexiform layer, outlined in blue. A single glycine+amacrine cell (outlined in green) within the remnant inner plexiform layer is completely surrounded by neuropil. (B) Registered γGτ→rgb mapping of the same field. (C) Overlay of the γGτ image on the ultrastructural channel. (D) Enlarged inset (box) of two GABA+ amacrine cell presynaptic sites (arrows) on the soma of a repositioned glycine+ amacrine cell. Abbreviations as in Fig. 2. ECM, extracellular matrix. Scales: A–C, 10 μm; D, 500 nm. Reproduced from Jones et al. (2003a), by copyright permission of the authors and Wiley Interscience.

1997; Finneman et al., 1997; Georges et al., 1998; Sherry and Proske, 2001), unlike down-regulated developmental IgCAMs, cadherins and protocadherins, and some may be particularly critical for neuronal positioning (Cann et al., 1996). Remodeling Müller cells may produce transmembrane ADAMs (A Disintegrin And Metalloprotease) acting as neuronal integrin receptors (Chen et al., 1999) or new extracellular matrix patterns, yielding integrin receptor motif arrays that neurons preferentially track via integrin binding and release as in growth-cone movements (Condic and Letourneau, 1997; Condic, 2001). Müller cells produce ECM at the inner

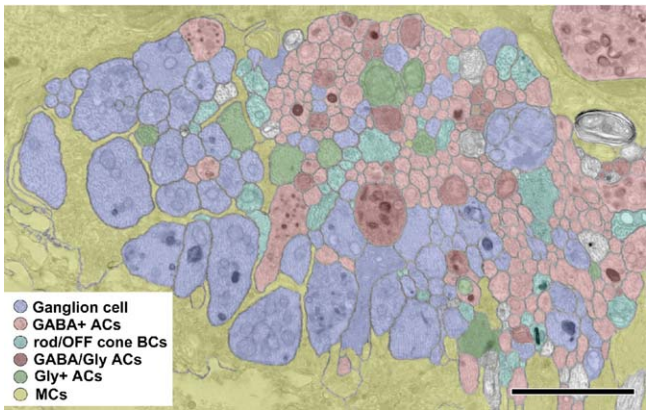


Fig. 21. Neurite fascicle ≈2 μm away from distal margin of the retina and the Müller cell seal viewed as an ultrastructural theme map. Six classes of elements are color coded according to characteristic signatures: ganglion cells (blue; high glutamate, low taurine); GABAergic amacrine cells (light red; high GABA), glycinergic amacrine cells (olive; high glycine), a mixed glycine+ and GABA+- class (dark red); bipolar cells (cyan, high glutamate, high taurine); Muller cells (yellow, high taurine, high glutamine). Unclassified elements are not colored. Scale: 250 nm.

limiting membrane in both normal and remodeled retinas (Fig. 20) and it is clear that remodeling involves a radical change in glial surface area. There is also evidence that integrins may be involved in synaptic stabilization and plasticity and peptides that bind integrins can influence LTP (Murase and Schuman, 1999). Finally, glial hypertrophy likely involves proteolysis of the surrounding extracellular matrix and subsequent neuronal movements may be adventitious. Receptor-mediated adhesion and extracellular matrix decomposition likely coexist.

7.6.3. Emergence of new neurite fascicles, microneuromas and rewiring

Computational molecular phenotyping and electron microscopic visualizations have revealed an abundance of new neurites generated by the neural retina in phase 3 of retinal degeneration. Single GABA, glycine or glutamate channels display fine steaks of immunoreactivity in the distal retina, sometimes appearing as a beaded curtain or waterfall of neurites. Ultrastructural visualization of these structures shows them to be fine processes gathered into fascicles of ≈100–200 processes embedded in Müller cell corridors (Fig. 21). The processes bear the signatures of GABAergic and glycinergic amacrine cells, ON center and OFF center bipolar cells, and ganglion cells. The ganglion cell processes tend to be the large elements and are neurofilament-rich. The GABAergic amacrine cells form the very finest neurites and are biased towards enriched microtubule content. Occasional myelinated processes are found in these fascicles and since oligodendrocytes are thought to be absent from the mature retina, these must represent (1) invading external neurites, (2) successful invasion of the retina by Schwann cells (Sullivan et al., 2003) or precursors, or (3) anomalous axonal wrapping by Müller cells themselves. On balance, the invasion of Schwann cells proposed by Sullivan et al. has the greatest merit.

Perhaps the most insidious feature of phase 3 remodeling is the de novo emergence of synaptic neuropil fragments: *microneuromas*. They are invisible to passive light microscopy, intercalate in otherwise nondescript areas between aggregates of neuronal somas, and are abundant (tens of thousands form in a mouse retina). The tendency of stressed photoreceptors to form new neurites and send them afar; the apparent ability of bipolar cells to transiently switch partners; the propensity of horizontal cells to send new processes with the inner plexiform layer—taken together with new fascicle and microneuroma formation—suggests that no neurons remain 'normal' in the face of deafferentation or photoreceptor stress. Microneuromas resemble the inner plexiform layer in that all types of conventional and ribbon synapses are formed (Fig. 19), including abundant amacrine→amacrine cell synapses, the most common synapses in the vertebrate retina. It is not possible to determine whether synapses in microneuromas represent "normal" circuitry without serial reconstruction to cells of origin. But the presence of synaptic ribbons within microneuroma means that bipolar cells must have sent new axons into the remnant inner nuclear layer or elaborated new dendrites that contain presynaptic ribbons. There is also evidence that microneuromas and the remnant inner plexiform layer might engage in direct bipolar cell→bipolar cell synapses (Fig. 19C and D), which could create re-entrant, functionally corrupting circuits. While many of the synapses in microneuromas appear immature, with very small ribbons or presynaptic vesicle accumulations, rodent retinas normally display some small ribbon and conventional synapses in the inner plexiform layer. The presence of ganglion cell neurites in ectopic fascicles complicates interpretations further. Are these merely dendrites or do they represent occasional axons, as implied by the occasional myelination of processes (Fig. 21)? Molecular phenotyping may answer this question, but it would not be surprising if ganglion cells remodeled to produce intraretinal axon collaterals, as have been described in the normal retinas of non-mammalian vertebrates. All ganglion cells are glutamatergic (Marc and Jones, 2002; Marc, 2003), and such axons would an additional pathway for re-entrant excitation.

How much rewiring is really going on? It is hard to know, outside of the evolution of microneuromas, whether any given synapse represents a normal circuit. We know that the characteristic coupling of certain glycinergic amacrine cells to ON center cone bipolar

cells persists in remodeling retinas because certain bipolar cells express a normal glycine+signature and amacrine-bipolar cell gap junctions can be observed in the inner plexiform layer. However, it does not take much corruption to subvert the operations of the micronetworks of individual filtering channels (see below). In addition, apparently abnormal connections can be detected, e.g. GABAergic synapses onto an ectopic glycinergic amacrine cell in the remnant ganglion cell layer (Fig. 20) and numerous unusual synapses made onto and from amacrine and bipolar cell somas in the remnant inner nuclear layer.

7.6.4. Endogenous retinal signaling in the blind

What transpires in the remnant neural retina of humans and animals deprived of a sensory retina? There is some evidence that circadian signaling and even pupillary responses can be preserved by non-traditional photopigment signaling elements that drive subcortical pathways (Freedman et al., 1999; Lucas et al., 2001a, b), but these systems do not serve vision in any way. It is not uncommon, however, for RP patients to report scintillating illusions known as photopsias (Weleber and Gregory-Evans, 2001). Heckenlively et al. (1988) describe photopsias as the second most common patient complaint (34.6%) in a sample of 500. We propose that photopsias are evidence of retinal rewiring into sporadic oscillatory circuits and that such corruption may begin as early as phase 2, even before all photoreceptors are lost. Many photopsias are probably generated in the retina, based on based on two circumstantial observations. First, photopsias eventually disappear, suggesting ganglion cell death. Second, Delbeke et al. (2001) describe transocular current induction of phosphenes in patient who had no light perception:

> Patient D had occasional spontaneous phosphenes before testing. These had not been considered as a major hindrance at the time of initial recruitment. Near-threshold electrical pulses, however, induced clearly delayed phosphenes in this person. Above threshold, the stimulation did trigger a short shower of spontaneous phosphenes, similar to fireworks, as described by the patient. This spontaneous outburst eventually lasted more than one-half hour and was compared by the patient to the phosphenes she had experienced at the very beginning of her visual loss, approximately 40 years earlier. After some rest, the spontaneous phosphenes returned to a lower level than before the test. They nevertheless further disturbed the search for the threshold of electrically generated perceptions (from: Delbeke J, Pins D, Michaux G, Wanet-Defalque M-C, Parrini S, Veraart C. 2001. Electrical stimulation of anterior visual pathways in retinitis pigmentosa. Invest Ophthalmol Vis Sci 42:291–297).

As it is difficult to similarly interrogate blind rodents (and there has previously been little impetus for doing so), we have explored the excitation histories of remnant retinal neurons in blind *rdcl* mice in collaboration with R.J. Lucas (Imperial College UK) using excitation mapping via organic cation permeation (Marc, 1999b). Intraocular injection of 1-amino-4-guanidobutane (AGB), yielding ≈5 mM, followed by a 45 min survival in light or dark yields maps of endogenous activity in both normal and *rdcl* mice. Even after complete loss of photoreceptors, many neurons in the *rdcl* mouse exhibit endogenous activation (Fig. 22). The activation strengths are mixed but many are more active than normal retinas, (not shown). Regardless of light history, the *rdcl* retina shows a pattern equivalent to bright photopic adaptation. Rod bipolar cells and their targets in the most proximal sublayer of the inner plexiform layer are completely inactive: they are fully hyperpolarized. But, in the absence of synaptic glutamate release

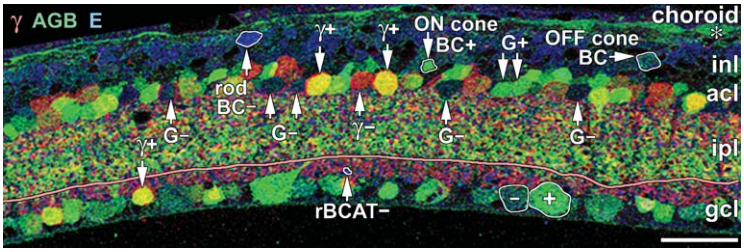


Fig. 22. Self-signaling in the blind *rdcl* mouse. γ -AGB-E→rgb mapping encodes neuronal excitation as increasing brightness of the green image channel (Marc, 1999a, b). In a collaboration with R.J. Lucas of Imperial College, we compared in vivo excitation mapping in normal and *rdcl* dual transgenic mice by microinjection of AGB calibrated to yield ≈5 mM in the vitreous, followed by a 45 min survival in dark and light regimes. Even after complete loss of photoreceptors, there is higher endogenous signaling in some neurons of the *rdcl* retina than in normal retina (not shown). Classification of neurons is based on a 7-dimensional signature set (e.g. Marc and Jones, 2002). In each cell cohort, there are active (+) and inactive (−) elements. Adjacent active and inactive ganglion cells are outlined. Rod bipolar cells, their axon terminals (rBCAT) and the entire rod-driven sublayer of the inner plexiform layer (the red zone below the pale red line) are uniformly inactive. Most cone bipolar cells are inactive, but a subset of ON cone bipolar cells is extremely depolarized, while some OFF cone bipolar cells are mildly activated. Inactive (γ−) GABAergic amacrine cells are red while active (γ+) GABAergic amacrine cells are yellow. Inactive glycinergic amacrine cells (G−) are nearly black, while active (G+) glycinergic amacrine cells are green, due to the absence of a glycine channel in this image. Scale: 20 μm.

from rods, the rod bipolar cells should be depolarized via loss of mGluR6-gated closure of cation channels. That they are impermeant suggests that rod bipolar cells receive constitutive glutamate signals from a new source or the cation channel and/or transduction pathway is deconstructed at dendritic and/or molecular levels (Strettoi and Pignatelli, 2000; Strettoi et al., 2002). The behavior of cone bipolar cells is more complex. Most are inactive, which is expected for OFF center cone bipolar cells, as absence of cone-derived glutamate will prevent opening of ionotropic glutamate receptors (iGluRs). Inactive ON center cone bipolar cells must, like rod bipolar cells, either be driven by a new source of glutamate or have deconstructed transduction pathways. But some bipolar cells are active, and ON center cone bipolar cells are strongly depolarized. It is difficult to see how they could have become so depolarized. Either they must be expressing mGluRs and cation channels without inhibition, leading to passive signaling, or they are expressing new anomalous iGluRs and receiving glutamatergic input. Some OFF center bipolar cells show weak but significant signals, very similar to those activated in normal bipolar cells with kainate receptor agonists. But where does the glutamate come from for such activation? Our interpretation of synaptic ultrastructure suggests that self-signaling arises, in part, from re-entrant bipolar cell excitation. The responses of amacrine cells are consistent with strong driving in the ON cone bipolar cell pathway, moderate driving in the OFF cone bipolar cell pathway and no driving in the rod pathway. These images represent integrated activity over a long epoch and do not imply any coherence in signaling. These degenerating retinas are singing to themselves of light, in the dark.

8. Remodeling of circuitry

8.1. Basic mammalian pathways

Even in rod-rich mammalians, cone circuitry dominates (Strettoi et al., 1994). Of the ≈55–60 classes of retinal elements that constitute a generalized mammalian retina (MacNeil et al., 1999a, b; Masland, 2001a, b; Marc and Jones, 2002; Rockhill et al., 2002), all but five are predominantly or exclusively driven by cones. The mammalian rod pathway is composed of but two purely rod-driven neurons (rod bipolar cells and horizontal cell axon terminals functioning as autonomous rod 'horizontal cells') and three rod dominated amacrine cells (Dacheux and Raviola, 1986; Strettoi et al., 1992, 1994; Li et al., 2002). If the maintenance of circuitry depends on intact photoreceptor signaling, major remodeling effects will be delayed until cone populations are substantially impaired. Cones provide the sole synaptic input to ≈9 classes of bipolar cells and the somas of horizontal cells. Thus the observations of early rod bipolar cell dendrite and rod axon terminal truncations (Strettoi and Pignatelli, 2000; Strettoi et al., 2002, 2003) but essential preservation of the rest of neural circuitry in the *rd1* mouse reflects the numerical dominance of cone driven neurons in distal retina. Rod bipolar cells drive a set of three rod-dominated amacrine cells, including the glycinergic AII amacrine cell and GABAergic AI amacrine cells (subtypes S1 and S2). However, AII amacrine cells are photopically functional and clearly driven by cone bipolar cells (Xin and Bloomfield, 1999), receiving direct OFF center cone bipolar cell input and are coupled to ON center cone bipolar cells (Kolb and Famiglietti, 1975). The coupling might be attenuated in photopic states (Mills and Massey, 1995), though other data suggest that changes are small (Bloomfield et al., 1997). Neurite re-patterning in A_{II} amacrine cells is expected to be minor during phase 1 of rod initiated retinal degenerations. Though rod bipolar cells are thought to be the sole excitations for both S1 and S2 amacrine cells, these cells also display inputs from other amacrine cells (Nelson and Kolb, 1985; Sandell et al., 1989). The remaining ≈25+ classes of amacrine cells (MacNeil and Masland, 1998; MacNeil et al., 1999a, b) and ≈12–14 classes of ganglion cells (Marc and Jones, 2002; Rockhill et al., 2002) are driven directly by cone bipolar cells (Strettoi et al., 1994). The disruption of cone function triggers the bulk of retinal remodeling.

Nocturnal rodents have cone densities similar to or higher than those of most of the primate non-foveal retina. The basic cone circuits of rodents accurately mirror both human circuitry and topology, though the scaling of the rodent eye prevents behavioral comparisons. Though we do not understand the evolutionary basis of bipolar cell diversity, comprehensive analyses of bipolar cell networks in many vertebrates (Strettoi et al., 1994; Marc and Liu, 2000; Pang et al., 2002) have shown these networks to form a stereotyped circuitry (Fig. 23), where signals *encoded* as extracellular amino acid concentrations are *decoded* by specific patterns of ionotropic receptors and GPCRs. Because remodeling disassembles and rearranges the remnant retina on molecular and cellular scales, it is essential that we track the molecular devices that enable the retina to function as an image processor. The molecular mechanisms of retinal synaptic signal encoding and decoding are known in some detail (reviewed by Marc, 2003). Synaptic glutamate release encodes the entire fast, high gain, narrow field vertical channel from photoreceptors to cortex. Photoreceptor and bipolar cell ribbon synapses mediate all known retinal glutamatergic excitation. Synaptic GABA and glycine release respectively encode fast, low gain, wide and narrow field lateral transmission from amacrine cells. GABA is the likely horizontal cell transmitter, but the physiology of

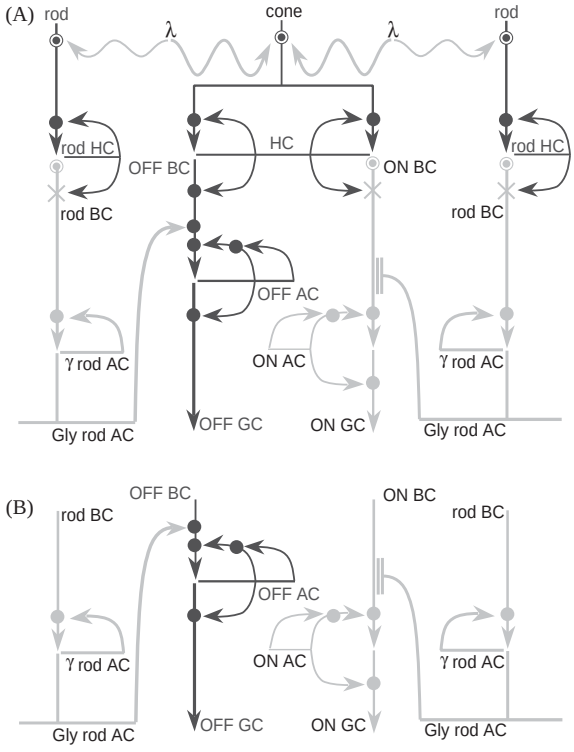


Fig. 23. Circuitry of normal and deafferented mammalian retinas. (A) Normal. The essential cone-driven pathway architecture is common to all vertebrates. The rod-driven architecture is uniquely mammalian. The rod bipolar cell drives a glycinergic rod amacrine cell that acts as a system buffer to distribute sign conserving signals to ON center cone bipolar cells via heterocellular coupling and sign inverting signals to OFF center cone bipolar cells via glycinergic synaptic transmission. The element labeled as a rod horizontal cell is actually the axon terminal field of a cone-driven horizontal cell. However, as the axon does not conduct signals between the soma and terminal, the axon terminal functions autonomously. (B) Deafferentation leaves the neural retina without glutamatergic drive. This is consistent with the anatomical evidence for retraction of dendrites. Symbols: dark and pale symbols indicate hyperpolarizing and depolarizing neurons, respectively; arrowheads are presynaptic elements; postsynaptic transfer processes are (|) high gain sign conserving (classical ionotropic AMPA, KA and NMDA receptor systems), (×) low gain sign conserving (associated with ON center bipolar cell dendritic surrounds), (⊙) high gain sign inverting (associated with ON center bipolar cell dendritic centers), (●) low gain sign inverting, and (‖) low gain sign-conserving paths mediated by gap junctions.

horizontal cell lateral signaling remains to be solved. All vertebrate retinas also display high gain, narrow field cholinergic amacrine cell lateral transmission.

This spatial and temporal array of signals is decoded by corresponding receptor classes and subclasses expressed subsets of neurons. The decoders of the vertical channels are fast, high gain, sign conserving ionotropic (iGluRs) for the OFF channel and sign inverting GCPRs for the ON channel. OFF center bipolar cells decode glutamate signals with KA receptors and/or AMPA receptors. Horizontal cells and all amacrine and ganglion cells use AMPA receptors for initial decoding; subsets of amacrine and ganglion cells also express excitation-dependent NMDA receptors. The decoders of the lateral channels are fast, low gain, sign inverting GABA and glycine receptors, with variants of each expressed in almost every neuronal type. These two sets of common decoders (the sign inverting and sign conserving receptors) enable the construction of nearly every fundamental type of biological circuit.

Both photoreceptors and ON center bipolar cells express GPCRs with sign inverting transduction sequences. Opsins and mGluR6 glutamate receptors encode signal strength increases (photon density, glutamate concentration) with membrane hyperpolarization, in both cases gated by GPCR-gated decreases in cation channel permeability, but via different transduction schemes. Thus light increments are encoded as decrements in photoreceptor synaptic glutamate levels, and decoded as depolarizations of ON center bipolar cells. This single transformation constructs ON center channels as nearly mirror images of OFF center channels. There is a further specialization: the insertion of an ionic inverter—a Cl importer—in ON center bipolar cell dendrites to locally elevate intracellular Cl concentrations (Vardi et al., 2000). This ensures that direct horizontal cell inputs to ON center bipolar cells, mediated by the same kinds of $GABA_C$ receptors in all bipolar cells apparently, is always of opposite polarity to cone synaptic drive.

All spatial image processing channels, whether build from chips or neurons, are chains of amplification regulated by local sign inverting feedback and feedforward (Marc and Liu, 2000; Pang et al., 2002). The mammalian retina contains two parallel structural channels that implement all the encoders and decoders just described (Fig. 22). At every stage of vertical channel synaptic transmission, lateral elements provide essential spatiotemporal gain control: horizontal cells in the outer plexiform layer and amacrine cells in the inner plexiform layer. Cone horizontal cells provide sign inverting feedback to cones, sign inverting feedforward to OFF center bipolar cells, and (through the ionic inverter described above) sign conserving feedforward to ON center bipolar cells. However, cone-driven ON and OFF channels are completely stereotyped beyond this stage and sign inverting GABAergic amacrine cell control dominates lateral feedback, nested feedback and feedforward processing in the inner plexiform layer.

Finally, there are dopaminergic and peptidergic amacrine cells to contend with. We have not included such amacrine cells in our analyses or models, but that does not mean their roles are trivial. The consequences of neuronal cell death or rewiring in these populations is difficult to predict, but it is quite likely that normal visual circuitry cannot function without them. Dopaminergic amacrine cells are particularly critical in regulating network adaptation in the retina, as they control

photoreceptor homeostasis, horizontal cell coupling, AMPA receptor sensitivity, amacrine cell coupling and ganglion cell response kinetics (Witkovsky and Dearry, 1991; Vaney and Weiler, 2000; Vaquero et al., 2001; Marc, 2003). Thus fate of these cells, as yet unknown, will be a key target of future research in retinal degenerations.

8.2. Corrupted networks

Connectivity may begin to alter before photoreceptor death, with the emergence of rod and perhaps cone neurites entering the inner plexiform layer, but there is no evidence they are functional. But sprouting rods may deprive bipolar cells of inputs. In the *rd1* mouse, where phase 1 rod and phase 2 cone death clearly overlap, any likely targets for rod bipolar cells disappear early in life and the retraction of dendrites may reflect a global loss of synaptic activation. Conversely, phase 2 is prolonged and cone survival is protracted in the P347L transgenic pig model (Petters et al., 1997; Peng et al., 2000). Slow cone degeneration may provide contact sites for otherwise denervated rod bipolar cells. But eventually, these different events likely converge on a common phase 3.

Regardless of the changes displayed by photoreceptors, bipolar cells or horizontal cells during phase 1 and 2, phase 3 begins with (i) dendritic truncation of bipolar cells; (ii) terminal truncation of horizontal cells; (iii) the emergence of anomalous axon-like processes from apparently all horizontal cells. The loss of glutamatergic inputs to bipolar and horizontal cells suggests fundamental changes in their resting ionic permeabilities and membrane potentials. Both OFF center bipolar cells and horizontal cells should become constitutively hyperpolarized and their intracellular calcium levels should drop accordingly. Whether they display functional iGluRs is largely unknown, but it will matter not as there is no photoreceptor glutamate to activate them. Conversely, the retraction of ON center bipolar cell dendrites also involves the down-regulation of mGluR6 expression (Strettoi et al., 2002, 2003; Varela et al., in press). This is a critical observation and is consistent with physiological observations. Thus both the ON center and OFF bipolar cells should be hyperpolarized and quiescent during phase 2 and 3. However, in vivo excitation mapping (Fig. 22) clearly shows massive endogenous signaling in the *rdcl* retina after loss of photoreceptors. This suggests that endogenous glutamatergic excitation is available. We propose that this could arise from new re-entrant or cross-channel bipolar cell inputs or intraretinal ganglion cell synapses.

Why might cells engage in apparently unregulated, anomalous neurite extension, switching of targets by dendrites, and the evolution of self-signaling networks? Some clues are offered by consideration of other systems. In CNS deafferentation, survivor neurons appear to be those that develop compensatory connections (Fiala et al., 2002) or prevent expression of cell death programs (Mostafapour et al., 2000). It is not clear that such new pathways process information properly. Neurons in culture are highly promiscuous, often engaging in improper, even fictive synapses (Rao et al., 2000), and CNS damage is known to provoke dendrite invasion. We propose that neurons are in search of an essential basal level of Ca^{2+} influx; that absence of normal Ca^{2+} fluxes, due to depressed or absent glutamatergic synaptic drive, triggers growth to seek new synaptic partners (e.g. Fiala et al., 2002).

If bipolar cells sought out new targets to drive or new sources of input, what are their options? Our initial ultrastructural data suggest that some bipolar cells target other bipolar cells. If recovery of excitation is an active goal of neurite extension by any remnant neurons, then bipolar cells are the most likely source. We now systematically consider how retinal networks might become rewired and the consequences of these new pathways for the function of the remnant retina. Cone and rod degeneration leaves remnant circuits without high-gain glutamatergic drive (Fig. 24) and, if new synapses target remnant ON and OFF channels, they will necessarily form new architectures. If we consider only the remnant arrays of cone bipolar cells and amacrine cells, excluding the complication of horizontal cells, 10 single unique (Table 4) and thousands of combinatorial errors can occur. Far more are possible if we include all other neuron types and all subclasses of bipolar cells (Euler et al., 1996; Haverkamp et al., 2003). Only if remodeling perfectly recapitulates normal circuitry can signaling errors be avoided. The movement of neurons and evolution of new processes already means that electromorphologies may be corrupted. Remodeling that restores glutamatergic input to bipolar cells is explicitly corruptive, whether as re-entrant (ON→ON and OFF→OFF) or cross-channel (ON→OFF and OFF→ON) signaling. Re-entrant amacrine cell circuits are already part of normal nested feedback processes and any additional loops will likely be inconsequential (Marc and Liu, 2000). We modeled all major types of errors as linear systems, using complete network architectures as described in Marc and Liu (2000) and determined that all single connective errors corrupt encoding to variable degrees (Table 3, Fig. 24B). To mimic recovery of photoreceptor input, we simply drove all bipolar cells with a theoretical pulse of glutamate. Re-entrant and cross-channel bipolar cell signals seriously corrupt outputs in characteristic ways. OFF→OFF bipolar cell loops create positive feedback, creating persistent step responses to any input and preventing proper spatiotemporal encoding. ON→ON bipolar cell loops are self-attenuating due to sign-inverting mGluR6 transduction. This raises an interesting problem, since evidence from

phase 1 remodeling suggests that that cone-driven ON center bipolar cells appear to lose mGluR6 immunoreactivity. Excitation mapping suggests that some ON center bipolar cells somehow restore their cation channel permeability, which need not involve mGluR6. In any case, functional ON→OFF center bipolar cell crossings shorten OFF center bipolar cell responses and make them briefly oscillatory. OFF→ON bipolar cell crossings greatly enhance and slow ON center bipolar cell responses. But these are merely single error effects, read out from OFF or ON center bipolar cell channels. Multiple errors are even more likely and most of these trigger resonant responses that preclude visual processing. If all bipolar cells engage in crossing inputs, outputs resonate without damping once activated, and if all bipolar and amacrine cells cross circuits, oscillations damp slowly, on a scale of many seconds (Fig. 24B). There are many possible variations on these networks, but single and complete crossing errors bracket the outcomes. Stable visual processing can only occur if all novel synapses exactly recapitulate normal wiring, which is clearly impossible. Most rewiring assemblies will produce circuits that display oscillatory behavior when activated, largely but not exclusively due to re-entrant iGluR-mediated sign conserving signaling, perhaps similar to that observe in ostensibly random assemblies of cultured retinal neurons (Harris et al., 2002). As remodeled networks derive from complex mature rather than simple immature arrays, which can also produce periodic activity (Butts et al., 1999), the range of errors is quite large. The similarity of the long-term oscillatory behaviors of circuits with mixed connections and persistent oscillatory phosphenes (Delbeke et al., 2001) is obvious. Finally, excitatory cholinergic amacrine cells may be central to self-signaling in retinal remodeling.

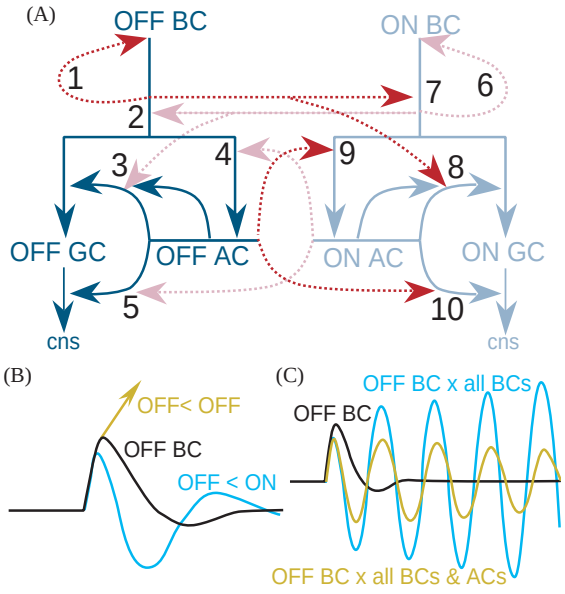


Fig. 24. Modeling of circuit corruption via cross-talk and re-entrant excitation in remnant cone bipolar cell circuits. (A) Deafferented ON channels are formed by ON bipolar, ON amacrine and ON ganglion cell networks shown as solid pale blue lines; deafferented OFF channels are formed by OFF bipolar, OFF amacrine and OFF ganglion cell networks shown as dark blue solid lines. Ten single types of wiring errors (Table 3) are shown as dotted lines; pale red lines indicate errors arising from ON channel cells; dark red lines arise from OFF channel cells. All bipolar cells are glutamatergic; all amacrine cells are GABAergic. (B) Modeled linear impulse responses of OFF bipolar cells to brief 'glutamate' excitation pulses (10 ms, dot) applied to all bipolar cells in normal circuits (OFF BC, black), single re-entrant bipolar cell circuits (OFF < OFF, gold, error 1), and single cross-channel bipolar cell circuits (OFF < ON, cyan, error 2). Vertical axis is relative voltage; trace duration 0.5 s. (c) Modeled impulse responses in normal circuits (OFF BC, black), complete bipolar cell cross-channel circuits (OFF BC × all BCs, cyan, errors 2+3+7+8), and complete neuronal cross-channel circuits (OFF BC × all ACs and BCs, gold, errors 2+3+4+5+7+8+9+10). Vertical axis is relative voltage; trace duration 1 s.

9. Implications of remodeling for rescue strategies

The clinical relevance of remodeling in retinal blinding diseases is substantial. The fundamental strategies of subretinal and epiretinal prosthetic implants, photoreceptor transplants, stem cell therapies,

Table 3
Single types of wiring errors in bipolar-amacrine cell circuits

ID	Circuit	Definition	Effect on bipolar cell response
1	OFF BC > OFF BC	Re-entrant KAr loop	OFF BC step-function
2	ON BC > OFF BC	Cross-channel KAr signal	OFF BC transient oscillation
3	ON BC > OFF AC	Cross-channel AMPAr signal	OFF BC slowed
4	ON AC > OFF BC	Cross-channel GABAr signal	OFF BC slowed
5	ON AC > OFF AC	Cross-channel GABAr signal	OFF BC undershoot slightly larger
6	ON BC > ON BC	Re-entrant mGluR6 loop	ON BC attenuated, transient oscillation
7	OFF BC > ON BC	Cross-channel mGluR6 signal	ON BC larger and slowed
8	OFF BC > ON AC	Cross-channel AMPAr signal	ON BC slowed
9	OFF AC > ON BC	Cross-channel GABAr signal	ON BC slowed
10	OFF AC > ON AC	Cross-channel GABAr signal	ON BC undershoot slightly larger

Abbreviations: KAr, kainate receptor; AMPAr, AMPA receptor; mGluR6r, mGluR6 receptor; GABAr, GABA receptor.

gene rescue therapies, survival factor treatments and combinations thereof are based upon the hope that the neural retina remains viable after extensive photoreceptor degeneration; that the neural retina should act as a platform to accept donor cells and quantitatively respond to transplanted photoreceptors or spatially patterned currents injected by electronic implants. In reviewing the literature regarding remodeling one cannot avoid encountering the conflict between dispassionate evaluation and passionate hopes for a specific outcome.

Our discussions of remodeling have focused more on the biology of the phenomenon rather than its clinical significance. This is partly because the questions are explicitly biological and not at all clinical. Remodeling is the process of changing a retina into something else, another kind of neural system. We also do not refer to remodeling as plasticity per se. Plasticity formally involves transformations of neural cells and networks as part of their normal repertoires and is clearly reversible in many of its manifestations. Remodeling may invoke normal plastic mechanisms, or represent the removal of inhibitory mechanisms that maintain structural homeostasis. But, in the aggregate, remodeling is a *negative* process leading to cell death, disruption of spatial cell patterning, deregulation of structural stability, de novo synaptic repatterning, and evolution of circuits formally inimical to information processing. As such, its clinical implications are profound.

9.1. Subretinal bionic implants

The strategy of replacing lost sensory drive via an epiretinal or subretinal bionic device is under serious consideration and good designs have been proposed and tested in model mammalian systems or pre-tested in humans (see reviews by Zrenner et al., 1998; Margalit et al., 2002; Zrenner, 2002). The existence of phase 3 remodeling is a major challenge to all of those strategies. In particular, the evolution of the glial seal with its high impedance intermediate junctions, and the complete occlusion of the subretinal space means that there is no place to insert a subretinal device once most cones have been lost. The spatial resolution of subretinal devices is critically dependent on an intimate positioning of current sources relative to the surviving bipolar cell array and the deeply invested glial seal prevents such positioning. Placement distal to the seal will likely induce massive choroidal trauma and bleeding, and may shunt contacts. Subretinal implants have variable outcomes even in normal retinas (Hesse et al., 2000), and most claims of normal morphology are not accompanied by supporting data.

The true relationship between the density of surviving deconstructed cones and visual function is not known. It is possible that cones lacking the ability to drive visual perception still maintain synaptic contacts with remnant bipolar and horizontal cells, offering a window of opportunity between loss of functional vision and entombment by the seal. But subretinal devices will have to be positioned prior to formation of the seal, which may require determination that the vision prospectively allowed by the implant is worth the likely loss of vision incurred by early intervention. There is no evidence that implants will retard continued remodeling, though they might. If an implant can provide patterned excitation, neurons might be deterred from making new contacts. But the continued loss of retinal neurons might prove an insuperable barrier. Part of the ongoing neuronal death in remodeling could arise from a persistent deficiency in oxygen and nutrient supply (Stone et al., 1999) via a normal choroid→RPE→Müller cell transport pathway, especially in cases where RPE cells are lost. While retinas survive for along time under the seal, they still lose neurons. Previous histologic evidences of neuronal status beneath long-term subretinal implants in normal mammalian retinas are due for re-evaluation. At the least, the data show increases in glial GFAP expression (Pardue et al., 2001), and since no analysis of neurite remodeling or class-specific loss has been considered, it is difficult to expect that subretinal implants will form supportive environments for retinas that are already in the process of remodeling.

Subretinal implants are particularly dependent on the maintenance of intact, non-corrupting retinal circuitry. Progressive neuronal loss, spatial corruption by cell migration and the emergence of new neurites and microneuromas, as well as cryptic synapse formation within the inner nuclear and inner plexiform layers, offers a significant challenge. Will re-institution of external drive enable re-patterning of retinal circuits? There seems no reason that it should and many reasons why it might not. The most obvious barrier is that retinal neurons don't know anything about vision. Any source of excitation likely suffices for survival and the spatial distribution of excitation is probably irrelevant.

9.2. Epiretinal bionic implants

Epiretinal implants (Margalit et al., 2002; Zrenner, 2002), championed by De Juan, Humayun, Greenbaum, and others, successfully bypass the problem of the glial seal and depend largely on the survival and proper spatiotopy of the remnant ganglion cell layer. To the extent that ganglion cells survive, the key to successful epiretinal implants resides in the ability of patterned extraretinal current sources to directly drive patches of ganglion cells. However, theoretical considerations cannot exclude the possibility that human phosphene percepts based on acute epiretinal stimulation arise from activation of intraretinal elements such as bipolar cells

(Greenberg et al., 1999). The fact that some RP patients do in fact lack current-induced phosphenes or express unstable phosphene patterns (Delbeke et al., 2001) demonstrates that ganglion cell loss can be severe and that anomalous rewiring can induce percepts that are likely incompatible with vision. Conversely, even after long-term retinal degenerations, epiretinal stimulation evoked phosphene percepts in patients with and without light perception (Humayun et al., 1996), shows long-term survival of ganglion cells. Thus there is extreme variability in ganglion cell survival and this likely depends on the form of retinal degeneration. Various CORDs and certain recessive rod-initiated disorders may remodel more aggressively than some forms of adRP, where cone survival is protracted. Improved spatial resolution of epiretinal implants may face biologic limits if retinas rewire anomalously. It is likely impossible to isolate ganglion cells from retinal circuitry via surface stimulation for the very simple reason that many ganglion cells are functionally coupled to amacrine cells via gap junctions (Xin and Bloomfield, 1997; Marc and Jones, 2002; Vaney, 2002) and any spike elicited from axons may invade retinal networks. The final challenges to epiretinal stimuli are migrations of amacrine and bipolar cells into the ganglion cell layer (Jones et al., 2003a) and the eventual formations of preretinal membranes (Milam et al., 1999; Weleber and Gregory-Evans, 2001).

9.3. *Photoreceptor, retinal sheet and neuroprogenitor cell transplants*

Advances in transplantation (Aramant and Seiler, 2002) and neuroprogenitor cell technologies (Young et al., 2000) proffer hope of restoring visual function to damaged retinas via transplantation or recruitment and transcriptional control of endogenous stem cells, or even use of transformed stem cells. Like bionic implants, cell implants or transplants face a race with time as placement of exogenous cells or cell sheets must occur before seal formation. Most research on transplants has been done in phase 1 or 2 and the extent of glial seals is rarely assessed. However, attempted transplants into the presumed (but now ablated) subretinal space in phase 3 retinal degenerations appear uniformly unsuccessful (e.g. Radner et al., 2001). As cone vision may persist in some retinal degenerations until seal formation, this narrows the window for treatment. Some transplants of embryonic retinal sheets display good survival and apparent fusion of transplant inner plexiform layer (which tends to lose ganglion cells) and the host remnant inner nuclear layer. However, analyses of morphology, circuitry and cell number have not exploited strong visualization methods and it is impossible to determine whether transplants and hosts connect at all, or whether by normal or aberrant paths.

In very exciting work, Young et al. (2000) demonstrated the ability of hippocampal progenitor cells to invade the neural retina of RCS rats at ≈pnd 70, with less efficacy at pnd 127. The latter effect may be attributable to an emerging glial seal. Cells moved into the retina and assumed polyform shapes similar to neurons and extended neurites. In the context of active remodeling and the propensity of remnant retinal neurons to extend new process, this is perhaps not surprising. The key questions that emerge from these and similar studies using stem or progenitor cell lines involve the instruction of alien cells. Who shall do it and how? Some recent findings of stem cells assuming proper phenotypes in complex tissues have now been shown to arise from inadvertent cell fusion (e.g. Terada et al., 2002). Given the pervasiveness of remodeling by degenerating retinas, it has become clear that the analysis of transplants and alien cell invasions will require far more than simple light and electron microscopy.

9.4. *Abandoning transplantation 'integration' for transplantation benchmarks*

The root of many ambiguities in transplantation studies, not only in retina and CNS, but in non-neural tissues as well, is the non-specific end point of *integration*. As used in most retinal research, this end point lacks precision and ranges from demonstrations of alien cell presence, apposition, co-mingling of processes, to presumed synapse formation. We propose that the word be abandoned and left to its proper mathematical and Sherringtonian meanings.

Dissections of the retinal circuits that produce the multiple filtered versions of the visual world teach us that partial views of any pathway taken out of context are ambiguous. Though we lack details of any given retinal circuit, the designs of the major modules are clear (Masland, 2001a), as are the formal principles for generating spatial and temporal filters from the toolkit presented by the retina (Rekeczky et al., 2001; Roska and Werblin, 2001). As remodeling of the neural retina begins cryptically in phase 1–2 and only becomes grossly evident in phase 3, analysis of transplantation data requires new standards and we propose *benchmarks* of increasing stringency. These benchmarks address the need to discriminate promiscuous from selective contacts, fictive from active synapses, corrupt from conformal circuits, and adequate from deficient systems performance. They are formulated with respect to laminar, synaptic, biophysical, and topologic rules that govern circuit architecture and the systems transfer functions that constitute visual experience. More importantly, the benchmarks locate critical points where deployment of ectopic cell systems may fail. Technologies for assessing benchmarks may not exist for all cases, but failure at any benchmark can corrupt vision.

Table 4
Transplantation benchmarks

	Benchmark	Classes and *subclasses*			
1	Occupancy	External	Clustered	Diffuse	Laminar
2	Shape	Mismatched	Adventitious	Functional	Matched
3	Molecular phenotype	Mismatched *Coherent* *Mixed*	Matched *Coherent* *Mixed*		
4	Contacts	Nonselective *Fictive* *Active*	Antiselective *Fictive* *Active*	Selective *Fictive* *Active*	
5	Circuitry	Corrupt	Imperfect	Conformal	Novel
6	Patterning	Disordered	Ordered	Conformal	
7	Channels	Corrupt	Imperfect	Conformal	
8	Systems	Threshold sensitivity *Scotopic* *Photopic*	Contrast sensitivity *Spatial* *Temporal*	Spectral sensitivity	Oculomotor performance

Eight benchmarks characterize the extent to which alien cell types or arrays of types reconstitute new or merge with extant circuitries in the vertebrate retina (Table 4): (1) occupancy, (2) shape, (3) molecular phenotypes, (4) contacts, (5) circuitry, (6) topology, (7) channels, and (8) systems metrics.

1. Occupancy. Occupancy refers to selective positioning of cells or tissues within the retina. Cells or tissues remaining outside are *external*; if they invade but do not spread, they are *clustered*; if they migrate to all layers, their occupancy would be characterized as *diffuse*. The extent to which the cells become positioned in increasingly precise zones (inner nuclear layer→proximal inner nuclear layer→amacrine cell layer) represents *laminar* specificity. Many standard tools quantitatively track laminar precision.

2. Shape. No feature classifies neurons with the rigor of shape (MacNeil et al., 1999b; Rockhill et al., 2002) . If cells from non-retinal sources express their own unique mature morphologies (e.g. hippocampal pyramidal cells) shapes then they are *mismatched*. Cells of any provenance may assume *adventitious* morphologies permitted by the excavation of space via cell death, migration or remodeling of the extracellular matrix. A neuron might assume a morphology similar to a cortical stellate cell, yet quite adequately implement proper circuit element and a formally mismatched cell would then possess an obvious *functional* shape. Finally, new cells might assume morphologies of resident neurons, achieving *conformal* shape. Defining shape requires sophisticated tools (dye injection and ballistic dye particle labeling) and the ability to unambiguously track ectopic cells.

3. Molecular phenotypes. Molecular phenotypes are part of the defining phenotype of a retinal cell and can be used in shape- or pattern-independent analyses. Entire populations can be characterized in terms of the mixtures of distinctive macromolecules or small molecules. Emergent phenotypes of alien cells can be *matched* (e.g. expressing tyrosine hydroxylase like dopaminergic amacrine cells) or *mismatched* (expressing molecular mixtures not found in retina), and the phenotype can be *coherent* (all cells expressing the same matched/mismatched signature) or *mixed*. Strategies for acquiring macromolecular and micromolecular phenotypes are established (Marc et al., 1995; Kalloniatis et al., 1996; Haverkamp and Wassle, 2000; Marc and Cameron, 2002; Haverkamp et al., 2003).

4. Contacts. The functional display of contacts between pre- and postsynaptic elements can be independent of vesicle release and receptor expression systems. Contacts may be *non-selective* and based on the probability of encountering or inducing expression of appropriate adhesion proteins. Non-selective contacts can be *fictive*, i.e. ineffective, due to *inactive* presynaptic or postsynaptic components (lack of release mechanisms or receptor decoding mechanism) or *mismatched* components (e.g. Rao et al., 2000). Non-selective contacts may also result in *active* synapses, whose efficacies are dependent on quantitative attributes of synaptic transmission. Ineffective release due to small vesicle accumulations or low expression of Ca^{2+} channels, and ineffective decoding due to a host of mechanisms ranging from receptor properties to lack of postsynaptic voltage gated channels can lead to active but subliminal

signaling. If contacts avoid developmentally specified or expected targets (e.g. rod neurites in phase 1 and 2 remodeling), they are *antiselective* and may result in fictive or active outcomes. *Selective* contacts can be fictive if synapses are improperly assembled or the participating cells change receptor expression patterns. Mapping these activities will be particularly difficult and will demand extremely rigorous receptor localization methods (Brandstatter et al., 1998; Wässle et al., 1998; Koulen, 1999), tools to map activity at the single cell and ultrastructural levels (Marc, 1999a, b), and multiple label methods that accurately identify ectopic, host, presynaptic and postsynaptic elements (Rao et al., 2000).

5. Circuitry. The intercalation of a new cell in a pathway (whether mediated by neurites from invading cells or external sheets) can have a number of consequences. Non-selective or antiselective contacts can *corrupt* circuits so that outputs do not reflect inputs, yielding resonant, aperiodic, saturating or attenuated responses. Such responses might be induced by a glutamatergic element being both driven by and feeding back onto another glutamatergic cell. Such circuits, driven by transplanted cells or bionic implants, may evoke light responses and even percepts, but might not result in vision. Other elements (e.g. GABAergic cells) can induce strong delayed oscillations in otherwise normal circuits whose synaptic weights must be precisely balanced to remain stable (Marc and Liu, 2000). Such *imperfect* pathways may produce normal polarities, but with altered transfer characteristics, such as poor frequency response or saturation. *Conformal* circuits may mimic normal signaling. Finally, unconventional *novel* circuits, such as direct photoreceptor driving of ganglion cells, with amacrine cell-mediated feedback acting as a stabilizing mechanism, may be able to support adequate vision.

6. Patterning. Vision is feature detection implemented with patterned neurons (Vaney, 1990; Cook and Chalupa, 2000; Reese and Galli-Resta, 2002; Vaney, 2002). The movement of ectopic cells into the retina may result in either clumped or sparse arrays that are *disordered*. *Ordered* patterns may arise at densities different than expected for the targeted phenotype, and may or may not serve vision. Ultimately, an ectopic population may assume *conformal* patterning, indistinguishable from target population to be replaced or augmented. For most cells this will be essential. For some, such as dopaminergic amacrine cells that regulate a wide array of states, disordered seeding may suffice.

7. Channels. Even though individual circuit assemblies may seem stable, vision is dependent upon the formation of appropriate numbers of many different channels, perhaps 10–15 filter functions sent to the CNS, from which vision is constructed and eye movements controlled (Roska and Werblin, 2001). This diversity, based on the 55–60 neuronal classes that make up a normal mammalian retina, requires the appropriate weights of ON and OFF channels, sustained and transient channels, hue weighted channels, fast and slow moving channels, wide field and narrow field channels. We know from CNS plasticity that corruption of channel function in development (e.g. spatial blurring) leads to corrupted adult vision. Channel arrays can cover the spectrum from perfectly *corrupt*, to acceptable but *imperfect*, to *conformal*. Assessments of such data will require use of electrode arrays and CNS optical imaging.

8. Systems. Systems performances, whether garnered by involuntary measures (fMRI) or rigorous psychophysics require direct comparisons with expected normal performances, preferably guided by bias-reducing methods (Green and Swets, 1974). Our benchmarks do not specify performance levels, but rather performance areas. This includes both absolute and increment *threshold sensitivities* for scotopic and standardized photopic regimes, spatiotemporal *contrast sensitivities*, *spectral sensitivities* (color vision may not be essential, but life without blue cones may be difficult), and perhaps most critical of all, oculomotor functions. Restoring β ganglion cell drive to cortex may be an exercise in vertigo without proper control of pretectal and collicular assemblies to regulate eye position.

10. The future: retinal plasticity and remodeling

The scope of true physiological plasticity in the adult mammalian retina is unknown, but given our knowledge of the extent of network adaptation and structural revision displayed by non-mammalian retinas, extensive functional plasticity in terms of synaptic strengths or even structural changes may be expected. Further, the processes invoked in early development of retinal lamination (Johnson et al., 1999), spatial patterning (Reese and Galli-Resta, 2002) and functional activity (Tian and Copenhagen, 2001) clearly overlap into the domain of environmental influence. Is self-signaling in retinal remodeling at all related to developmental self-signaling (Bansal et al., 2000)?

The processes that control neurite evolution and extension during development may or may not be the same as those invoked by remodeling. But it seems that every adult neuron can form new neurites and will do so given the opportunity. What are the primary signals that direct growth? Can transduction pathways that control dendritic growth be isolated from general GPCR processes? There is evidence that overexpression of small rho-related GTPases or expression of dominant negative mutant versions can bias the forms of neuronal dendritic arbors in mouse cortical development (Threadgill et al., 1997). Further, some of the growth can be regulated by NMDA receptor activation in *Xenopus*

(Li et al., 2000), suggesting that self-signaling and growth can be coordinately related. These processes, as well as homophilic *trans*-binding interactions that permit neurite fasciculation (Freigang et al., 2000) are almost certainly activated in remodeling. But they appear poorly controlled. The stabilization of synapses via cadherin (Garner et al., 2002) or protocadherin (Wu and Maniatis, 2000; Tasic et al., 2002) homophilic binding in normal development may not be the same as the processes used in remodeling, but are obvious starting points. The apparently purposeless migration of retinal neurons suggests changes in integrin expression by remodeling neurons and/or Müller cells.

Can remodeling be prevented? Phase 3 remodeling in rodent retinal degenerations does not begin until over 100 postnatal days in the fastest models and may take up to 500–600 days in animal models of adRP using dominant negative protein expression, often at unknown levels. A cohort of test subjects must be prepared to explore attenuation of remodeling, arguably based on fast models such as the TG9N mouse or LD rat. The LD rat offers the benefit of decoupling remodeling from development. We offer three non-exclusive hypotheses for the nature and scope of remodeling by survivor neurons. 1. Diminished glutamatergic synaptic drive leads to reduced mean intracellular Ca^{2+} levels and triggers dendritic growth to seek new synaptic partners (e.g. Fiala et al., 2002). If loss of excitation triggers neurite growth, it may be possible to prevent growth by restoring excitation through physical (e.g. transocular current stimulation) or pharmacologic means (Watanabe and Fukuda, 2002). 2. Retrograde transsynaptic neurotrophin signaling may play a critical role in neuronal survival (reviewed in Quigley, 1999; Yip and So, 2000). Though we tend to think of retrograde neurotrophin signaling as attributes of long-range projection neurons, loss of rods may deprive horizontal cells of a survival factor, absence of which may activate axon growth, leading to extensive sprouting. The use of survival factors as protectants in phases 1 and 2 (Faktorovich et al., 1990) may deserve re-examination during phase 3 remodeling. 3. Modification of cell adhesion mechanisms promotes neuron migration and neurite extension, as in retinal detachment (Lewis et al., 2002). The formation of fascicles of amacrine, bipolar and ganglion cell processes suggests that all cells can invade supportive environments. It may be possible to redirect or block neurite growth with integrin receptor motifs, providing impetus for future re-patterning experiments. Finally, preventing secondary loss of cones in rod-initiated degenerations seems an obvious strategy and survival factors that extend cone life may prevent remodeling, even if they do not preserve vision.

Can remodeling be exploited? Survivor neurons in late remodeling are healthy cells by ultrastructural and metabolic standards, even though deconstruction of their macromolecular phenotypes may have radically altered their connectivities and responsivities as circuit elements. Furthermore, growth of new neurites is robust and new synaptic contacts may retard cell death. A great deal is now known about the extracellular, membrane-dependent, and cytoskeletal signals that determine cell shape, process extension and cell migration (Chiu et al., 2000; Higgs and Pollard, 2000; Li et al., 2000; Pollard et al., 2000, 2001; Condic, 2001; Hutson and Chien, 2002). Retinas might be re-patterned, perhaps after augmentation with neuroprogenitor or stem cells (Young et al., 2000), as long as ganglion cells survive in significant numbers to provide both form vision and oculomotor control. Given the propensity of remodeling neurons to extend processes and likelihood that access through of the inner limiting membrane can be achieved, it may be possible to direct neurites to contact areas of epiretinal or intraretinal bionic devices. It may be possible to increase plastic behavior. After corticospinal tract transection in rat, axonal collateral sprouting has been driven by administration of myelin inhibitors to re-establish a dense plexus of fibres on the contralateral side of the cord (Schwab, 1996). Such long-distance regeneration of corticospinal fibres has led to significant functional improvements in locomotion. It is important that we accept the idea that remodeling is the rule in retinal disease *because* the retina is a portion of the CNS, and the CNS remodels in response to traumatic and pathological events. Remodeling is the rule; not the exception. That does not mean we cannot eventually circumvent it to cure blinding diseases.

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