Microglia

Denis Soulet[1] and Serge Rivest[2,*]

What are microglial cells?

Microglia — from micro (small) and glia (glue) — are the resident immune cells of the brain and constantly patrol the cerebral microenvironment to respond to pathogens and damage. These cells are present throughout the central nervous system (CNS), including the spinal cord, although some regions are more populated than others, with the white matter generally containing fewer microglia than the grey matter. Microglia are highly ramified cells and their processes are very active and dynamic even under non-pathological conditions. Microglia that are found close to blood vessels seem to lose their ramifications during chronic immune challenges, becoming more amoeboid in such conditions. It is not clear whether this process depends on phenotypic changes of the resident cells or whether it is a step involved during the differentiation of blood-derived cells. Amoeboid cells are also found throughout all stages of development of the CNS. Microglial cells are found in similar numbers to neurons, representing around 10–20% of all glial cells and ranging from 100 to 200 billion cells depending on the condition (i.e., healthy, infected, diseased). In contrast to neurons, microglia can proliferate, particularly during infection and injury and in the presence of endogenously produced toxic proteins.

What is the origin of microglia?

Although the exact origin of microglia still remains to be fully established, both perivascular and parenchymal microglial cells and macrophages derive from myeloid progenitors. It is currently believed that parenchymal microglia originate from neuroectodermal matrix cells and that pial macrophages or mesenchymal progenitors originate from the yolk sac, establishing themselves in the brain during the embryonic stage (Figure 1). However, recent data suggest the existence of other subpopulations of microglial cells, each of which may have different origins, i.e. those arising from the primitive macrophages from the yolk sac and those newly differentiated from monocytes or their progenitors. Over 95% of all microglia are generated after birth and after the formation of the blood–brain barrier (BBB) and there has been an ongoing debate regarding the maintenance of the microglial population in the adult CNS. One hypothesis is that adult microglia are maintained via self-replication or by the division of progenitor cells already present in the brain. Another hypothesis suggests that circulating precursors are able to infiltrate the CNS and differentiate into microglial cells. Recent studies have demonstrated the capacity of bone marrow stem cells (BMSCs) to populate the CNS and differentiate into functional parenchymal microglia as well as perivascular microglia (Figure 2). It is important to mention that recent studies have raised concerns about such a natural infiltration of

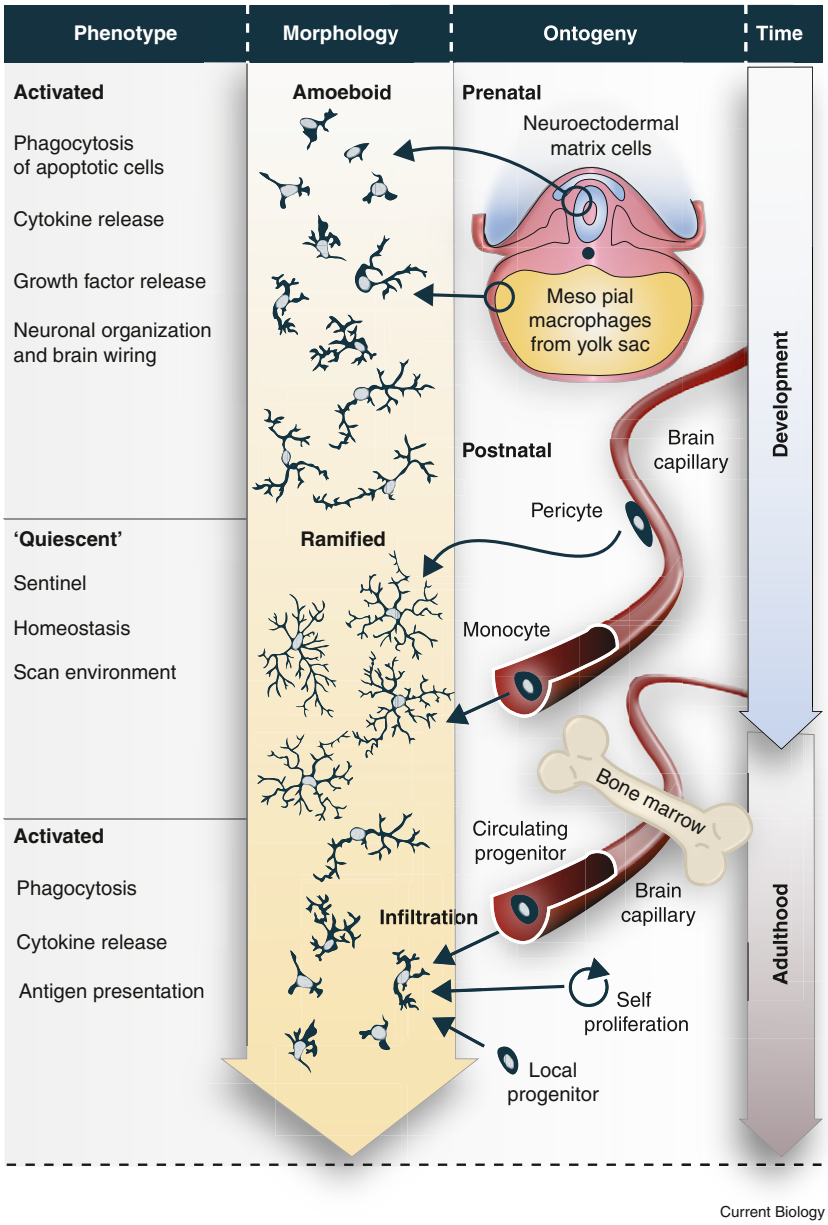

Figure 1. Phenotypes and morphologies of microglia during development and adulthood and under normal and inflammatory conditions. Various hypotheses for the ontogeny of microglia are proposed.

bone-marrow-derived microglia and about whether this mechanism is a physiological event in the intact CNS. Although the debate is still running, there is no doubt that BMSCs can at least populate the infected, injured and diseased brain.

Are microglial cells active during non-pathological conditions? The second debate about microglia relates to whether they are found in either a resting state or a vigilant state or whether they are only activated in the presence of immune stimuli (Figure 2). The identification of these states is, obviously, largely dependent on the tools used to evaluate such an activity and on the role of microglia under specific conditions. *In vivo* two-photon imaging in the neocortex generated spectacular evidence that microglial cells are actually highly active in their presumed resting state, continually surveying their microenvironment with extremely motile processes and ramifications. It seems, therefore, that these immune cells are never in a resting condition and they are dynamically patrolling the brain environment to clear it of any possible toxic molecules. It is interesting to note that BBB disruption causes an immediate switch in their behavior from patrolling the brain to shielding the injured site via a mechanism that is dependent on ATP/P2Y G-protein-coupled receptor signaling. The high basal level of motility of microglial processes may thus reflect the fluctuation of the ATP concentration in the surrounding tissue and may not necessarily be related to the inflammatory properties of microglia.

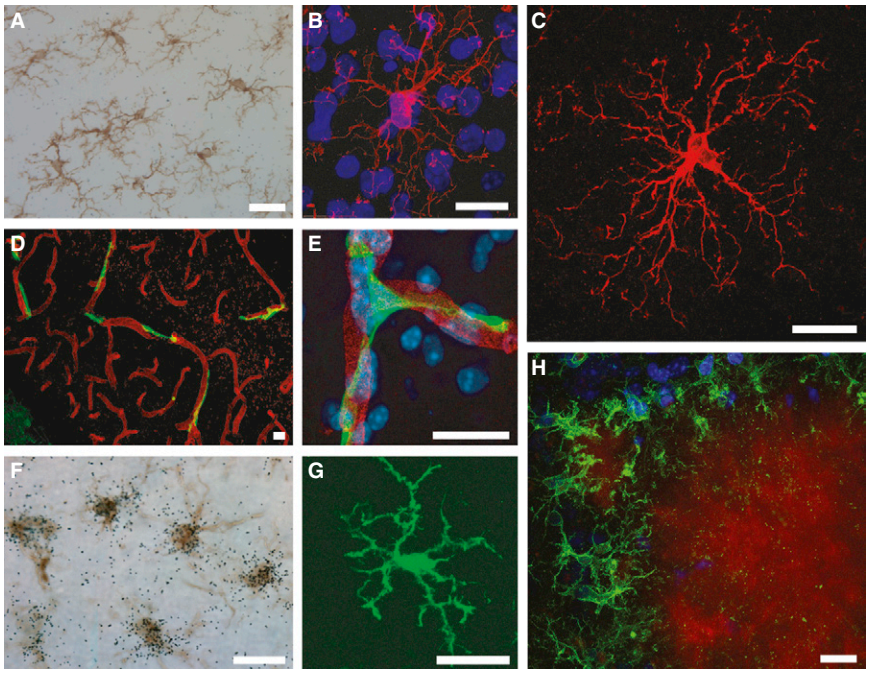

Figure 2. Microglia subtypes in the mouse CNS.

(A) Resting microglia (brown cells, immunoperoxidase staining using a primary antibody directed against Iba1 (ionized calcium binding adapter molecule 1), a specific marker for macrophage/microglia). (B) Highly ramified microglial cell (red, immunofluorescence using a primary antibody directed against Iba1; nuclei in blue). (C) Highly ramified microglia (immunofluorescence using a primary antibody directed against Iba1). (D,E) Bone-marrow-derived perivascular microglia (green) from chimeric mice transplanted with BMSCs expressing green fluorescent protein, GFP (blood vessels in red, and nuclei in blue in panel E). (F) Activated microglia expressing TLR2 (brown ramified cells, immunoperoxidase staining using a primary antibody directed against Iba1; silver grains represent radioactive *in situ* hybridization for TLR2 mRNA). (G) Bone-marrow-derived microglia from chimeric mice transplanted with GFP-expressing BMSCs. (H) Infiltration of microglial cells restricting amyloid plaques in a transgenic mouse model of Alzheimer's disease (microglia in green; amyloid plaque in red; and nuclei in blue). Scale bar represents 20 μm in all panels. Images courtesy of Paul Préfontaine, Denis Soulet and Luc Vallières.

How do pathogens activate microglia? Microglia are isolated in the brain parenchyma by the BBB. Their direct interaction with pathogens and other types of immune cells is therefore quite limited, at least in the intact brain. The characterization of the Toll-like receptor (TLR) family has greatly contributed to a better understanding of the natural innate immune response by microglial cells. TLRs recognize pathogen-associated molecular patterns (PAMPs) produced by microorganisms, such as bacteria and viruses. The interaction between lipopolysaccharide (LPS) and TLR4 has been widely studied in microglia both *in vivo* and *in vitro*. Systemic challenge with LPS triggers transcriptional activation of inflammatory genes in microglial cells throughout the brain parenchyma. Such widespread microglial reactivity to LPS is dose- and time-dependent. Some genes are induced very rapidly (e.g., IκBα, TNF-α, IL-1β, CD14), while others take between hours and days to be detected (e.g., members of the complement family). Direct injection of LPS into the CNS parenchyma also causes a strong, time-dependent transcriptional activation of inflammatory genes in microglial cells at the injection site. Such a robust and transient inflammatory response by microglia is not associated with neuronal damage or demyelination. Inhibition of these activated cells would seriously compromise the natural immune surveillance of the brain and prevent proper elimination of pathogenic substances in the cerebral microenvironment. If left unchecked, however, microglia may produce an inflammatory milieu that is highly detrimental.

How do injured neurons activate innate immunity in microglia? In addition to PAMPs produced by infectious microorganisms, a few host proteins are believed to act as endogenous ligands for TLRs, such as heat shock protein (HSP) 60, HSP70 and fibrinogen (all of which are able to stimulate proinflammatory signaling via TLR4 and possibly TLR2). Recognition of these endogenous ligands is likely to be a natural defense mechanism allowing the host to mount an immune reaction in the presence of damaged tissue or severely stressed cells. Microglia elicit a natural innate

immune response during acute injuries and this activity is believed to be critical for restricting damage and facilitating repair. Indeed, a timely and controlled innate immune response limits CNS toxicity by eliminating foreign materials and debris, thus contributing to the creation of an environment that is more permissive for regeneration and recovery.

How are toxic proteins cleared by microglia? Since microglia are the macrophages of the CNS, the promotion of an increase in their ability to phagocytose highly toxic proteins is a promising new therapeutic approach to prevent many diseases. Toxic proteins are produced in a variety of brain diseases, such as Alzheimer's disease (b-amyloid), amyotrophic lateral sclerosis (superoxide dismutase 1), and Parkinson's disease (a-synuclein). Microglia are recruited in such conditions, but they are not necessarily efficient at phagocytosis and removal of these toxic proteins from the extracellular environment. In the case of Alzheimer's disease, increasing the infiltration of blood-derived microglial cells seems likely to be a useful therapeutic approach, since these cells are able to eliminate or prevent the formation of b-amyloid deposits. Immunization against b-amyloid stimulates the recruitment of bone-marrow-derived microglia and improves both the clearance of the protein and cognitive function. It is tempting to propose that such a strategy could also be efficient in clearing secreted and toxic proteins involved in many other diseases that affect the CNS.

Where can I find out more?

Simard, A., Soulet, D., Gowing, G., Julien, J.P., and Rivest, S. (2006). Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron *49*, 489–502.

Hanisch, U.K., and Kettenmann, H. (2007). Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. *10*, 1387–1394.

Nimmerjahn, A., Kirchhoff, F., and Helmchen, F. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science *308*, 1314–1318.

[1]Neuronal Survival Unit, Wallenberg Neuroscience Center, Department of Experimental Medical Science, Lund University, BMC A10 221 84 Lund, Sweden.
[2]Laboratory of Molecular Endocrinology, CHUL Research Center, 2705 Laurier Blvd, Sainte Foy, Quebec, G1V4G2, Canada.
*E-mail: Serge.Rivest@crchul.ulaval.ca

Primer

X chromosome drive

John Jaenike

In the past 10 years, the world record for the men's 100 meter dash has declined from 9.79 to 9.74 seconds, the detection of such small differences being made possible by sophisticated electronic timing devices. If someone were to run the 100 meters in 9.73999 seconds in the 2008 Olympics, would the timers be sensitive enough to show him to be the world's fastest human? Natural selection could, as differences in fitness of that magnitude (10^{-6}) can be detected in species with large effective population sizes. In this way, natural selection can bring about the evolution of exquisitely well-adapted creatures.

Getting back to the race, imagine that one of the runners somehow manages to get a 50-meter head start. With such an advantage, even an overweight, out of shape, or injured athlete could win the gold. An analogous situation applies in evolution. Mendelian segregation, in which the two alleles carried by a heterozygous individual are passed to equal numbers of gametes, ensures that alleles compete fairly and that they succeed (or fail) on the basis of their effects on survival and fertility. Meiotic drive — the process by which alleles are not represented equally in an individual's gametes — subverts the entire process. In the best documented examples of drive, one allele may be passed on to ~100% of an organism's gametes, equivalent to a runner getting a 50-meter head start in the 100 meter dash. The overrepresentation of such alleles in gametes can more than make up for any associated deficiencies in survival and fertility. As a result, these alleles — and those closely linked to them — can rapidly spread through a population, and thus actually cause a decline in the adaptation of a species to its environment. If such an allele drives all the way to fixation, the species may end up a little less well adapted, but there would be no evidence that meiotic drive was the cause, as drive would no longer be expressed.

Other genes in the genome not linked to those causing drive suffer the adverse consequences of being transmitted to suboptimally adapted individuals, but they do not enjoy the transmission advantage associated with drive. Consequently, alleles present in individuals expressing drive may have lower fitness than those present in individuals that do not express drive. Thus, one way for the unlinked genes to fight back is to suppress drive.

X chromosome drive appears to be particularly common, in part because it is so easy to detect, being manifest as skewed offspring sex ratios; autosomal drive can only be detected using genetic markers. Furthermore, strongly driving X (or Y) chromosomes cannot go to fixation, as this would result in the loss of one sex and extinction of the species. These are systems in which frequency-dependent mechanisms may stabilize the polymorphism long enough for suppression to evolve.

Sex chromosome drive brings about another cost. For simplicity, I will specifically consider X drive in species with XY males. As a driving X increases in frequency, the population becomes ever more biased towards females. Because every individual in a sexual population has one mother and one father, the total fitness of males equals the total fitness of females in terms of offspring production. Consequently, as R.A. Fisher showed, individuals of the rarer sex are more fit on average. Because the driving X chromosome more frequently winds up in females, the autosomal genes associated with such X chromosomes suffer reduced fitness. Thus, autosomal genes that suppress X chromosome drive are favored, as are resistant variants of the Y, the direct target of X chromosome drive.

X chromosome drive has been known since the 1920s and has been documented in a number of species of *Drosophila* and other flies. Until recently, these cases were generally regarded as evolutionary novelty items, of no great consequence for larger evolutionary processes. But that is now changing, as the consequences of antagonistic coevolution between genes that cause drive and those that suppress drive are coming into focus.

Nowhere is this more evident than in *Drosophila simulans*, in which there are both ongoing, as well as apparently resolved, conflicts between X drive and various suppressors. Figure 1 illustrates cytologically, in