REVIEW ARTICLE

MECHANISMS OF DISEASE

Age-Related Macular Degeneration

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Since 1874, when it was first described in the medical literature as "symmetrical central choroido-retinal disease occurring in senile persons,"[1] age-related macular degeneration has also been referred to as senile, or diskiform, macular degeneration, among many other terms. About 25 years ago, the term "age-related maculopathy" was coined and its end stage was acknowledged as age-related macular degeneration. In this review, I use the commonly accepted age-related macular degeneration, although I have reservations about its appropriateness. After briefly describing the clinical features of age-related macular degeneration, I turn to the physiology of the aging macula and to mechanisms implicated in the cause. Reviews of treatment and detailed ocular data can be found elsewhere.[2-4]

CLINICAL SIGNS AND SYMPTOMS

The diagnosis of age-related macular degeneration rests on signs in the macula (Fig. 1), irrespective of visual acuity.[5] Drusen, derived from the German word for geodes, cavities in rocks often lined by crystals, are the characteristic physical signs of age-related macular degeneration (Fig. 2). As seen through the ophthalmoscope, drusen are dots ranging in color from white to yellow, sometimes with a crystalline, glittering aspect. The origin of drusen has remained unresolved for more than a century.[7,8] Moreover, there is no agreement as to whether drusen in the absence of other ocular abnormalities always point to early age-related macular degeneration.[9,10] In this review, I consider all drusen to be a sign of age-related macular degeneration unless other clearly identifiable ocular or systemic abnormalities are present.

The stages of age-related macular degeneration are categorized as early, in which visual symptoms are inconspicuous,[11] and late, in which severe loss of vision is usual. Early age-related macular degeneration is characterized by drusen or by hyperpigmentations or small hypopigmentations, without visible choroidal vessels. Drusen become visible on ophthalmoscopy when their diameter exceeds 25 μm.[9] The larger the drusen, the greater the area they cover, and the larger the areas of hyperpigmentation and hypopigmentation of the retinal pigment epithelium (RPE) in the macula, the higher the risk of late age-related macular degeneration.[12] Late age-related macular degeneration has "dry" and "wet" forms, but the question of whether these two forms are really the same disease is a controversial one.[4] Both dry and wet age-related macular degeneration can be found in the same patient: dry age-related macular degeneration can occur in one eye and wet age-related macular degeneration in the other, or both dry and wet age-related macular degeneration can be seen in the same eye. In follow-up studies, dry age-related macular degeneration can become wet age-related macular degeneration, and wet age-related macular degeneration can become dry. Dry and wet age-related macular degeneration can resemble end stages of other retinal diseases, and for this reason, late age-related macular degeneration is a diagnosis of exclusion.

Dry age-related macular degeneration, also called geographic atrophy, starts with a sharply demarcated round or oval hypopigmented spot that is often juxtafoveal and in which large choroidal vessels are visible (Fig. 2B and 2D). The initial symptoms of dry age-related macular degeneration are usually indicated by gaps in an image, as if letters had dropped out of a line of text. The first sign of wet age-related macular degeneration is serous or hemorrhagic fluid that causes the neuroretina or the RPE to detach from Bruch's membrane (Fig. 2E and 2F). The fluid originates in a subretinal neovascular membrane. The detachment disturbs the fine arrangement of the photoreceptors and causes an image distortion called metamorphopsia, which is often the first symptom of wet age-related macular degeneration. These new subretinal vessels tend to grow toward the fovea. Within days or months, more extensive hemorrhages and scars can appear (Fig. 2G and 2H). Usually, a similar type of late age-related macular degeneration develops in both eyes. Each successive year after the initial diagnosis, about 15% of patients with unilateral wet age-related macular degeneration are found to have wet age-related macular degeneration in the opposite eye. If left untreated, wet age-related macular degeneration usually causes legal blindness (visual acuity ≤0.1, 6/60) within months after the second eye becomes affected; in contrast, these events may take years in patients with dry age-related macular degeneration. Late age-related macular degeneration often gives the patient enough vision to be ambulatory because the peripheral visual field around a central scotoma is intact (Fig. 1).

In epidemiologic studies, an age of 50 years is arbitrarily chosen as the minimum age for the diagnosis of age-related macular degeneration.[5] In the population-based Rotterdam Study, 64% of 825 participants who were 80 years old or older showed signs of early or late age-related macular degeneration (unpublished data). Late age-related macular degeneration is now the most common cause of untreatable blindness in the Western world, with a prevalence that is 0.05% before the age of 50 years and that rises to 11.8% after 80 years of age.[13] Unless effective methods of prevention and treatment are found, the prevalence of age-related macular degeneration is expected to double in the coming decades because of the projected increase in aging populations.[13]

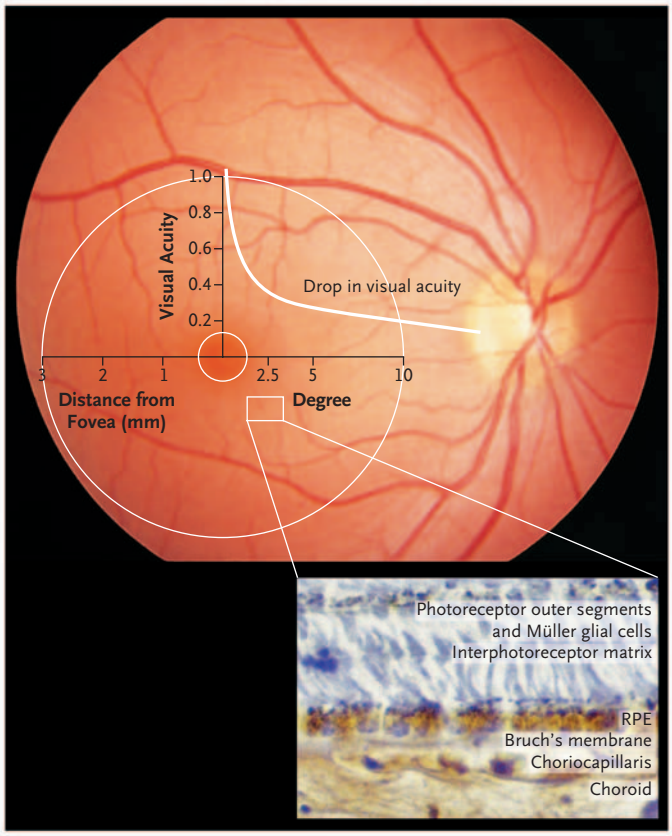

Figure 1. Normal Fundus.

The area within the outer white circle (indicating a retinal diameter of about 6 mm) is the macula lutea, which is Latin for yellow spot or stain. The inner circle (diameter, 0.8 mm) borders the fovea, which is the central pit of the macula, where the preponderance of cones over rods is highest for sharp vision. The graph superimposed on this normal fundus shows the drop in attainable visual acuity in relation to the distance from the fovea. The effect on visual acuity of the location and area covered by a central age-related macular degeneration scar can be estimated on the basis of this measure. The retina, which has 10 layers, is the inner lining at the back of the eyeball. The inset shows the two outer layers that contain the purple light-sensitive rod and cone photoreceptor cells supported by Müller cells, all embedded in the interphotoreceptor matrix, in close contact with the retinal pigment epithelium (RPE). The RPE is surrounded by two extracellular matrixes, the interphotoreceptor matrix and Bruch's membrane. Between the RPE and the outer wall of the eye (sclera) are Bruch's membrane, the choriocapillaris, and a larger vessel layer, the choroid. Ruysch's complex includes the RPE, Bruch's membrane, and the choriocapillaris.

THE OUTER RETINA AND ADJACENT TISSUES

Age-related changes that predispose a person to age-related macular degeneration occur in the outer retina (Fig. 1). The inner retina is adjacent to the vitreous and the outer retina is adjacent to the choroid. The outer retina includes the photoreceptors (rods and cones), the RPE, and Bruch's

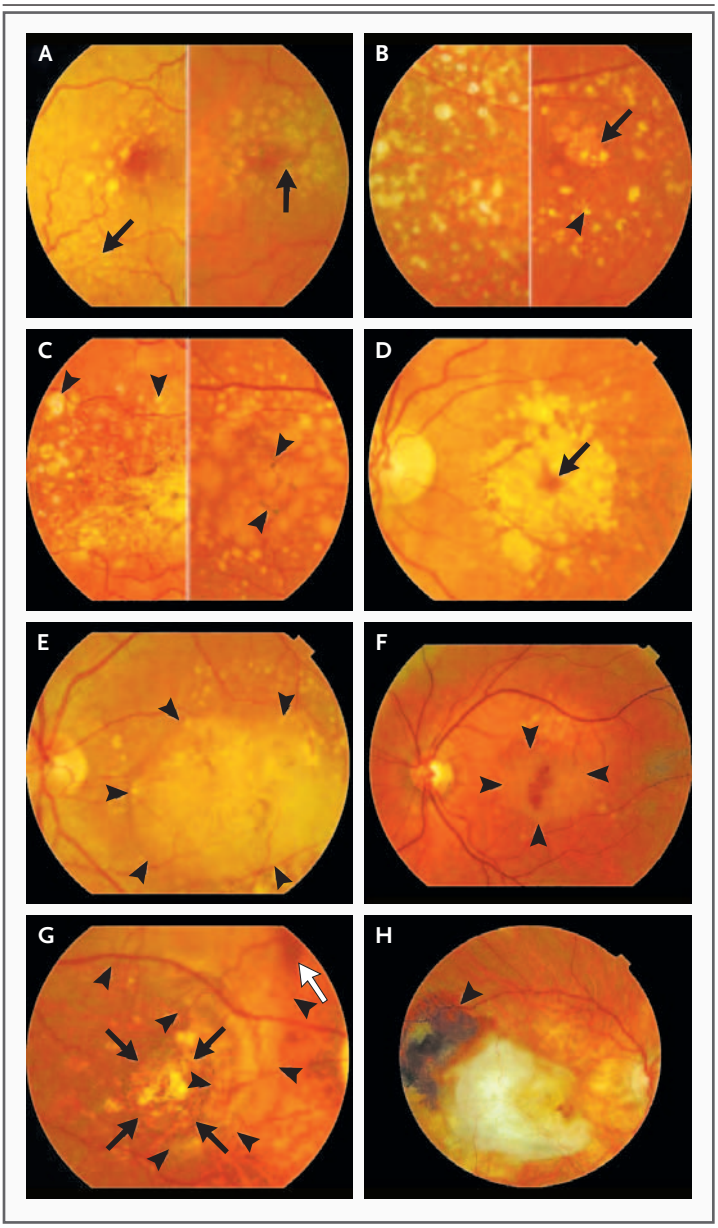

Figure 2. Progression from Early to Late Age-Related Macular Degeneration.

Drusen can be classified according to size, appearance, biochemical composition, and examination technique.[5,6] With increasing age, drusen become confluent and larger, sometimes crystalline, less circumscribed, or accompanied by hyperpigmentations or hypopigmentations of the RPE. Panel A shows early age-related macular degeneration in two maculas: the macula shown on the left-hand side contains small drusen (arrow) and some large, indistinctly bordered drusen in the fovea; the macula shown on the right-hand side contains more drusen and focal hyperpigmentation (arrow). The left-hand side of Panel B shows early age-related macular degeneration characterized by extensive small and large drusen in and around the macula; the right-hand side shows crystalline drusen (arrowhead) and a small patch of late dry age-related macular degeneration (arrow). The left-hand side of Panel C shows early age-related macular degeneration, with crystalline and calcified drusen (arrowheads); on the right-hand side (also early age-related macular degeneration) are large confluent drusen leading to a drusenoid detachment of the RPE, with hyperpigmentation (arrowheads). Panel D (late age-related macular degeneration) shows dry age-related macular degeneration, with a central island in which photoreceptors are still functioning (arrow); this eye has a complete ring scotoma around a small central visual-field remnant. Panel E (late age-related macular degeneration) shows wet age-related macular degeneration in the form of a large serous detachment of the RPE (with borders marked by arrowheads) caused by fluid leaking from a subretinal neovascular membrane. Panel F (late age-related macular degeneration) shows the development of wet age-related macular degeneration with a subfoveal hemorrhage surrounded by detachment of the RPE (arrowheads). Panel G (late age-related macular degeneration) shows dry age-related macular degeneration (black arrows), in which the orange lines are large choroidal vessels, surrounded by glial scar tissue (arrowheads) resulting from a large subretinal hemorrhage with a small remnant (white arrow). Panel H (late age-related macular degeneration) shows cicatricial wet age-related macular degeneration, with glial scarring in the macula and remnants of hemorrhages at its temporal border (arrowhead).

membrane. The adjacent choriocapillaris, the capillary layer of the choroid, is the vascular system that feeds the outer retina (Fig. 1). These structures, collectively called Ruysch's complex,[14] provide an optimal environment for retinal function — high-resolution and color vision (cones), and peripheral vision and vision at dusk (rods).

THE RETINAL PIGMENT EPITHELIUM

The RPE is a central element in the pathogenesis of age-related macular degeneration. It is a postmitotic, cuboidal monolayer of cells with a very high metabolic rate. The RPE cell derives its name from the numerous melanosomes within its cytoplasm (Fig. 3). Of the 10 known functions of the RPE, the most important are regeneration of bleached visual pigments; formation and maintenance of two extracellular matrixes, the interphotoreceptor matrix and Bruch's membrane (Fig. 1 and 3); transport of fluids and ions between photoreceptors and the choriocapillaris; and phagocytosis.

A pivotal function of the RPE is the regeneration of the visual pigment rhodopsin. The absorption of light by rhodopsin creates a visual signal and results in a change in the molecule that ne-

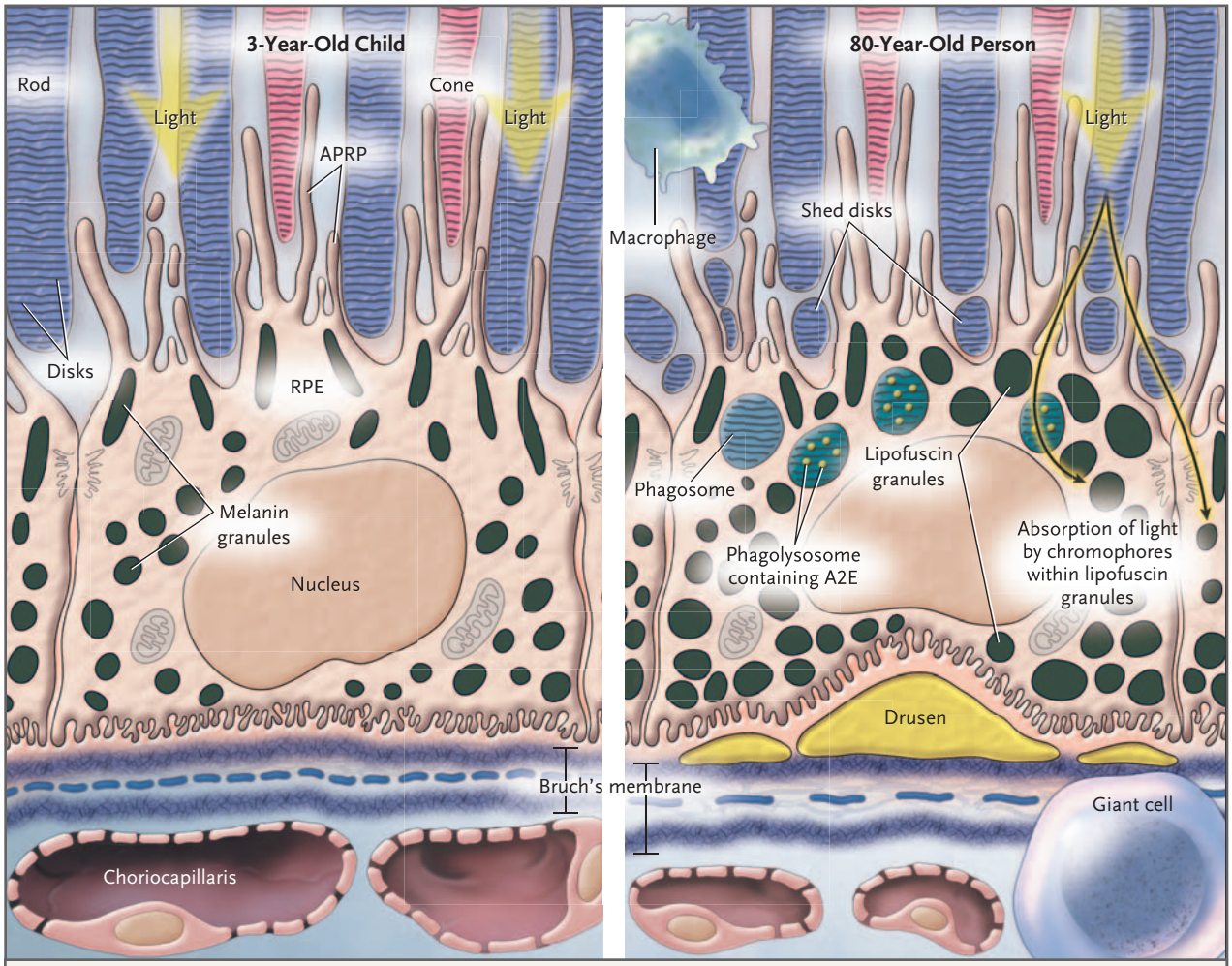

Figure 3. RPE Cell in a 3-Year-Old Child (Left-Hand Panel) and an 80-Year-Old Person (Right-Hand Panel).

The outer segments of the rods and cones are embedded in the interphotoreceptor matrix (blue-gray areas) and partially surrounded by apical pseudopodial RPE processes (APRP). The shed disks (right-hand panel) become encapsulated in the phagosomes and are digested in phagolysosomes in the cell cytoplasm of the RPE. Macrophages and fused macrophages (giant cells) remove cellular debris around the cell. Light-induced toxicity occurs as light is absorbed by the various chromophores in the lipofuscin granules. This damages DNA and cell membranes and causes inflammation and apoptosis. The right-hand panel shows enlarged lipofuscin granules, the thickened Bruch's membrane, and the attenuation of the choriocapillaris. The central elastic lamina in Bruch's membrane becomes more porous in old age.

cessitates the reconstitution of dark-adapted visual pigment. This process occurs largely within the RPE through many complex intermediate steps. One of them entails RPE65, an enzyme that converts all-*trans* retinyl esters into 11-*cis* retinal, which is essential for the function of rods and cones.[15]

Phagocytosis by RPE Cells

The RPE is a phagocytic system that is essential to the renewal of photoreceptors. Each photoreceptor has an inner and outer segment, separated by an invagination, the connecting cilium. The outer segment of each rod has about 1000 disks,[16] and the outer segment of every cone has a membrane that is folded 700 times, stacked like a roll of coins. The disks are necessary for the conversion of light into electrical potentials. In each disk membrane, the transmembrane protein rhodopsin is positioned in combination with four phospholipids and docosahexanoic acid.[17] The tips of both types of photoreceptors are shed from their outer segments and engulfed and degraded within the RPE.[18] The shedding is balanced by the addition

of membranes at the base of the outer segments of rods and the replacement of nucleic acids, proteins, and lipid throughout the cones. In the rhesus monkey, about 3000 disks are shed daily from 30 photoreceptors in each RPE cell.[19] These shed disks fuse with lysosomes, forming phagolysosomes (Fig. 3). The contents of the phagolysosomes are incompletely degraded within acid lysosomal compartments and form the residual bodies that are the substrates for lipofuscin formation. At least eight lysosomal enzymes are active in the RPE.[20]

From the age of 16 months on, the accumulation of lipofuscin imposes an ever-increasing burden on RPE cells.[21] Moreover, RPE cells have a limited capacity to sequester malfunctioning cytoplasm before delivering it to lysosomes. This autophagic process cannot handle the immense amount of metabolic waste that accumulates in RPE cells over a lifetime. The parafoveal ring, where rod density is highest[22] and where dry age-related macular degeneration often begins, has the highest concentration of lipofuscin in the retina (Fig. 2D). When signs of early age-related macular degeneration progress toward late age-related macular degeneration and RPE cells die, lipofuscin disappears from the cells — a sign that foretells a poor outcome.

Lipofuscin and A2E

The retinoid A2E is an autofluorescent component of lipofuscin.[23] Precursors of A2E are formed within the outer segments of the photoreceptors,[24] but A2E itself arises within the phagolysosomal compartment of RPE cells. When it reaches a critical concentration, A2E inhibits the proton pump of lysosomes,[25] causing leakage of the contents of the lysosomes into the cytoplasm of RPE cells.[23] A2E can also damage the DNA in RPE[26] and mitochondrial membranes. All these effects cause apoptosis.[27] An important feature of A2E is its broad light-absorption spectrum, with peaks in the visible range, especially in the blue range, which predisposes RPE cells to light-induced lesions. Additional photosensitizing molecules in lipofuscin remain to be investigated.[28]

Chromophores

The number of RPE cells diminishes with age, increasing the phagocytic burden on the remaining cells. In old age, pheomelanin[29] and all-*trans* retinal dimers[30] are formed. The absorption of light energy by these colored chromophores depends on the wavelength of the light. Chromophores impair the function of lysosomes in RPE cells. The injured RPE cells attract dendrites from choroidal dendritic cells,[31] which are powerful antigen-presenting DC1 cells and constitute the core of approximately 40% of all drusen.[32] Further impairment with age causes the accumulation of debris in the cytosol of RPE cells. This debris contains various chromophores, which increase the risk of phototoxic damage, and in people over 80 years of age, the debris can occupy more than one fifth of the total volume of an RPE cell.[33]

BRUCH'S MEMBRANE

Bruch's membrane, which lies behind the RPE, has three layers: a central elastic layer sandwiched between two collagenous layers. These are lined by the basement membranes of the RPE and the choriocapillaris (Fig. 3). The elastic layer is one third to one fifth as thick in the fovea as in the peripheral retina.[34] This feature could cause the centripetal growth of wet age-related macular degeneration, owing to lowered tissue resistance. Proteoglycans are an important constituent of Bruch's membrane.[35,36] Their negative charge hampers the passage of the positively charged macromolecules that are necessary for maintenance of the RPE.

Changes in Bruch's membrane start at a relatively early age.[37,38] Basal laminar deposits and membranous debris, considered to be precursors of age-related macular degeneration, can appear in Bruch's membrane as early as the third decade of life.[38,39] Coated, membrane-bound bodies and hard drusen appear between the basement membrane of the RPE and the inner collagenous layer of Bruch's membrane in the third decade of life, and basal laminar deposits appear around the age of 40 years.[40] How drusen develop and why they can vary in location and features are unknown. Drusen often have a core of glycoproteins,[32,41] and their outer domes contain crystallins,[10,42] chaperone proteins, apolipoprotein E (APOE), vitronectin, and proteins related to inflammation (amyloid P, C5, and C5b–9 complement complex).[43] Drusen also contain fragments of RPE cells.[4,10,32]

Bruch's membrane calcifies and doubles in thickness between the ages of 10 and 90 years.[44] It contains no lipids during the first 30 years of

life, but lipid concentrations rise in later years, reaching 220 mg per square meter of the membrane by the age of 100 years.[45-48] As lipid concentrations increase, the fluid permeability of Bruch's membrane decreases.[49,50] Uncontrolled proteolytic degradation of the membrane forms advanced glycation products that damage adjacent cells and increase the formation of extracellular matrix.[4] In the aging Bruch's membrane, there is a linear thickening in which deposits of collagen, lipids, and debris cause a sharp reduction in fluid and nutrient transport across the membrane.[50] Reductions in the concentration of metalloproteinases can cause Bruch's membrane to thicken further. Bruch's membrane functions as an intercellular matrix acting as a scaffold for adjacent RPE and choriocapillaris cells and regulating their survival. Its diminished function results in diminished cell adhesion and anoikis — apoptosis resulting from incorrect cell adhesion.[51] Anoikis occurs in photoreceptors and RPE cells and probably in choriocapillaris endothelial cells. The extracellular deposits around Bruch's membrane instigate chronic local inflammation, which promotes the development of age-related macular degeneration.[9,32] Such deposits can induce invasion by dendritic cells, which act as phagocytes and immune cells.[32,52] Furthermore, RPE cells, macrophages,[37,53-55] and dendritic cells release inflammatory cytokines,[56,57] angiogenic factors, and immune complexes, and by these means sustain chronic inflammation.[58] The spontaneous disappearance of drusen before wet age-related macular degeneration begins[59] may be due to macrophages originating in the choriocapillaris.

RUYSCH'S COMPLEX

Ruysch's complex, comprising the RPE, Bruch's membrane, and choriocapillaris, receives its blood supply from the choriocapillaris, which has extensive fenestrations on the side facing Bruch's membrane. The inner retina on the side of the vitreous cavity has a limited oxygen supply as compared with the oxygen-rich Ruysch's complex. Photoreceptors consume more than 90% of this oxygen.[60] With increasing age, the lumina of the choriocapillaris and the choroidal thickness become reduced by half (Fig. 3).[44] In the dark, oxygen consumption by photoreceptors increases by 50%, creating a near-hypoxic environment.[61] With thinning or destruction of the RPE, the underlying choriocapillaris becomes less fenestrated, reducing the transport of macromolecules, and then disappears altogether.[62,63] The resulting hypoxia stabilizes hypoxia-inducible factor 1α by inhibiting its degradation in proteasomes. Hypoxia-inducible factor 1α activates genes encoding proteins such as erythropoietin that protect the photoreceptors.[64] Hypoxia also increases the secretion of growth factors such as vascular endothelial growth factor A within Ruysch's complex on the basal side of the RPE cells, causing development of choroidal neovascular membranes.[65,66]

MECHANISMS

Is age-related macular degeneration a normal process of aging,[38,67,68] which will affect us all if we live long enough? More likely, physiologic aging of the RPE is not the sole factor — genetic and environmental influences are also important. Age-related macular degeneration has a strong genetic component. Mutations in several genes (Table 1) are now known to predispose people to age-related macular degeneration in various ways. The most consistently identified environmental risk factor is smoking; recently, the role of dietary antioxidants in the prevention of age-related macular degeneration has become of interest.

GENETICS

Genetic influences on age-related macular degeneration are well known from family and twin studies.[1,79,84-91] First-degree relatives of patients with age-related macular degeneration, as compared with first-degree relatives in families without the disorder, are at increased risk for the condition (odds ratio, 2.4),[90] are affected at a younger age,[92,93] and have an increased lifetime risk of late age-related macular degeneration (risk ratio, 4.2).[92] Studies have implicated many genes in age-related macular degeneration,[69] but most of these studies are inconclusive. Table 1 lists the genes that have the best-documented associations with age-related macular degeneration. An increased risk of age-related macular degeneration has been reported among carriers of the *APOE* ε2 allele, and a protective effect has been found for carriers of the *APOE* ε4 allele.[79,94] It is possible that these allelic variants are not causally related to the disease but are associated with it because of their close position to an unknown causative genetic

Table 1. Selected Candidate Genes Most Likely Associated with AMD.*

Gene	Putative Mechanism of Normal Gene	Estimated Population Attributable Risk (%)	References
CFH	Complement factor H inhibits activation of alternative complement pathway by binding to heparin and C-reactive protein, thus increasing affinity for complement protein C3b	24–61	Haines et al.,[70] Klein et al.,[71] Edwards et al.,[72] Hageman et al.,[73] Despriet et al.,[74] Schmidt et al.[75]
CFB and *C2*	Similar to that of *CFH*; 1 risk and 2 protective haplotypes	60	Gold et al.[76]
LOC387715	Unknown	NI	Jakobsdottir et al.,[77] Rivera et al.[78]
APOE	Apolipoprotein E transports lipids and cholesterol in the central nervous system	NI	Klaver et al.,[79] Baird et al.,[80] Schmidt et al.[81]
ABCA4–ABCE	ATP-binding protein transports vitamin A derivatives	1.3	Allikmets et al.,[82] Allikmets[83]

* A complete overview of candidate genes associated with age-related macular degeneration is available elsewhere.[69] NI denotes not informative.

variant on chromosome 19q. The same holds for *LOC38755*, which probably flags an unknown causative variant. Mutations in the ATP-binding cassette transporter A4 (*ABCA4*) and E (*ABCE*) genes are rare, and their role in age-related macular degeneration is uncertain.

Single-nucleotide polymorphisms in the complement factor H (*CFH*), factor B (*CFB*), and *C2* genes, which probably render the protein products of these genes ineffective in inhibiting or regulating the complement pathway, are associated with 50 to 70% of cases of age-related macular degeneration.[70-73,76] Estimates of the relative risk of age-related macular degeneration among carriers of these polymorphisms, as compared with noncarriers, range from 2.7 to 7.4. The CFH protein is involved in inhibiting the alternative complement cascade, in part by binding to the C-reactive protein that is induced by damaged tissues.[95,96] CFH is detectable in drusen and plays a role in type II membranoproliferative glomerulonephritis, a disease associated with retinal drusen.[97] These findings suggest causal relations among CFH, drusen formation, and neovascular macular degeneration in both age-related macular degeneration and the renal disorder. The membrane-attack complexes (which consist of the terminal lytic components of complement) that form when CFH is ineffective or deficient may destroy the photoreceptor and RPE membranes in the vicinity of the drusen. Complement is also activated by hypoxia of the vascular endothelium.[98]

The *CFH* Y402H polymorphism has the strongest association with age-related macular degeneration. The proportion of carriers of this polymorphism is 39% in white populations, 31% in black populations, and only 8% in persons of Japanese ancestry and 7% in persons of Chinese ancestry.[99] The equally high prevalence of this polymorphism in blacks and whites should be associated with a high prevalence of age-related macular degeneration in both groups. For unknown reasons, however, late age-related macular degeneration is much less common in blacks than in whites.

The view that age-related macular degeneration is a multifactorial disorder is supported by the following findings: the odds ratio for late age-related macular degeneration is 11.0 among persons who are homozygous for *CFH* Y402H as compared with noncarriers of this polymorphism[74]; in the presence of an elevated erythrocyte sedimentation rate, the odds ratio is 20.2; and in the presence of an elevated concentration of serum C-reactive protein, it is 27.7.[74] The population attributable risk for late age-related macular degeneration that varies between 24[75] and 54%[74] for *CFH* Y402H was recently adjusted to 61% when both *CFH* and *LOC387715* polymorphisms were present in former or current smokers (Table 1).[75]

SMOKING

There is reproducible evidence of a consistent association between smoking and age-related macular degeneration.[100,101] Analysis of pooled data from three population-based cohort studies showed that the relative risk of late age-related macular degeneration is 2.4 among current smokers as compared with those who never smoked, with an insignificant risk of 1.29 among former smokers.[102] However, current smokers who are homozygous for the *CFH* Y402H polymorphism have a relative risk of 34.0 for late age-related macular degeneration as compared with nonsmokers who do not have this polymorphism.[74] The risk is 7.6 for nonsmokers who are homozygous for the *CFH* Y402H polymorphism.[74]

Smoking reduces the concentration of macular pigment by as much as 50% in a dose–response relationship.[103] The nicotine and cotinine in the plasma of smokers activate retinal phospholipase A2, causing the formation of arachidonic acid, a precursor of prostaglandins and leukotrienes, which are inflammatory mediators.[104] Tar from cigarettes also contains a high concentration of a pro-oxidant hydroquinone. Lesions similar to those in the aging Ruysch's complex develop in the eyes of mice that are exposed to cigarette smoke or dietary hydroquinone.[105] There is no validated evidence, however, that environmental hydroquinone explains the rising prevalence of age-related macular degeneration in some countries.[106-108]

LIGHT-INDUCED TOXIC EFFECTS

Because it is difficult to measure lifelong light exposure in humans, there is only weak epidemiologic evidence that excessive exposure to light is associated with age-related macular degeneration.[109,110] It appears that the shorter the wavelength and the higher the light intensity, the greater the chance of photochemically induced light damage. For this reason, artificial lenses inserted after cataract extraction now usually have blocking filters for ultraviolet and blue light.

Light can induce the formation of reactive oxygen species, which in turn can lead to the formation of toxic lipid and protein peroxidation products.[111] In principle, all light, even ambient natural light, can damage the retina, provided the exposure is long enough. Retinal degeneration occurs in rodents exposed to normal light levels for 5 to 7 days and nights. Rodents became blind within 1 to 2 days after being exposed to bright (3000 lux) fluorescent light for 1 hour. In animals, ultraviolet, blue, or white light can induce irreversible lesions in the central retina.[112-114] The visual pigments of rods and cones are the primary mediators of these lesions. In mice lacking rhodopsin, the retina cannot be injured by intense white light.[115] Moreover, the rate of regeneration of rhodopsin is a crucial determinant of the threshold for light-induced damage.[115] There is indirect evidence that metabolites of visual pigments can trigger phototoxic lesions that culminate in protein and lipid oxidation.[10] Light-induced damage in humans depends on the duration of exposure, the wavelength, age, the degree of oxygenation of the retina, unknown genetic factors, and endogenous chromophores. Furthermore, exogenous chromophores — amiodarone, chloroquine, phenothiazines, lithium, and herbs such as St. John's wort — can increase susceptibility to light-induced toxic effects.[116]

Light absorption by lipofuscin, chiefly retinoid A2E and other retinoids or chromophores,[117,118] can also damage the RPE. The presence of low concentrations of A2E in genetically modified animals seems to lower the potential for light-induced damage.[119] Dendritic cells in the choriocapillaris present the cell debris left by phototoxic effects to the immune system[32] and attract macrophages, which in turn can evoke a local autoimmune response[120] and chronic inflammation.[121] Antioxidants partially protect photoreceptors and the RPE against light-induced damage.[112,122]

There may be a link between phototoxic effects and chronic inflammation in the retina. Exposure to light releases arachidonic acid from fatty acids in the outer segments of photoreceptors.[123,124] The prostaglandins and leukotrienes thus generated up-regulate inflammatory cytokines and attract macrophages to the damaged retina (Fig. 3).[114] The light-damaged photoreceptors and RPE cells undergo apoptosis, and the apoptotic cells signal microglia or macrophages or both to invade the injured region. Dying photoreceptors and RPE cells are substrates for the formation of drusen, which in turn activate dendritic cells, thereby sustaining a vicious circle of inflammation within the retina.

CONVERGING RISK FACTORS

The main risk factors for age-related macular degeneration — smoking, exposure to light, and in-

flammation — are all associated with local activation of macrophages. In the retina, the invasion and activation of macrophages require adhesion molecules, chemokines, cytokines, complement components, free radicals, proteases, and protease inhibitors.[121] All these molecules are abundant in Ruysch's complex, and they lead to an increase in photochemically damaged lipids and proteins to induce apoptosis of RPE cells and photoreceptors.

There are reports that antioxidants provide protection against age-related macular degeneration, although the data are inconsistent.[125] A case–control study showed a protective effect of high doses of vitamins C and E and β-carotene, combined with zinc.[126] A protective effect of the upper third as compared with the lower third of normal dietary concentrations of these nutrients has been reported in a population-based cohort in which only 14% of the subjects used supplements,[127] but the finding remains unconfirmed.

A FINAL NOTE ON NOMENCLATURE

Our thinking about the pathophysiology of diseases changes continually, and this evolution in thought is reflected in their various names. Patients today do not like to hear that they are senile or have a degenerative disease. To avoid the use of such derogatory terms and to emphasize that the aging process of the RPE is a key component of this disorder, I prefer to use the term "aging macula disorder."

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REFERENCES

1. Hutchinson J, Tay W. Symmetrical central choroido-retinal disease occurring in senile persons. R Lond Ophthalmic Hosp Rep J Ophthalmic Med Surg 1874; 8:231-44.
2. Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000;342:483-92.
3. Schachat AP. New treatments for age-related macular degeneration. Ophthalmology 2005;112:531-2.
4. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004;122: 598-614.
5. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. Surv Ophthalmol 1995;39:367-74.
6. Hageman GS, Mullins RF. Molecular composition of drusen as related to substructural phenotype. Mol Vis 1999;5:28.
7. Donders FC. Beitraege zur pathologischen Anatomie des Auges. Arch Ophthalmol 1854;1:106-18.
8. Abdelsalam A, Del Priore L, Zarbin MA. Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression. Surv Ophthalmol 1999;44:1-29.
9. Sarks SH, Arnold JJ, Killingsworth MC, Sarks JP. Early drusen formation in the normal and aging eye and their relation to age related maculopathy: a clinicopathological study. Br J Ophthalmol 1999; 83:358-68.
10. Crabb JW, Miyagi M, Gu X, et al. Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proc Natl Acad Sci U S A 2002;99: 14682-7.
11. Hogg RE, Chakravarthy U. Visual function and dysfunction in early and late age-related maculopathy. Prog Retin Eye Res 2006;25:249-76.
12. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam eye study. Ophthalmology 2002;109:1767-79.
13. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-72.
14. Ruysch F. Asser primus: Thesaurus Anatomicus secundus. Amsterdam: J. Waesbergios, 1722:3-14.
15. Redmond TM, Poliakov E, Yu S, Tsai JY, Lu Z, Gentleman S. Mutation of key residues of RPE65 abolishes its enzymatic role as isomerohydrolase in the visual cycle. Proc Natl Acad Sci U S A 2005;102: 13658-63.
16. Young RW. Shedding of discs from rod outer segments in the rhesus monkey. J Ultrastruct Res 1971;34:190-203.
17. Besharse JC, Defoe DM. Role of the retinal pigment epithelium in photoreceptor membrane turnover. In: Marmor MF, Wolfensberger TJ, eds. The retinal pigment epithelium: function and disease. New York: Oxford University Press, 1998: 152-72.
18. Young RW, Bok D. Participation of the retinal pigment epithelium in the rod outer segment renewal process. J Cell Biol 1969;42:392-403.
19. Bok D, Young RW. Phagocytic properties of the retinal pigment epithelium. In: Zinn KM, Marmor MF. The retinal pigment epithelium. Cambridge, MA: Harvard University Press, 1979:148-74.
20. Boulton M, Moriarty P, Jarvis-Evans J, Marcyniuk B. Regional variation and age-related changes of lysosomal enzymes in the human retinal pigment epithelium. Br J Ophthalmol 1994;78:125-9.
21. Streeten BW. The sudanophilic granules of the human retinal pigment epithelium. Arch Ophthalmol 1961;66:391-8.
22. Curcio CA, Millican CL, Allen KA, Kalina RE. Aging of the human photoreceptor mosaic: evidence for selective vulnerability of rods in central retina. Invest Ophthalmol Vis Sci 1993;34:3278-96.
23. Eldred GE. Lipofuscin fluorophore inhibits lysosomal protein degradation and may cause early stages of macular degeneration. Gerontology 1995;42:Suppl 2:15-28.
24. Mata NL, Weng J, Travis GH. Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration. Proc Natl Acad Sci U S A 2000;97:7154-9.
25. Bergmann M, Schutt F, Holz FG, Kopitz J. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related

macular degeneration. FASEB J 2004;18:562-4.
26. Sparrow JR, Zhou J, Cai B. DNA is a target of the photodynamic effects elicited in A2E-laden RPE by blue-light illumination. Invest Ophthalmol Vis Sci 2003;44:2245-51.
27. Suter M, Reme C, Grimm C, et al. Age-related macular degeneration: the lipofusion component N-retinyl-N-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. J Biol Chem 2000;275:39625-30.
28. Sparrow JR, Fishkin N, Zhou J, et al. A2E, a byproduct of the visual cycle. Vision Res 2003;43:2983-90.
29. Hu DN, Savage HE, Roberts JE. Uveal melanocytes, ocular pigment epithelium, and Müller cells in culture: in vitro toxicology. Int J Toxicol 2002;21:465-72.
30. Fishkin NE, Sparrow JR, Allikmets R, Nakanishi K. Isolation and characterization of a retinal pigment epithelial cell fluorophore: an all-trans-retinal dimer conjugate. Proc Natl Acad Sci U S A 2005;102:7091-6.
31. Forrester JV, McMenamin PG, Holthouse I, Lumsden L, Liversidge J. Localization and characterization of major histocompatibility complex class II-positive cells in the posterior segment of the eye: implications for induction of autoimmune uveoretinitis. Invest Ophthalmol Vis Sci 1994;35:64-77.
32. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retin Eye Res 2001;20:705-32.
33. Feeney-Burns L, Hilderbrand ES, Eldridge S. Aging human RPE: morphometric analysis of macular, equatorial, and peripheral cells. Invest Ophthalmol Vis Sci 1984;25:195-200.
34. Chong NH, Keonin J, Luthert PJ, et al. Decreased thickness and integrity of the macular elastic layer of Bruch's membrane correspond to the distribution of lesions associated with age-related macular degeneration. Am J Pathol 2005;166:241-51.
35. Hewitt AT, Nakazawa K, Newsome DA. Analysis of newly synthesized Bruch's membrane proteoglycans. Invest Ophthalmol Vis Sci 1989;30:478-86.
36. Kliffen M, de Jong PT, Luider TM. Protein analysis of human maculae in relation to age-related maculopathy. Lab Invest 1995;73:267-72.
37. Sarks SH. New vessel formation beneath the retinal pigment epithelium in senile eyes. Br J Ophthalmol 1973;57:951-65.
38. Hogan MJ, Alvarado J. Studies on the human macula. IV. Aging changes in Bruch's membrane. Arch Ophthalmol 1967;77:410-20.
39. van der Schaft TL, de Bruijn WC, Mooy CM, Ketelaars DA, de Jong PT. Is basal laminar deposit unique for age-related macular degeneration? Arch Ophthalmol 1991;109:420-5.
40. van der Schaft TL, Mooy CM, de Bruijn WC, Oron FG, Mulder PG, de Jong PT. Histologic features of the early stages of age-related macular degeneration: a statistical analysis. Ophthalmology 1992;99:278-86.
41. Rudnew A. Ueber die Entstehung, der sogenannten Glaskoerper der Choroides des menschlichen Auges und über das Wesen der hyalinen Degeneration der Gefässe derselben. Arch Pathol Anat Phyiol Klin Med 1871;53:455-65.
42. Nakata K, Crabb JW, Hollyfield JG. Crystallin distribution in Bruch's membrane-choroid complex from age-related macular degeneration and age-matched donor eyes. Exp Eye Res 2005;80:821-6.
43. Umeda S, Suzuki MT, Okamoto H, et al. Molecular composition of drusen and possible involvement of anti-retinal autoimmunity in two different forms of macular degeneration in cynomolgus monkey (Macaca fascicularis). FASEB J 2005;19:1683-5. [Erratum, FASEB J 2005;19:2088.]
44. Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PT. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. Invest Ophthalmol Vis Sci 1994;35:2857-64.
45. Bird AC, Marshall J. Retinal pigment epithelial detachments in the elderly. Trans Ophthalmol Soc U K 1986;105:674-82.
46. Pauleikhoff D, Harper CA, Marshall J, Bird AC. Aging changes in Bruch's membrane: a histochemical and morphologic study. Ophthalmology 1990;97:171-8.
47. Holz FG, Sheraidah G, Pauleikhoff D, Bird AC. Analysis of lipid deposits extracted from human macular and peripheral Bruch's membrane. Arch Ophthalmol 1994;112:402-6.
48. Marshall J, Hussain AA, Starita C, Moore DJ, Patmore AL. Aging and Bruch's membrane. In: Marmor MF, Wolfensberger TJ, eds. The retinal pigment epithelium: function and disease. New York: Oxford University Press, 1998:669-92.
49. Lyda W, Eriksen N, Krishna N. Studies of Bruch's membrane: flow and permeability studies in a Bruch's membrane-choroid preparation. Am J Ophthalmol 1957;44:362-9.
50. Starita C, Hussain AA, Pagliarini S, Marshall J. Hydrodynamics of ageing Bruch's membrane: implications for macular disease. Exp Eye Res 1996;62:565-72.
51. Gilmore AP. Anoikis. Cell Death Differ 2005;12:Suppl 2:1473-7.
52. Charbel Issa P, Scholl HP, Holz FG, Knolle P, Kurts C. The complement system and its possible role in the pathogenesis of age-related macular degeneration (age-related macular degeneration). Ophthalmologe 2005;102:1036-42. (In German.)
53. Wolfrüm M. Beitraege zur Anatomie und Histologie der Aderhaut beim Menschen und bei hoeheren Wirbeltieren. Graefes Arch Clin Exp Ophthalmol 1908;67:307-59.
54. Penfold PL, Killingsworth MC, Sarks SH. Senile macular degeneration: the involvement of immunocompetent cells. Graefes Arch Clin Exp Ophthalmol 1985;223:69-76.
55. Penfold PL, Liew SC, Madigan MC, Provis JM. Modulation of major histocompatibility complex class II expression in retinas with age-related macular degeneration. Invest Ophthalmol Vis Sci 1997;38:2125-33.
56. Duvall J, Tso MO. Cellular mechanisms of resolution of drusen after laser coagulation: an experimental study. Arch Ophthalmol 1985;103:694-703.
57. Guymer RH, Bird AC, Hageman GS. Cytoarchitecture of choroidal capillary endothelial cells. Invest Ophthalmol Vis Sci 2004;45:1660-6.
58. Cousins SW, Espinosa-Heidmann DG, Csaky KG. Monocyte activation in patients with age-related macular degeneration: a biomarker of risk for choroidal neovascularization? Arch Ophthalmol 2004;122:1013-8.
59. Bonnet M, Pingault C, Tapissier J. Gradual disappearance of macular hyalin verrucosities. Arch Ophtalmol (Paris) 1976;36:465-74. (In French.)
60. Ahmed J, Braun RD, Dunn R Jr, Linsenmeier RA. Oxygen distribution in the macaque retina. Invest Ophthalmol Vis Sci 1993;34:516-21.
61. Yu DY, Cringle SJ. Outer retinal anoxia during dark adaptation is not a general property of mammalian retinas. Comp Biochem Physiol A Mol Integr Physiol 2002;132:47-52.
62. Sarks SH. Changes in the region of the choriocapillaris in ageing and degeneration. In: Shimizu K, ed. XXIII Concilium Ophthalmologicum, Kyoto 1978, acta. Vol. 1. Amsterdam: Excerpta Medica, 1979:228-38.
63. Korte GE, Reppucci V, Henkind P. RPE destruction causes choriocapillary atrophy. Invest Ophthalmol Vis Sci 1984;25:1135-45.
64. Grimm C, Wenzel A, Groszer M, et al. HIF-1-induced erythropoietin in the hypoxic retina protects against light-induced retinal degeneration. Nat Med 2002;8:718-24.
65. D'Amore PA. Mechanisms of retinal and choroidal neovascularization. Invest Ophthalmol Vis Sci 1994;35:3974-9.
66. Spilsbury K, Garrett KL, Shen WY, Constable IJ, Rakoczy PE. Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal

neovascularization. Am J Pathol 2000;157:135-44. [Erratum, Am J Pathol 2000;157:1413.]
67. Peto R, Doll R. There is no such thing as aging. BMJ 1997;315:1030-2.
68. Powell DE. There is no such thing as ageing: ageing has been defined as to grow or make old. BMJ 1998;316:1531.
69. Haddad S, Chen CA, Santangelo SL, Seddon JM. The genetics of age-related macular degeneration: a review of progress to date. Surv Ophthalmol 2006;51:316-63.
70. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419-21.
71. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308:385-9.
72. Edwards AO, Ritter R III, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308:421-4.
73. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A 2005;102:7227-32.
74. Despriet DD, Klaver CC, Witteman JC, et al. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. JAMA 2006;296:301-9.
75. Schmidt S, Hauser MA, Scott WK, et al. Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. Am J Hum Genet 2006;78:852-64.
76. Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet 2006;38:458-62.
77. Jakobsdottir J, Conley YP, Weeks DE, Mah TS, Ferrell RE, Gorin MB. Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet 2005;77:389-407.
78. Rivera A, Fisher SA, Fritsche LG, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. Hum Mol Genet 2005;14:3227-36.
79. Klaver CC, Kliffen M, van Duijn CM, et al. Genetic association of apolipoprotein E with age-related macular degeneration. Am J Hum Genet 1998;63:200-6. [Erratum, Am J Hum Genet 1998;63:1252.]
80. Baird PN, Guida E, Chu DT, Vu HT, Guymer RH. The epsilon2 and epsilon4 alleles of the apolipoprotein gene are associated with age-related macular degeneration. Invest Ophthalmol Vis Sci 2004;45:1311-5.
81. Schmidt S, Saunders AM, De La Paz MA, et al. Association of the apolipoprotein E gene with age-related macular degeneration: possible effect modification by family history, age, and gender. Mol Vis 2000;6:287-93.
82. Allikmets R, Shroyer NF, Singh N, et al. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science 1997;277:1805-7.
83. Allikmets R. Further evidence for an association of ABCR alleles with age-related macular degeneration. Am J Hum Genet 2000;67:487-91.
84. Gass JD. Drusen and disciform macular detachment and degeneration. Trans Am Ophthalmol Soc 1972;70:409-36.
85. Melrose MA, Magargal LE, Lucier AC. Identical twins with subretinal neovascularization complicating senile macular degeneration. Ophthalmic Surg 1985;16:648-51.
86. Meyers SM, Zachary AA. Monozygotic twins with age-related macular degeneration. Arch Ophthalmol 1988;106:651-3.
87. Dosso AA, Bovet J. Monozygotic twin brothers with age-related macular degeneration. Ophthalmologica 1992;205:24-8.
88. Piguet B, Wells JA, Palmvang IB, Wormald R, Chisholm IH, Bird AC. Age-related Bruch's membrane change: a clinical study of the relative role of heredity and environment. Br J Ophthalmol 1993;77:400-3.
89. Klein ML, Mauldin WM, Stoumbos VD. Heredity and age-related macular degeneration: observations in monozygotic twins. Arch Ophthalmol 1994;112:932-7.
90. Seddon JM, Ajani UA, Mitchell BD. Familial aggregation of age-related maculopathy. Am J Ophthalmol 1997;123:199-206.
91. Seddon JM, Cote J, Page WF, Aggen SH, Neale MC. The US twin study of age-related macular degeneration: relative roles of genetic and environmental influences. Arch Ophthalmol 2005;123:321-7.
92. Klaver CC, Wolfs RC, Assink JJ, van Duijn CM, Hofman A, de Jong PT. Genetic risk of age-related maculopathy: population-based familial aggregation study. Arch Ophthalmol 1998;116:1646-51.
93. Assink JJ, Klaver CC, Houwing-Duistermaat JJ, et al. Heterogeneity of the genetic risk in age-related macular disease: a population-based familial risk study. Ophthalmology 2005;112:482-7.
94. Souied EH, Benlian P, Amouyel P, et al. The epsilon4 allele of the apolipoprotein E gene as a potential protective factor for exudative age-related macular degeneration. Am J Ophthalmol 1998;125:353-9.
95. Rodriguez de Cordoba S, Esparza-Gordillo J, Goicoechea de Jorge E, Lopez-Trascasa M, Sanchez-Corral P. The human complement factor H: functional roles, genetic variations and disease associations. Mol Immunol 2004;41:355-67.
96. Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2006;51:137-52.
97. Leys A, Vanrenterghem Y, Van Damme B, Snyers B, Pirson Y, Leys M. Fundus changes in membranoproliferative glomerulonephritis type II: a fluorescein angiographic study of 23 patients. Graefes Arch Clin Exp Ophthalmol 1991;229:406-10.
98. Collard CD, Vakeva A, Morrissey MA, et al. Complement activation after oxidative stress: role of the lectin complement pathway. Am J Pathol 2000;156:1549-56.
99. Magnusson KP, Duan S, Sigurdsson H, et al. CFH Y402H confers similar risk of soft drusen and both forms of advanced age-related macular degeneration. PLoS Med 2006;3(1):e5.
100. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. Eye 2005;19:935-44.
101. Evans JR, Fletcher AE, Wormald RP. 28,000 Cases of age related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking. Br J Ophthalmol 2005;89:550-3.
102. Tomany SC, Wang JJ, Van Leeuwen R, et al. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. Ophthalmology 2004;111:1280-7.
103. Hammond BR Jr, Wooten BR, Snodderly DM. Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration. Vision Res 1996;36:3003-9.
104. Sastry BV, Hemontolor ME. Influence of nicotine and cotinine on retinal phospholipase A2 and its significance to macular function. J Ocul Pharmacol Ther 1998;14:447-58.
105. Espinosa-Heidmann DG, Suner IJ, Catanuto P, Hernandez EP, Marin-Castano ME, Cousins SW. Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry age-related macular degeneration. Invest Ophthalmol Vis Sci 2006;47:729-37.
106. Guymer R, Bird AC. Bruch's membrane, drusen, and age-related macular degeneration. In: Marmor MF, Wolfensberger TJ, eds. The retinal pigment epithelium: function and disease. New York: Oxford University Press, 1998:693-705.
107. DeCaprio AP. The toxicology of hydroquinone — relevance to occupational and environmental exposure. Crit Rev Toxicol 1999;29:283-330.
108. Monks TJ, Jones DC. The metabolism and toxicity of quinones, quinonimines, quinone methides, and quinone-thioethers. Curr Drug Metab 2002;3:425-38.

109. Taylor HR, West S, Munoz B, Rosenthal FS, Bressler SB, Bressler NM. The long-term effects of visible light on the eye. Arch Ophthalmol 1992;110:99-104.
110. Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmology 1998;105:1359-63.
111. Margrain TH, Boulton M, Marshall J, Sliney DH. Do blue light filters confer protection against age-related macular degeneration? Prog Retin Eye Res 2004; 23:523-31.
112. Organisciak DT, Winkler BS. Retinal light damage: practical and theoretical considerations. Prog Retin Eye Res 1994; 13:1-24.
113. Reme CE, Hafezi F, Marti A, Munz K, Reinboth JJ. Light damage to retina and pigment epithelium. In: Marmor MF, Wolfensberger TJ, eds. The retinal pigment epithelium: function and disease. New York: Oxford University Press, 1998: 563-86.
114. Reme CE. The dark side of light: rhodopsin and the silent death of vision: the Proctor Lecture. Invest Ophthalmol Vis Sci 2005;46:2671-82.
115. Grimm C, Wenzel A, Hafezi F, Yu S, Redmond TM, Reme CE. Protection of Rpe65-deficient mice identifies rhodopsin as a mediator of light-induced retinal degeneration. Nat Genet 2000;25:63-6.
116. Terman M, Reme CE, Rafferty B, Gallin PF, Terman JS. Bright light therapy for winter depression: potential ocular effects and theoretical implications. Photochem Photobiol 1990;51:781-92.
117. Gaillard ER, Atherton SJ, Eldred G, Dillon J. Photophysical studies on human retinal lipofuscin. Photochem Photobiol 1995;61:448-53.
118. Algvere PV, Marshall J, Seregard S. Age-related maculopathy and the impact of blue light hazard. Acta Ophthalmol Scand 2006;84:4-15.
119. Kim SR, Fishkin N, Kong J, Nakanishi K, Allikmets R, Sparrow JR. Rpe65 Leu450Met variant is associated with reduced levels of the retinal pigment epithelium lipofuscin fluorophores A2E and iso-A2E. Proc Natl Acad Sci U S A 2004;101: 11668-72.
120. Savill J, Dransfield I, Gregory C, Haslett C. A blast from the past: clearance of apoptotic cells regulates immune responses. Nat Rev Immunol 2002;2:965-75.
121. McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. Ann N Y Acad Sci 2004;1035:104-16.
122. Davies NP, Morland AB. Macular pigments: their characteristics and putative role. Prog Retin Eye Res 2004;23:533-59.
123. Jung H, Reme C. Light-evoked arachidonic acid release in the retina: illuminance/duration dependence and the effects of quinacrine, mellitin and lithium: light-evoked arachidonic acid release. Graefes Arch Clin Exp Ophthalmol 1994; 232:167-75.
124. Reinboth JJ, Gautschi K, Clausen M, Reme CE. Lipid mediators in the rat retina: light exposure and trauma elicit leukotriene B4 release in vitro. Curr Eye Res 1995; 14:1001-8.
125. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2000;45: 115-34.
126. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-36.
127. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 2005;294:3101-7.