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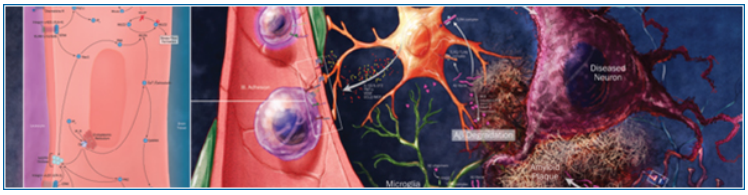
# Journals & Books
# Microglia in Neurodegenerative Diseases

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**Microglia**:
Microglia are specialized macrophage cells. Macrophages are immune system cells that are found in blood and other tissues of the body. When macrophages enter the brain, they change into microglia. Microglia assume a stationary sentry role, exploring the tissue around them with fine processes that continuously extend and retract. If the brain is damaged or infected, microglia are activated and can resume their mobile form, which is able to engulf and destroy pathogens, foreign material, and necrotic tissue. They also signal to other cells of the immune system for assistance.

Microglia: Nerve cells and synapses: Charles Watson, George Paxinos, in The Brain, 2010

**Microglia in Neurodegenerative Diseases:**
Microglia are involved in multiple sclerosis, Alzheimer's disease, Parkinson's disease, HIV dementia, retinal degenerative diseases and many other conditions. In multiple sclerosis, phagocytic microglia are located in the lesion sites. In animal models, phagocytic microglia have been identified with lysosomes containing myelin degradation products. The overactivation and recruitment of microglia in Alzheimer's disease is due to accumulation of amyloid-β proteins, which further activate microglia through neuronal damage. Activated microglia migrate to the site of plaque formation and penetrate the plaques, which leads to production of pro-inflammatory, cytotoxic molecules such as NO and TNFα. The dying dopaminergic neurons in Parkinson's disease result in overactivation of microglia through their release of matrix metalloproteinase-2, α-synuclein and neuromelanin—signals that subsequently trigger pro-inflammatory events in the activated microglia. In HIV dementia, microglia function as storage cells for the virus in the brain. The interaction of the HIV viral proteins with microglia results in their activation. Chronic activation of microglia in the retina leads to overactivation and results in retinal cell damage as an early event in retinal degenerative diseases.

Neuroinflammation: Nicolas G. Bazan, et al, Basic Neurochemistry (Eighth Edition), 2012

**Dementia and Alzheimer's disease:**
has a neuroinflammatory component. Microglia are activated and proliferate locally at the sites of AD lesions. Microglia then produce cytokines and free radicals, which could produce a chronic inflammatory response. In both head injury and ischaemia, activation of microglia and increases in APP expression appear very rapidly. Aβ is known to activate microglia. Whether activated microglia secrete Aβ or not is a contentious issue. The complement receptor, C1q, binds to Aβ, triggering the complement cascade. In this way, the inflammatory process may be both initiated and potentiated by Aβ. There is possibly a critical role of proinflammatory cytokines in AD. Interestingly, the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with a decreased risk of developing AD.

Dementia: Adina Michael-Titus, Peter Shortland, in The Nervous System (Second Edition), 2010

**Nervous System Injury:**
**Role of Microglia in Neuronal and Oligodendrocyte Apoptosis**

Microglia are known to react quickly in response to CNS injury or disease, proliferating and migrating into an injury site. Microglia secrete a wide array of molecules that have been shown to be toxic to neurons and oligodendrocytes, including glutamate, free radicals, and TNF-*α*. Microglial activation has been linked to neuronal apoptosis in several diseases and TBI. Minocycline, a drug that decreases microglial activation, has been shown to reduce neuronal apoptosis in animal models of brain injury. Additionally, treatments antagonizing TNF-*α* and free radicals, both of which can be produced by microglia, have been shown to improve outcomes in experimental TBI.

It has been shown that activated microglia contribute to oligodendrocyte death in models of MS and PVL. Microglia-induced oligodendrocyte damage may be further exacerbated by the fact that many factors that lead to oligodendrocyte death also lead to microglial activation, such as glutamate and proinflammatory cytokines. Microglia may exert their effects on oligodendrocytes and OPCs both at a distance and via direct cell–cell interaction. *In vitro*, microglia have been shown to be capable of inducing OPC death without being in direct contact with OPCs. However, *in vivo*, microglia have been observed in close proximity to dying oligodendrocytes after SCI. This proximity of microglia to oligodendrocytes after CNS injury may increase the influence of microglia on oligodendrocyte and OPC survival, as it has been shown *in vitro* that physical contact between microglia and oligodendrocytes is a key factor in mediating oligodendrocyte death via microglial TNF-*α*. While it is possible that microglia induce oligodendrocyte apoptosis by TNF-*α*, glutamate, or free radical generation, it is also possible that activated microglia near apoptotic oligodendrocytes are only removing the debris left from oligodendrocyte death, similar to apoptosis during development. The relationship between apoptotic oligodendrocytes and activated microglia remains under investigation.

Microglia are also observed to undergo apoptosis in neurological injury. Microglial apoptosis occurs after SCI, peripheral nerve injury, and *in vitro* as a result of activation. This may be caused by excessive free radical production by activated microglia, which could lead to self-induced apoptosis. Microglial apoptosis after CNS injury may be a beneficial self-regulatory process that reduces the number of microglia and the amount of damage microglia do to other CNS cells. On the other hand, microglia have also been suggested to play a beneficial role after CNS injury, and microglial apoptosis may have a detrimental effect on recovery.

Apoptosis in Nervous System Injury: B.A. Miller, ... M.S. Beattie, in Encyclopedia of Neuroscience, 2009

**Role of Inflammation in Environmental Neurotoxicity: Overview of Microglia:**

Microglia play an important role in maintaining normal brain activity: they are vital for brain development, homeostasis and function (Perry et al., 2010; Wolf et al., 2017). While upon activation they produce a host of inflammatory mediators and contribute/drive the neuroinflammatory process, they also produce trophic factors and exhibit phagocytic activity, which are essential for maintenance of normal neural networking and communication (Wolf et al., 2017). Compared to peripheral cells of the innate immune system, microglia are long-lived, but recent evidence suggests that in both mice and humans there is a substantial microglial turnover such that the whole population is renewed several times over the course of a lifetime (Askew et al., 2017). This substantial remodeling further supports the critical role microglia play in the maintenance of brain homeostasis, as well as in their ability to respond to diverse stimuli.

Spatially, microglia are not uniform and areas of the brain, such as the hippocampus, striatum, and cortex, have disproportionately higher microglia numbers (Lawson et al., 1990; Perry et al., 1996). It is interesting to note that not only are microglia-rich brain regions of critical functional importance, but they are also the major targets of neurodegenerative diseases, such as Parkinson's and Alzheimer's (De Lucia et al., 2016; Moehle and West, 2015).

Role of Inflammation in Environmental Neurotoxicity: Nikolay M. Filipov, in Advances in Neurotoxicology, 2019

**Microglial Response to Injury:**

**Microglia** ubiquitously exist in the neural parenchyma and exhibit ramified morphology under the normal brain, and they are called 'resting microglia.' In neuronal injuries, microglia are activated to show a number of features, including morphological changes; cell migration and proliferation at lesion sites; induction of wide-ranging myeloid markers, cytokines, free radicals, and nitric oxide; and acquisition of phagocytic phenotype in extensive neuronal cell death (Figure 1). The activated microglia are recognized during neuronal degeneration and then revert to the resting phenotype in parallel with the neuronal regeneration. Therefore, the activated microglia are thought to participate in the degeneration and regeneration of neuronal cells and to play an important role in the repair of the injured nervous system.

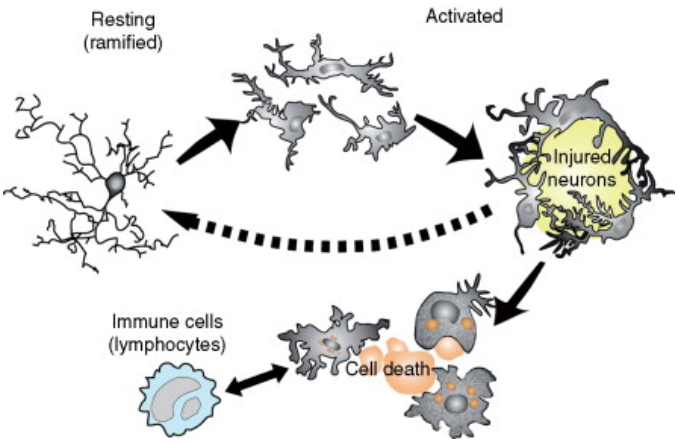


Figure 1. A schematic summary of microglial response to neuronal injury. Neuronal injury induces a rapid transformation of resting (ramified) microglia to the activated form. Microglia change their morphology, migrate toward the injured sites, and proliferate and accumulate around the injured neurons. Activated microglia produce and release various molecules in response to several stimuli from surroundings. Cell death leads to a further transformation of microglia into phagocytic cells. Activated microglia also interact with the immune cells infiltrating through the blood–brain barrier. In parallel with the regeneration of neuronal cells, microglia gradually return to a resting state.

Microglial Response to Injury: K. Ohsawa, S. Kohsaka, in Encyclopedia of Neuroscience, 2009

**Microglia: Development and Maintenance of the Blood–Brain Barrier:**

Microglia are the resident macrophage of the CNS. These specialized cells derive from yolk sac primitive macrophages and are distinct from bone marrow–derived monocytes and their lineage. Microglia are ubiquitous across brain regions and each individual microglial cell surveys a defined and relatively small territory, often in close proximity to CNS capillaries (Fig. 9.3). In response to chemical insult, infection, or necrosis, microglia adopt a response phenotype in which these cells defend the brain by mechanisms including proliferation, phagocytosis, release of proinflammatory cytokines and antimicrobial factors.

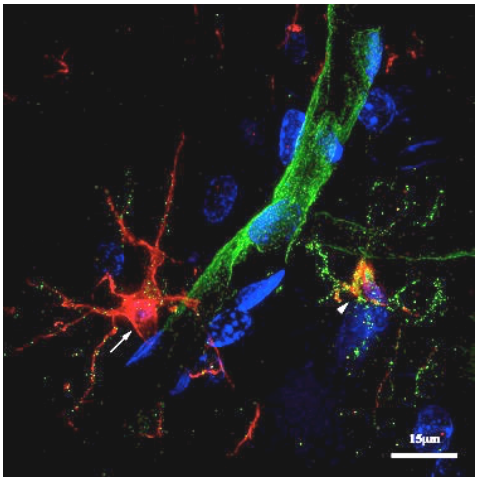


Figure 9.3. Perivascular microglial cells.
This image illustrates the proximity of microglial cells to a cerebral capillary in the adult rat hindbrain. A 30-μm rat brain section was stained for the microglial marker Iba1 (red), and major histocompatibility complex (MHC) II (green), which is upregulated in activated microglia but also stains endothelial cells. Nuclei were stained with (DAPI) 4',6-diamidino-2-phenylindole (blue). The white arrow highlights a surveillance microglia and the arrowhead highlights an activated microglia that has increased expression of MHC II. Note the capillary between the two microglia. This image is a maximum intensity projection of a 10-μm segment of the brain slice and was processed for brightness, contrast, and RGB levels.

Microglia play vital roles in the development of the CNS. These cells participate in the pruning and remodeling of neurons during embryonic development. Microglia also shape CNS vasculature during embryonic development, as mice lacking the macrophage-critical transcription factor PU.1 exhibited reduced vascular intersections in the subventricular vascular plexus. Microglia modulate a number of neuronal processes via the release of molecules that signal to neighboring cells in a paracrine fashion. Microglia elicit responses such as increasing excitatory postsynaptic current frequency via paracrine signaling. Activated microglia increase permeability of the BBB via the release of nitric oxide and interleukin-1β.

Development and Maintenance of the Blood–Brain Barrier: J.M. Herndon, ... T.P. Davis, in Primer on Cerebrovascular Diseases (Second Edition), 2017