PERSPECTIVE

Changing Face of Microglia

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Microglia are resident brain cells that sense pathological tissue alterations. They can develop into brain macrophages and perform immunological functions. However, expression of immune proteins by microglia is not synonymous with inflammation, because these molecules can have central nervous system (CNS)–specific roles. Through their involvement in pain mechanisms, microglia also respond to external threats. Experimental studies support the idea that microglia have a role in the maintenance of synaptic integrity. Analogous to electricians, they are capable of removing defunct axon terminals, thereby helping neuronal connections to stay intact. Microglia in healthy CNS tissue do not qualify as macrophages, and their specific functions are beginning to be explored.

Microglia are less numerous than neuroglia but about as common as nerve cells. However, until 1991, a leading textbook of neuropathology stated (at the beginning of its chapter on microglia) that "... the microglia have become the most controversial element of the central nervous system; indeed, their very existence is in doubt," and the chapter concluded, "... the term 'microglia,' which implies a single distinct cell system, is misleading and no longer applicable" (*1*). Less than 20 years and more than 11,000 publications later, the microglia field has developed into a very active branch of neuroscience.

Microglial cells have an extremely plastic, chameleon-like phenotype (Fig. 1). This was demonstrated conclusively with the advent of lectin and antibody markers, which label all microglial activation stages and their successful application in experimental models such as the facial nucleus axotomy paradigm. As a result, the historical controversy surrounding the "nature and identity" of microglial cells that had lasted for decades was resolved, and the microglial cell type became firmly established. Before special stains were available, anatomists would see ramified microglia but could see "amoeboid" (macrophagelike) microglia only during central nervous system (CNS) development, whereas pathologists would encounter brain macrophages in different types of CNS lesions but rarely make the connection to ramified microglia as the source. The recent debate about seemingly contradictory neurotrophic and neurotoxic properties of microglia has to be viewed against the backdrop of microglial plasticity. Opposite biological effects of one and the same cell type are well established for macrophages (*2*).

Although the activity of microglia in immunological disease states (such as multiple sclerosis) and in the removal of myelin debris is in line with their pathological role as macrophages and antigen-presenting cells, the discovery of microglial involvement in neurogenesis, postlesional "synaptic stripping," and neuropathic pain underscores the existence of additional, functionally adapted microglial phenotypes. The present review attempts to highlight aspects of this emerging face of microglial cells.

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The Microglial Immune Network Senses Threats to the CNS

In addition to their marked functional plasticity, microglial cells are characterized by a very low threshold of activation. They respond to even minor pathological challenges that affect the CNS (*3*), directly or indirectly. An early report on microglial activation detailed the detection of increased expression of complement receptors following a peripheral nerve lesion (*4*), demonstrating that a remote, sterile stimulus is a sufficient trigger for microglial activation. Microglial activation (*5*) occurs within minutes (*6*) but can be long-lasting. It is difficult to imagine any brain or spinal cord pathology without a microglial response. Based on this principle, an entirely new approach to cell type–specific nervous system imaging was developed by Banati *et al*. (see Fig. 2). However, the activation of microglia is anything but an unspecific process. The wide range of microglial response patterns and the great malleability of the microglial phenotype appear to be the result of the cells' ability to respond in a very graded manner to changes in their environment (Fig. 1) (*7*).

The microglial immune network has to be understood as a figurative system for catching or entrapping pathogens, because, in a strictly anatomical sense, microglial cells are not connected like neuroglia. Research has failed to demonstrate gap junctions between microglia in vivo at the ultrastructural level, although one study has suggested their existence under pathological conditions (*8*). In line with this anatomical constraint, the microglial response to lesions mirrors the location of an insult far more precisely than that of astrocytes, which, unlike microglia, establish a syncytial network. In other words, microglial cells are more individualistic and keep their distance from each other while covering their own surveillance territory. Because of this absence of direct intercellular coupling, microglial cell communication may have to rely more on auto- or parakrine mechanisms, as well as on purine and glutamate gradients (*9*).

The cell processes of normal microglia are mobile and scan their microenvironment, even in healthy state (*10*). Therefore, "resting" microglia are sessile, but they are not inactive cells (*10*). Consequently, the use of the term "resting microglia" without further explanation should be discouraged. Motility (that is, migration) of microglial cells is not usually observed in healthy CNS tissue, and the available literature suggests that when microglia become motile, considerable damage to CNS tissue has occurred, requiring structural and functional repair. In contrast, perivascular cells (*11*), which are resident in the Virchow-Robin spaces, can migrate and are constantly renewed from the bone marrow. Unlike most tissue macrophages, microglia have retained their proliferative potential. Perivascular cells constitutively express several molecules required for antigen presentation (*11*) and form an immunological blood-brain barrier. In contrast, microglia respond to threats to the CNS parenchyma proper and only express molecules such as major histocompatibility complex (MHC) antigens on demand. The expression of MHC class II molecules in human neurodegenerative diseases, which might be perceived as a nonspecific microglial reaction because it is so common, may in reality represent an important and, therefore, conserved mechanism to protect brain tissue that is already at risk (*12*). This view is supported by the intriguing finding that a human-specific gene expressed in cortical microglia, *SIGLEC11* (*13*), serves to mediate immunosuppressive signals and inhibits the function of microglial pattern-recognition receptors (*14*). The underlying human-specific gene conversion event has been said to be related to the evolution of the genus *Homo* (*13*), in keeping with the uniquely human evolution of sialic acid biology (*15*). Activation of the brain's microglial cells during systemic disease can provide an explanation for the feeling of illness and associated sickness behavior (*16*).

Activation of Microglia Can Be Painful

The role of microglia in the initiation of neuropathic pain appears to be crucial (*17*, *18*). Neuropathic pain that occurs after peripheral nerve injury depends on the hyperexcitability of neurons in the dorsal horn of the spinal cord (*18*). At least five paths seem to exist that can lead to microglial activation in neuropathic nociceptive states, and the relevant molecular pathways include fractalkine, interferon-γ, monocyte chemoattractant protein–1, TLR4, and P2X4 as the main signaling mediator and/or receptor (*17*). In addition, microglial P2X7Rs and their downstream signaling pathways play a pivotal role in the induction of spinal long-term potentiation (LTP) and persistent pain induced by tetanic stimulation, which produces LTP of C-fiber–evoked field potentials in the spinal cord (*19*). Activation of

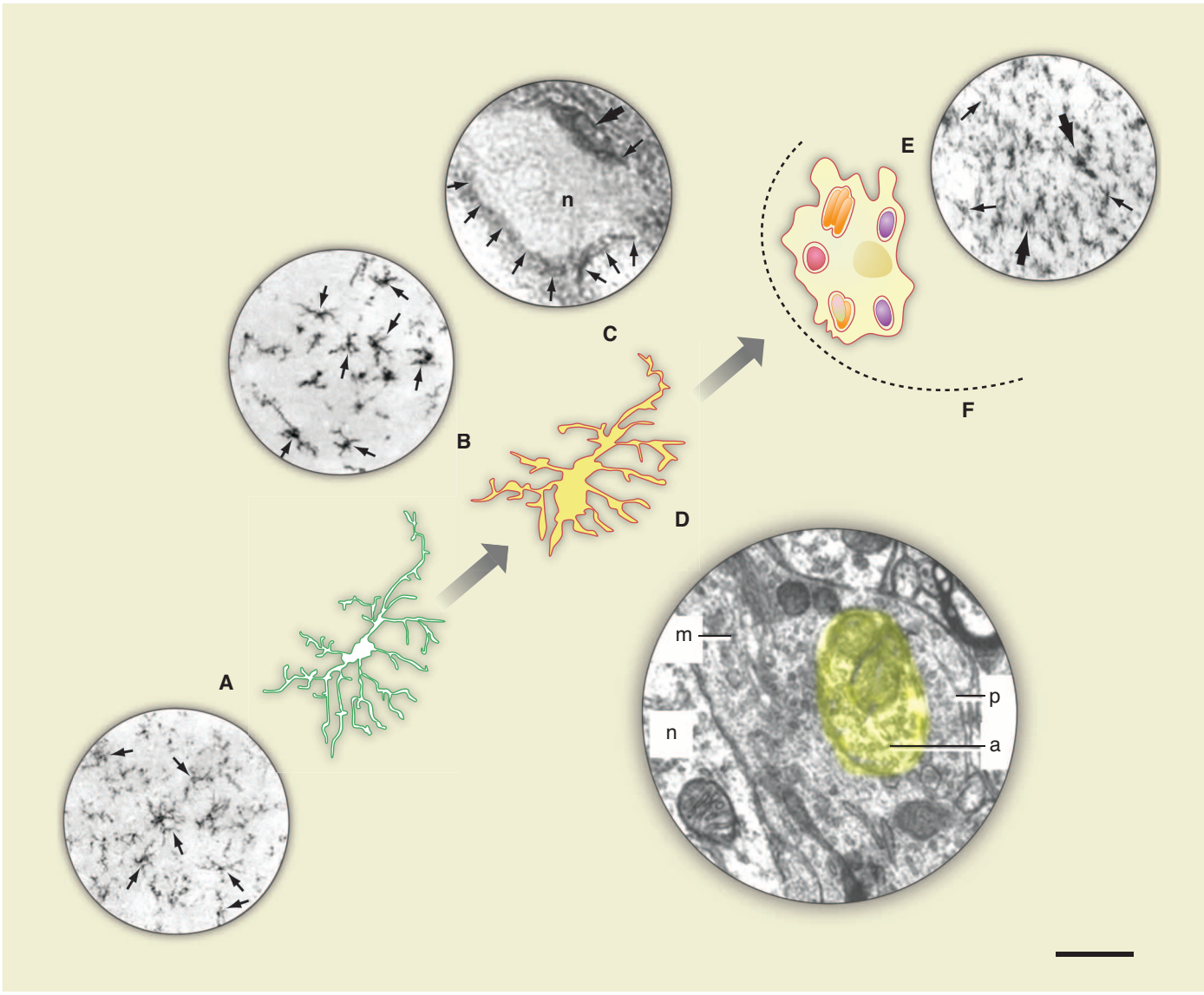

Fig. 1. Schematic drawing showing the microglial activation cascade and associated phenotypic plasticity [modified from (*7*)]. (**A**) Ramified "resting" microglia (arrows) in the normal rat facial nucleus labeled with the use of the OX-42 monoclonal antibody, which recognizes the rat equivalent of human CD11b, the iC3b complement receptor. (**B**) Activated microglia (arrows), still ramified but with stouter cell processes 24 hours after facial nerve axotomy. (**C**) OX-42 immunoreactive perineuronal microglial cell (large arrow) and microglial processes (small arrows) apposed to a regenerating facial motor neuron (n) 4 days post axotomy [(A to C) taken from figures 1 and 2 of Graeber *et al*. (*4*)]. (**D**) Image from day 4 after facial nerve axotomy, a microglial cell process (m) on the surface of a regenerating facial motoneuron (n). Two short pseudopods (p) can be seen arising from the microglial cell process embracing a displaced axonal terminal [a, yellow; from figure 5 of Blinzinger and Kreutzberg (*28*)]. (**E**) Macrophages can develop from activated microglia, but this transformation is tightly controlled in vivo; that is, there is a substantial threshold that needs to be overcome [symbolized in (**F**)]. OX-42 labeling of phagocytic facial nucleus microglia (larger arrows) [taken from figure 2 of Graeber *et al*. (*53*)]. Scale bar: 50 μm in (A), (B), and (E); 30 μm in (C); 2 μm in (D).

microglia in the trigeminal subnucleus caudalis has been implicated in the central mechanisms of pain associated with dental inflammation (*20*), and microglial activation has also been observed in the hypothalamic paraventricular nucleus after myocardial infarction (*21*). There is an intimate association between the spinal microglia-expressed P2X7R and the development of morphine tolerance (*22*).

The microglial involvement in pain mechanisms may be viewed as an extension of the microglial sensor function in pathologically altered tissue. Microglia appear to respond to internal and external threats to the entire body that are related but not always limited to the relevant neuronal projection area. Chronic stress increases the number of microglia in certain stress-sensitive brain regions (*23*). Collectively, microglial cells function as guardians of the brain and spinal cord, acting not only as a tissue alarm system but also exerting defense, as well as repair functions (*24*). Strongly activated microglia are capable of producing a broad spectrum of responses to stimuli in the same way as shown for peripheral macrophages (*5*). However, microglia that react to nociceptive stimuli are not necessarily inflammatory cells. Immune mediators can be produced by microglia under various conditions. Therefore, caution has to be exercised when interpreting this finding as microglial "inflammation." Increasing evidence suggests that many immune proteins

have brain-specific functions during development and synaptic plasticity (*25*).

Electricians in the Brain: Microglia Help to Maintain the Integrity of Synapses

In healthy CNS and in the vast majority of known CNS diseases, microglia do not present as macrophages. Therefore, their day-to-day function is different. Interestingly, nonphagocytic activated microglia also show an affinity for neuronal membranes. The initial evidence for this behavior came from studies by Nissl on the relation between nerve cell diseases and glial appearances in the cortex in different psychoses (*26*). His report on "strung-out, often infinitely long, extremely slim glial cells" that "may cross the entire layer of the large pyramidal neurons" represents the first description of microglia that were discovered in their activated state. Microglial rod cells typically align with apical dendrites, often extending to adjacent neuronal surfaces and even wrapping somatic membranes (Fig. 3). Clinically, cortical rod cells are associated with an acutely dementing process that appears to be reversible, in principle, as demonstrated by the successful treatment of patients suffering from early stages of general paralysis of the insane. Most contemporary researchers will be unfamiliar with microglial rods, because neurosyphilis has become very rare in developed countries. However, general paralysis of the insane affected roughly 1 in 10 hospitalized psychiatric patients in Alois Alzheimer's time, and he wrote his habilitation thesis on this topic. Other well-known acute psychopathologies associated with microglial rod cells are lead encephalopathy, subacute sclerosing panencephalitis (SSPE), and various forms of viral encephalitis, including HIV-1. The virally induced fusion of microglia to neurons has been demonstrated in an experimental model. The authors argue that the consistent location of the fusion to apical dendrites and the lack of fusion to other neural cell types, both in vitro and in vivo, suggest a unique interaction that may exist between microglia and the dendrites of neurons (*27*). These dendrites are normally covered with afferent axon terminals. The displacement of synaptic terminals by microglial cells was first reported in the context of motor neuron regeneration in the brain stem (Fig. 1D) (*28*), but synaptic stripping also takes place in the cerebral cortex (*29*), and it probably occurs in the human brain as well (*30*).

Microglia are not electrotonically coupled like neuroglial cells. This biophysical independence probably allows microglia to stay outside the normal activity of neural circuits, enabling them to support the maintenance of synaptic connections analogous to electricians. An electrician maintains and installs electrical equipment but does not form part of the actual circuitry. In line with this idea, Wake *et al.* have proposed that microglia vigilantly monitor and respond to the functional state of synapses (*10*). This work

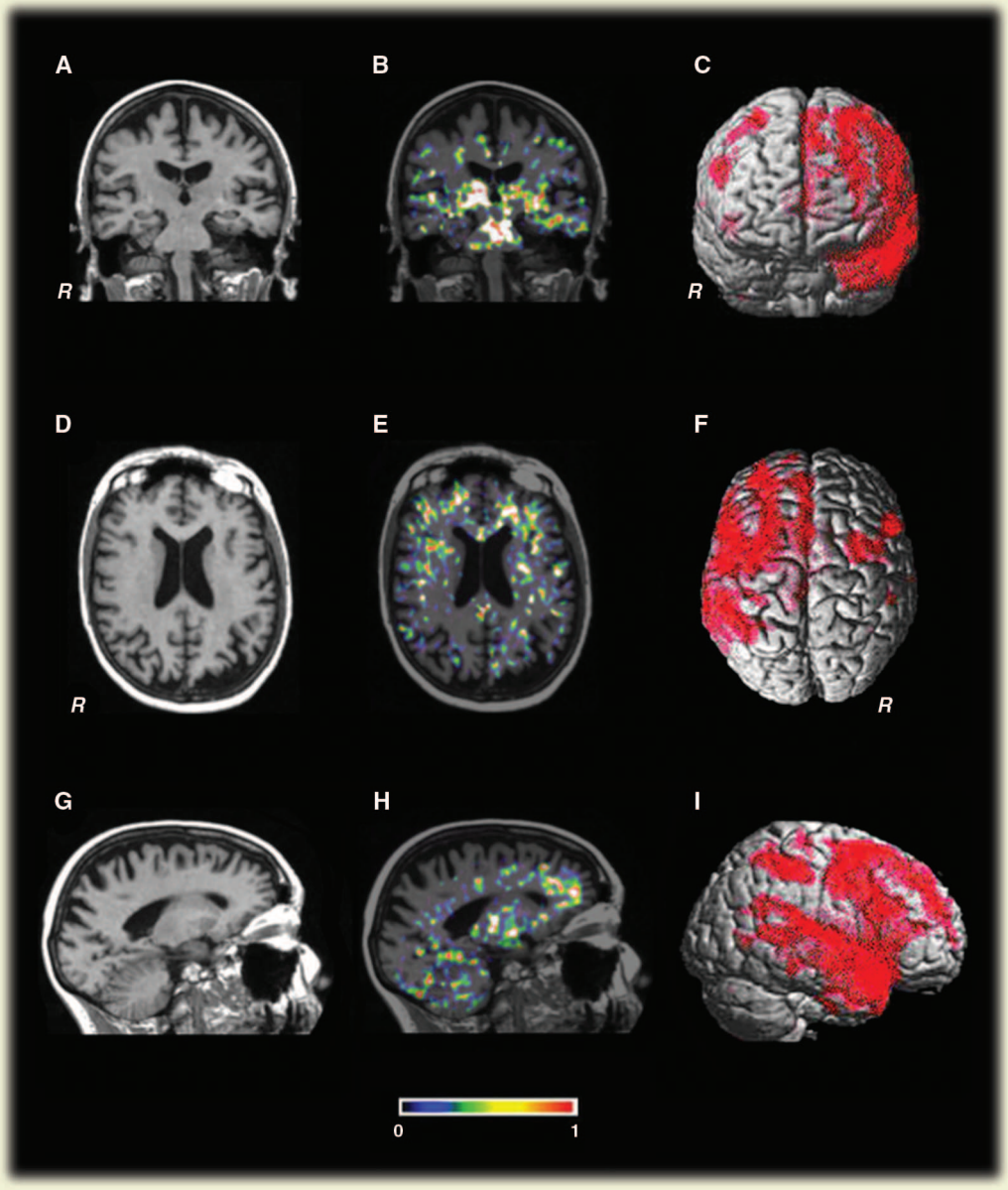

Fig. 2. [^{11}C](R)-PK11195 positron emission tomography images of a patient with predominantly left-hemispheric frontotemporal lobar dementia (age, 69 years; disease duration, 3 years) (**B**, **E**, **H**) coregistered to the same patient's magnetic resonance imaging scans (**A**, **D**, **G**). The red in the volume-render magnetic resonance imaging scans (**C**, **F**, **I**) indicates areas of substantial atrophy. These areas overlap with the regional pattern of increased [^{11}C](R)-PK11195 signal. At the bottom of the image, the color bar denotes [^{11}C](R)-PK11195 binding potential values between 0 and 1. The images are shown in radiological convention; that is, the left side of the image is the right of the patient, indicated by *R*. (F) Top-down view onto the cortex with the right side of the image also being the right of the patient. (G and H) Sagittal sections through the left hemisphere. [Courtesy of R. B. Banati, Sydney (*54*)]

demonstrates that microglia sense defunct synapses and eliminate them, a finding that is highly reminiscent of the posttraumatic synaptic stripping that affects motoneurons, as reported by Blinzinger and Kreutzberg more than 40 years ago (*28*). Interestingly, the classical complement cascade has been suggested to mediate the elimination of synapses in the CNS (*31*), and microglia involved in synaptic stripping strongly up-regulate complement receptors (*4*). However, there is no visible phagocytosis of axon terminals by microglia in either model (*10*, *28*), rendering retraction of the unused axon terminals a possibility. All resting microglia express complement receptor 3 (CD11b) (*21*), but additional pathways are likely to be involved in microglia-synaptic interactions. Microglial cells may also control synaptogenesis. This is suggested by the observation that a mutation in KARAP/DAP12, a key protein of microglial activation, influences synaptic functions in the hippocampus, as well as synaptic protein content (*32*). Moreover, it has been demonstrated that microglial brain-derived neurotrophic factor directly regulates synaptic properties in the spinal cord (*18*, *32*).

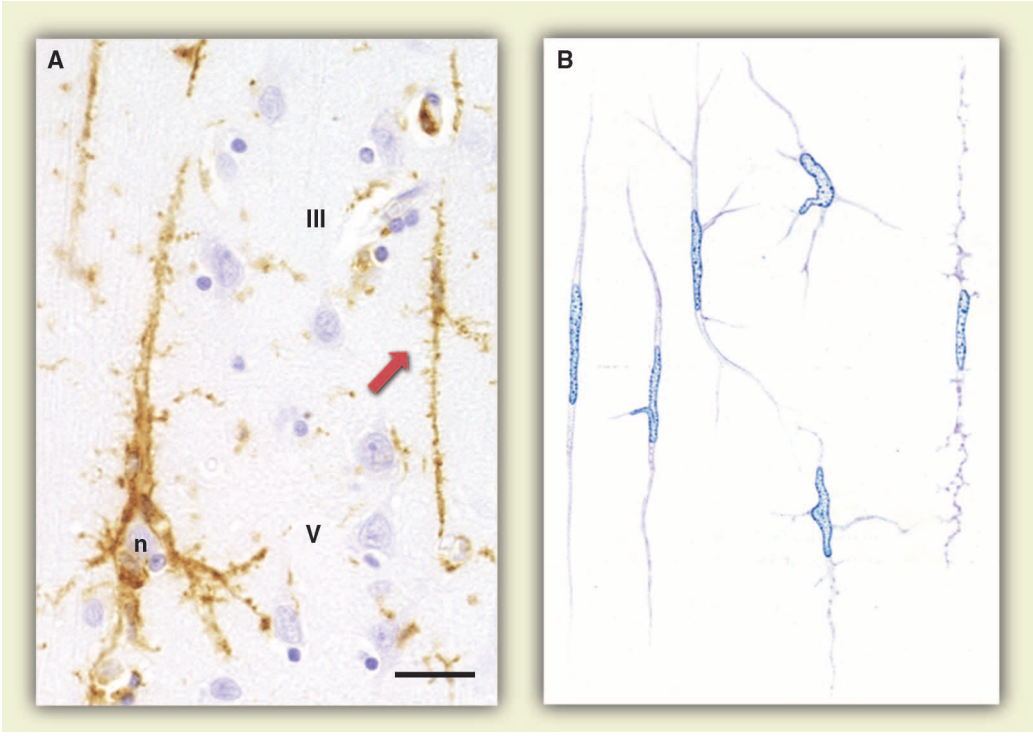

Fig. 3. Microglial rod cells expressing MHC class II molecules in a case of SSPE (**A**) and rod cells (**B**), as depicted by Spielmeyer (*55*). The arrow in (A) points to a single rod cell. "n" denotes a pyramidal neuron that is tightly wrapped by microglial cell processes; "III" and "V" indicate cortical layers. Human cerebral cortex is labeled with the use of the CR3/43 monoclonal antibody that recognizes the beta-chain of HLA-DR, DQ, and DP. Microglial rod cells arguably represent the most intriguing microglial phenotype, because they are typically found in the cerebral cortex in association with cognitive symptoms; they show a great affinity for neuronal surfaces and, notably, dendrites; they are not normally phagocytic; they adjust their shape to an extreme extent; and they represent the longest known but least investigated microglial phenotype. Scale bar: 60 μm.

Diseases That Make Microglia Sick

Neurodegenerative diseases are common and are caused by primary dysfunction and subsequent death of nerve cells. There are compelling reasons to complement this concept with that of primary gliodegeneration. This terminology is clearly preferable over "non–cell-autonomous degeneration," because the latter needs to be distinguished from glial non–cell-autonomous effects on neurons (that is, glial gain-of-function mutations that are toxic on nerve cells). Microglial non–cell-autonomous effects on neurons have been reported in a number of conditions. Microglial gain-of-function mutations: Mutant mSOD1G93A (where G93A is $Gly^{93} \rightarrow Ala^{93}$) microglia are cytotoxic (*33*), a phenomenon long known from virus-infected mononuclear phagocytes that secrete neurotoxins when infected with HIV-1. Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate (*34*). However, microglial loss of function ("insufficiency") also occurs. An example of microglial loss-of-function mutations can be found in Nasu-Hakola disease, which is a cognitive disorder caused by a primary defect of CNS microglia (*35*). It is due to a mutation in the *DAP12* or *TREM2* gene (*36*). The adaptor protein DAP12 is critical for the activity of mononuclear phagocytes. DAP12-mutant mice and humans show dysfunction of osteoclasts and microglia, as well as bone and brain abnormalities (*37*). Otero *et al.* (*37*) found substantially fewer microglia in the basal ganglia and the spinal cord of older DAP12-deficient mice, and those detectable showed extensive cytoplasmic fragmentation (cytorrhexis) and nuclear condensation characteristic of microglial degeneration and apoptotic cell death. Microglia are also affected in Creutzfeldt-Jakob disease (Fig. 4A), a noninfectious but transmissible condition, which may explain the failure to detect microglial involvement in the synaptic loss observed in prion disease (*38*). Thus, primary as well as secondary microgliopathic states have to be considered an alternative to "microglial activation" when phenotypic changes of microglia in pathological tissue are analyzed.

Is the Only Bad Microglial Cell a Dead Microglial Cell?

Microglia can kill exogenous pathogens. They are the cellular defense system of the brain and the spinal cord. Microglia also play a role in developmental neuronal death: for example, in the hippocampus, which requires the microglial CD11b integrin and the DAP12 immunoreceptor (*39*). Diseased microglia can turn into aggressors, as mentioned earlier, but the fact that microglial insufficiency itself causes disease provides a strong argument in favor of normal microglia being necessary and exerting a neurosupportive, rather than a neurotoxic, effect by default. Lack of preservation of tissue structure is an important determinant for the formation of microglia-derived macrophages. If there is extensive cellular damage or tissue necrosis, only phagocytic microglia/macrophages can be found. However, as the example of the microglial rod cell shows, the interaction of activated microglia with nerve cells does not automatically result in killing and phagocytosis. This sparing of neurons by reactive microglia also argues against the view that microglial cells are a threat to nerve cells as soon as they become activated. Indeed, synaptic stripping is associated with regeneration of motor neurons (*28*) and probably serves a protective function in the inflamed cerebral cortex (*29*). Therefore, the catchphrase statement that the only bad microglial cell is a dead microglial cell (*24*) appears justified in principle. For instance, in Alzheimer's disease, dystrophic (senescent), rather than activated, microglial cells are associated with tau pathology and likely precede neurodegeneration (Fig. 4C) (*40*). The emphasis in the literature on microglial neurotoxic prop-

erties seems arbitrary and more related to the high prevalence of Alzheimer's and Parkinson's diseases than actual pathophysiological evidence confirming that microglia pose a threat to neurons in vivo. It only adds to the confusion surrounding microglial neurotoxicity that the claim is often made in conjunction with the proposal that the expression of molecules that are of immunological importance in peripheral organs constitutes evidence of microglial "inflammation," in the absence of cells of the peripheral immune system. Current data support the idea that inflammatory mediators, which enhance the phenotypic and immunological activation of glia, do not promote Aβ accumulation but limit Aβ deposition (*41*). Therefore, we agree that the loss of microglial normal functions is sufficient to explain a range of disease conditions without the need to interpret microglial expression of immune molecules as evidence of inflammation.

Abnormal Behavior Caused by Mutant Microglia

Hoxb8 mutant mice show behavior reminiscent of humans with the obsessive-compulsive disorder trichotillomania (that is, these mice compulsively remove their hair). In these animals, the behavioral disorder is associated with mutant microglia (*42*). However, only a subpopulation of microglia that originate postnatally in the bone marrow and predominantly populate brain regions relevant to the syntactic groom chain (such as the cortex, striatum, and brainstem) are affected. This anatomical selectivity seems surprising at first but is not unheard of in relation to microglia: Although osteoclasts and spleen macrophages are entirely dependent on macrophage colony-stimulating factor (M-CSF), microglia require M-CSF only in specific areas of the CNS, and DAP12 deficiency exclusively affects microglia in restricted locations in the CNS, such as the basal ganglia and spinal cord (*37*). It is also worth noting that microglia display brain region–specific functional diversity (*43*). The Hoxb8 study is of major importance, because it directly links functional insufficiency of bone marrow–derived microglia to abnormal behavior.

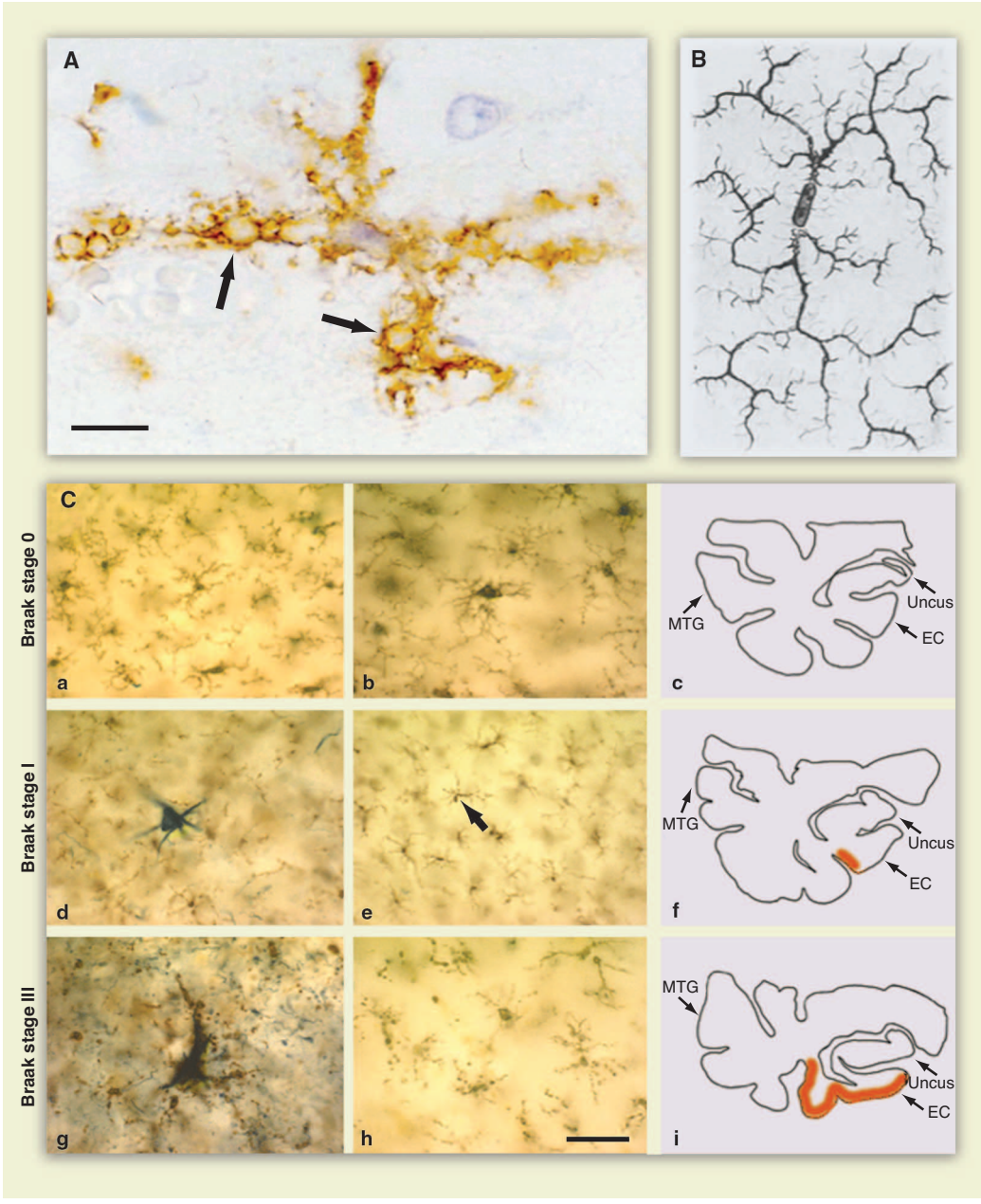

Fig. 4. (**A**) MHC class II immunoreactive "sick" microglial cell severely affected by spongiform change in Creutzfeldt-Jakob disease. The arrows point to large vacuoles that have destroyed the normal structure of the microglial cell processes. Scale bar: 10 μm. [Reproduced with permission from the *Journal of Neuropathology and Experimental Neurology* (*56*)] (**B**) Rio-Hortega's drawing of a microglial cell (*57*). There are no vacuoles in normal state [compare with (A)], nor is there any fragmentation of cell processes [compare with (C)]. (**C**) Microglial fragmentation precedes the spread of tau pathology in the temporal lobe of Alzheimer's patients. Double-label immunohistochemistry for microglia (iba1) and tau (AT8) is shown in three subjects with tau pathology increasing from Braak stage 0 to stage III. Camera lucida drawings of the actual sections are shown in (c), (f), and (i), indicating the uncus for orientation purposes, as well as both sampling areas in the entorhinal cortex (EC) and the middle temporal gyrus (MTG); areas of tau pathology are shaded orange. Representative micrographs of the EC (a, d, g) and MTG (b, e, h) reveal microglia (brown) and tau pathology (black) at the different stages. Normal ramified microglia are evident at stage 0 in both EC and MTG in the absence of tau pathology (a, b). Mostly fragmented microglia are seen in association with a neurofibrillary tangle and neuropil threads in (d), whereas mostly ramified and only a single fragmented cell (arrow) are present in (e) during stage I. Severe microglial fragmentation and loss of discernable cell shape are colocalized with extensive tau pathology in (g); microglial processes are fragmented also in (h) in the absence of neurodegeneration, but cells retain recognizable contours. Scale bar: 50 μm (a, b, d, e, g, h). [Reproduced from (*40*) with permission]

Microglia may be involved in other psychiatric conditions. For instance, there is evidence for activation of microglia in the brains of patients with schizophrenia and affective disorders (*44*). It has been suggested that schizophrenia is a disease that develops because of derangements to human-specific CNS functions that have emerged since our species diverged from nonhuman primates (*45*). The sialic acid–recognizing immunoglobulin-superfamily lectin SIGLEC11—which is expressed in human, but not in chimpanzee, brain microglia (*13*)—was mentioned above. The neural cell adhesion molecule (NCAM) is the predominant carrier of α2,8-polysialic acid (PSA) in the mammalian brain, and abnormalities in PSA and NCAM expression are associated with schizophrenia in humans and cause deficits in hippocampal synaptic plasticity and contextual fear conditioning in mice (*46*).

A Future for Self-Donated Bone Marrow–Derived Microglia

Although there are still questions today in regard to the number of microglial subpopulations in the CNS, it was demonstrated conclusively about a decade ago that ramified CNS microglia can derive from bone marrow precursors, even in adults (*47*). This finding immediately suggested possible new therapeutic avenues, and there are now reports on the successful treatment of CNS diseases by means of bone marrow transplantation. For instance, lentivirus-mediated gene therapy of hematopoietic stem cells has been used with great success in two 7-year-old boys suffering from a rare and fatal brain demyelinating disease (*48*). The ex vivo genetically modified cells were able to reach the CNS and stopped the progressive cerebral demyelination in the two patients, demonstrating the power of such cellular therapy for brain diseases. The Hoxb8 mutant microglia study (*42*) demonstrates that transplantation of normal bone marrow can efficiently rescue the Hoxb8 mutant grooming phenotypes, including restoration of hairless patches, healing of open lesions, and reduction of excessive grooming times back to normal. Bone marrow–derived cells further contribute to the recruitment of microglial cells in response to β-amyloid deposition in APP/PS1 double transgenic Alzheimer's mice (*49*), and it has been suggested that bone marrow–derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease (*50*). Infiltration of bone marrow–derived microglia in high-grade gliomas (*2*, *12*) is also of potential therapeutic importance. Consequently, autologous bone marrow–derived microglia have developed into an attractive target for genetic modification although there are a number of technical issues that still need to be addressed (*51*).

Conclusions

Microglia have come a long way within 20 years, from their existence being questioned (*1*) to providing a potentially very elegant handle on the treatment of higher brain-functional defects (*42*). Yet there are still many white spots on the microglia map: One is the precise extent of microglial turnover in humans (*52*). Trafficking of microglia precursors across the blood-brain barrier could cause brain dysfunction associated with systemic infection. When we feel unwell during a bout of fever, are microglial cell processes becoming wobbly in the brain, weakening their potentially stabilizing effect on neural circuits? Clearly, microglial involvement in synaptic plasticity should become a focus of research. Whether bone marrow–derived microglia (for example, in the brain of Hoxb8-animals) fuse with neurons is unknown, but fusion of macrophages is not a rare event. Glial cells are now accepted to provide more to neurons than mere structural and nutritional support, but genetically modified bone marrow–derived microglia precursors could provide a unique route of entry into the CNS. Genetically enhanced (that is, reprogrammed) microglia might revolutionize the treatment of CNS diseases, one step short of synthetic biology. Thus, the current focus on microglial inflammation as a cause of neurodegeneration appears misplaced.

References and Notes

1. C. L. Dolman, in *Textbook of Neuropathology*, R. L. Davis, D. M. Robertson, Eds. (Williams & Wilkins, Baltimore, MD, 1991), pp. 141–163.
2. A. Sica *et al.*, *Semin. Cancer Biol.* **18**, 349 (2008).
3. G. W. Kreutzberg, *Trends Neurosci.* **19**, 312 (1996).
4. M. B. Graeber, W. J. Streit, G. W. Kreutzberg, *J. Neurosci. Res.* **21**, 18 (1988).
5. C. A. Colton, D. M. Wilcock, *CNS Neurol. Disord. Drug Targets* **9**, 174 (2010).
6. T. Morioka, A. N. Kalehua, W. J. Streit, *J. Cereb. Blood Flow Metab.* **11**, 966 (1991).
7. M. B. Graeber, in *Encyclopedia of Neuroscience*, G. Adelman, B. H. Smith, Eds. (Elsevier, Amsterdam, ed. 3, 2004), article 335.
8. E. A. Eugenín *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 4190 (2001).
9. G. J. Liu, R. Nagarajah, R. B. Banati, M. R. Bennett, *Eur. J. Neurosci.* **29**, 1108 (2009).
10. H. Wake, A. J. Moorhouse, S. Jinno, S. Kohsaka, J. Nabekura, *J. Neurosci.* **29**, 3974 (2009).
11. K. Williams, X. Alvarez, A. A. Lackner, *Glia* **36**, 156 (2001).
12. M. B. Graeber, W. J. Streit, *Acta Neuropathol.* **119**, 89 (2010).
13. T. Hayakawa *et al.*, *Science* **309**, 1693 (2005).
14. A. Salminen, K. Kaarniranta, *J. Mol. Med.* **87**, 697 (2009).
15. A. Varki, *Proc. Natl. Acad. Sci. U.S.A.* **107** (suppl. 2), 8939 (2010).
16. A. W. Lemstra *et al.*, *J. Neuroinflammation* **4**, 4 (2007).
17. H. S. Smith, *Pain Physician* **13**, 295 (2010).
18. J. A. Coull *et al.*, *Nature* **438**, 1017 (2005).
19. Y. X. Chu, Y. Zhang, Y. Q. Zhang, Z. Q. Zhao, *Brain Behav. Immun.* **24**, 1176 (2010).
20. W. Fan *et al.*, *Arch. Oral Biol.* **55**, 706 (2010).
21. I. Rana *et al.*, *Brain Res.* **1326**, 96 (2010).
22. D. Zhou, M. L. Chen, Y. Q. Zhang, Z. Q. Zhao, *J. Neurosci.* **30**, 8042 (2010).
23. R. J. Tynan *et al.*, *Brain Behav. Immun.* **24**, 1058 (2010).
24. W. J. Streit, Q. S. Xue, *J. Neuroimmune Pharmacol.* **4**, 371 (2009).
25. L. M. Boulanger, *Neuron* **64**, 93 (2009).
26. F. Nissl, *Archiv für Psychiatrie* **32**, 656 (1899).
27. J. B. Ackman, F. Siddiqi, R. S. Walikonis, J. J. LoTurco, *J. Neurosci.* **26**, 11413 (2006).
28. K. Blinzinger, G. Kreutzberg, *Z. Zellforsch. Mikrosk. Anat.* **85**, 145 (1968).
29. B. D. Trapp *et al.*, *Glia* **55**, 360 (2007).
30. M. B. Graeber, K. Bise, P. Mehraein, *Acta Neuropathol.* **86**, 179 (1993).
31. B. Stevens *et al.*, *Cell* **131**, 1164 (2007).
32. A. Bessis, C. Béchade, D. Bernard, A. Roumier, *Glia* **55**, 233 (2007).
33. D. R. Beers *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 16021 (2006).
34. I. Maezawa, L. W. Jin, *J. Neurosci.* **30**, 5346 (2010).
35. J. C. Thrash, B. E. Torbett, M. J. Carson, *Neurochem. Res.* **34**, 38 (2009).
36. M. Kaneko, K. Sano, J. Nakayama, N. Amano, *Neuropathology* **30**, 463 (2010).
37. K. Otero *et al.*, *Nat. Immunol.* **10**, 734 (2009).
38. Z. Šišková, A. Page, V. O'Connor, V. H. Perry, *Am. J. Pathol.* **175**, 1610 (2009).
39. S. Wakselman *et al.*, *J. Neurosci.* **28**, 8138 (2008).
40. W. J. Streit, H. Braak, Q. S. Xue, I. Bechmann, *Acta Neuropathol.* **118**, 475 (2009).
41. P. Chakrabarty *et al.*, *FASEB J.* **24**, 548 (2010).
42. S. K. Chen *et al.*, *Cell* **141**, 775 (2010).
43. A. H. de Haas, H. W. Boddeke, K. Biber, *Glia* **56**, 888 (2008).
44. T. A. Bayer, R. Buslei, L. Havas, P. Falkai, *Neurosci. Lett.* **271**, 126 (1999).
45. B. Dean, *Aust. N. Z. J. Psychiatr.* **43**, 13 (2009).
46. G. Kochlamazashvili *et al.*, *J. Neurosci.* **30**, 4171 (2010).
47. A. Flügel, M. Bradl, G. W. Kreutzberg, M. B. Graeber, *J. Neurosci. Res.* **66**, 74 (2001).
48. N. Cartier *et al.*, *Science* **326**, 818 (2009).
49. T. M. Malm *et al.*, *Neurobiol. Dis.* **18**, 134 (2005).
50. A. R. Simard, D. Soulet, G. Gowing, J. P. Julien, S. Rivest, *Neuron* **49**, 489 (2006).
51. D. Soulet, S. Rivest, *Curr. Opin. Pharmacol.* **8**, 508 (2008).
52. E. R. Unger *et al.*, *J. Neuropathol. Exp. Neurol.* **52**, 460 (1993).
53. M. B. Graeber, W. J. Streit, R. Kiefer, S. W. Schoen, G. W. Kreutzberg, *J. Neuroimmunol.* **27**, 121 (1990).
54. A. Cagnin, M. Rossor, E. L. Sampson, T. MacKinnon, R. B. Banati, *Ann. Neurol.* **56**, 894 (2004).
55. W. Spielmeyer, *Histopathologie des Nervensystems* (Springer, Berlin, 1922).
56. U. V. Eitzen *et al.*, *J. Neuropathol. Exp. Neurol.* **57**, 246 (1998).
57. P. del Rio-Hortega, *Bol. de la Soc. Esp. de Biol.* **9**, 68 (1919).

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10.1126/science.1190929

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Manuel B. Graeber (November 4, 2010)

Science **330** (6005), 783-788. [doi: 10.1126/science.1190929]

Editor's Summary