

Microglial Cells are Major Sensors for CNS Homeostasis Disruption
Significance for the Stroke Penumbra and Neurodegenerative Diseases

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Microglia (about 10–15% of CNS glial cells) are immunocompetent cells, with a small soma and extensive branches (see Ch. 1) that actively monitor the cellular environment with a high degree of sensitivity to disruptions of homeostasis. Microglia responses are complex and include protection/repair as well as contributions to CNS function and to pathology. Microglial signaling is involved in protection, repair, neurotrophic bioactivity, synaptic circuitry plasticity and neurogenesis. In addition, these cells sense alterations in their surroundings and rapidly respond to trauma, stroke, and the onset and progression of neurodegenerative diseases, including Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (Belayev et al., 2011; Lue et al., 2010; Perry et al., 2010). Often, microglia—after becoming amoeboid, macrophage-like cells (often referred to as “resident” macrophages)—remove cellular debris or leukocytes. Another microglial phenotype furthers injury and neuroinflammation, thereby contributing to cell damage (Perry et al., 2010; Prinz & Mildner, 2011). Microglia may display the features of activated macrophage M1 as well as M2 phenotypes.

Activated M1 microglia release cytokines that induce inflammation, such as tumor necrosis factor alpha (TNF- α) and interleukin 1 beta (IL-1 β), as well as reactive oxygen species and nitric oxide (NO). Overexpression of TNF- α or IL-1 β exacerbates ischemic damage, whereas their inhibition decreases infarct size. The microglial production of TNF- α receptors TNFR1 and TNFR2 is upregulated after ischemia. However, both *in vitro* and *in vivo* evidence suggests that IL-1 β and TNF- α , have neurotrophic functions, in addition to harmful effects (Polazzi & Monti, 2010; Ransohoff & Perry, 2009). The differential TNF- α responses are likely mediated by its

receptors, where TNF-R1 is responsible primarily for the neurotoxic effects, and TNF-R2 for the protective responses. NO can combine with superoxide anion-radical (O^{2-}) to form peroxynitrite ($ONOO^-$). The resultant reactive nitrogen species (RNS) induces oxidative stress, and lipid peroxidation and produces alterations in proteins and DNA. This is a pathogenic factor for neurodegenerative diseases and especially stroke, based on the abundance of reactive oxygen species (ROS) during and after the infarct.

M2 microglia display enhanced neurotrophin synthesis, release insulin-like growth factor 1 (IGF-1) and transforming growth factor beta 1 (TGF β 1), attenuate pro-inflammatory cytokines, and likely play a role in inflammation resolution. The precise mechanism/s that governs the appearance and proliferation of these different microglial phenotypes are incompletely understood. Microglia and macrophages are major contributors to the development of the stroke penumbra. Radioligands to image microglia activation in experimental models as well for clinical studies have been developed. One of the ligands takes advantage of the increased abundance in TSPO (translocator protein 18-kDa) in injury-activated microglia as well as in arriving macrophages. The TSPO is a hetero-oligomeric complex of the voltage-dependent anion channel and an adenine nucleotide carrier of the permeability transition pore of the outer mitochondrial membrane. Its function in microglia is not clear, but it seems to be involved in steroid synthesis and cholesterol translocation. TSPO used to be referred to as the peripheral benzodiazepine receptor. TSPO expression in brain under resting conditions is low. TSPO ligands are being used for *in vivo* imaging in animals and humans using positron emission tomography and single-photon emission CT as a sensitive marker to detect early neuroinflammation (Ransohoff & Perry, 2009; Thiel & Heiss, 2011). This is very important because of the potential to use these markers to assess the evolution of the penumbra during

stroke. Timing the progression of infarct and penumbra evolution is critical to establishing the window for intervention methods (see references listed below).

References

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