

- Introduction and Objectives -

The immune system plays a critical role in maintaining the homeostasis throughout the body; and it is the main responsible for tissue repair and regeneration. Microglia are the immune resident cells of the central nervous system and, despite sometimes are detrimental, they principally exert a beneficial role.

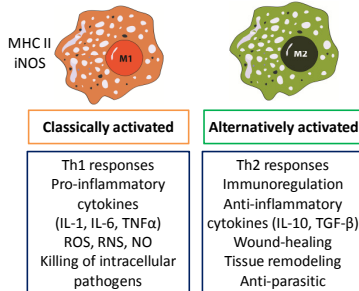
The aim of this work is to review the current knowledge about the role of microglia in the promotion of regeneration, tissue repair and homeostasis restoration in the central nervous system. Specifically focusing in the context of Multiple Sclerosis, the protective roles of microglia are explored.

- Materials and Methods -

- All data come from original research articles and reviews.
- A bibliographic search was performed using PubMed database in order to find relevant articles about the topic that were published in high impact factor journals.
- A posterior selection was done based on the quality of the information and the relevance of the publication.

Macrophages in inflammation and tissue repair

Infection (virus, bacteria)
Injury/tissue damage

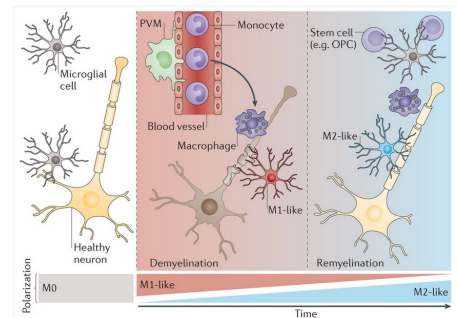


- Background -

Myeloid cells of the CNS

- Microglia:** yolk sac origin, downregulated phenotype in the highly regulated CNS microenvironment (continuous input of "OFF" signals), self-renewal (*in situ* proliferation).
The only immune cells in CNS parenchyma.
"Active sensors and versatile effectors" – Surveying microglia with all kind of receptors to sense changes in the parenchyma that will activate microglia acquiring a specialized effector phenotype to restore homeostasis.
- Meningeal, perivascular, ventricular and choroid plexus macrophages:** bone-marrow origin, normal immune features, antigen presentation capacity, maintained by blood-borne cells.

The immune-privilege of the CNS is not absolute and presence of immune cells is not always detrimental but aimed to restore homeostasis

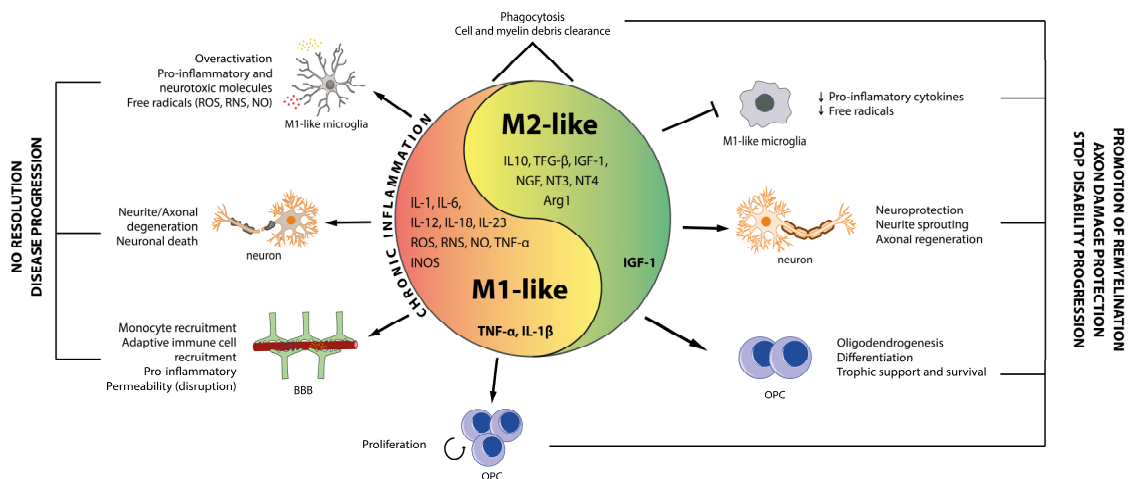


Dynamics of the functional states of microglia in response to damage.
Surveying ramified microglia is in a "M0" state. Upon homeostatic disturbances, microglia acquires the activated/effector M1-like phenotype and, if required, recruits monocyte-derived macrophages from the bloodstream. As time goes by, disturbances start to become neutralized while a shift towards M2-like phenotype occurs. The shift provides a means of tissue repair (growth factor secretion, stem cell recruitment) for homeostatic restoration (e.g., remyelination). *Abbreviations: OPC, oligodendrocyte precursor cell.* (From Prinz & Priller, Nature Reviews Neuroscience, 2014).

- Multiple Sclerosis and Potential Beneficial Implications of Microglia -

Multiple Sclerosis

- One of the most common causes of neurological disease among young adults, especially affecting females from the northern hemisphere (possible genetic and environmental factors).
- Chronic inflammatory disease, characterized by multifocal demyelination and progressive neurodegeneration affecting the CNS
- Three clinical courses: primary progressive-MS, secondary progressive-MS, relapsing remitting-MS (the most common, 85%)
- Immune mediated – all immune cell types have been somehow implicated, and different myelin destruction mechanisms proposed
- Primary autoimmune aetiology has been suggested, some authors claim that the primary event is neurodegenerative
- Cause and the exact pathophysiologic mechanisms are not currently known and only disease-modifying drugs are available for therapeutic management



Remyelination occurs spontaneously but fails to be complete due to the lack of a regeneration-supportive environment. As inflammatory response perpetuates, remyelination efficiency declines leading to disability progression. Microglia, due to its primary role for tissue repair and homeostasis, promotes remyelination, specially the M2-like phenotype.

- Issues to Consider -

- The current mouse models used in MS research (Experimental Autoimmune Encephalomyelitis - EAE - and cuprizone) may not accurately reflect the complexity of the pathophysiology seen in MS.
- Most of the research is conducted using mice or mouse derived cells. However, it is known that mice and human microglia have some distinct features.
- *In vitro* polarization protocols might not reflect *in vivo* conditions.
- The failure in the bench to bedside step might be a reflection of the aforementioned issues.

- Conclusions -

- The behaviour of mononuclear phagocytic cells of the CNS is similar to the behaviour found outside it: regulatory function for tissue homeostasis and repair in healthy and pathologic conditions.
- Although chronic inflammation will always be detrimental; rather than suppressing the immune system, a promising approach would be to modulate it towards its "positive version" (M2-like).
- In MS remyelination occurs spontaneously but fails to be complete. Boosting endogenous remyelination by taking advantage of microglial anti-inflammatory and regenerative roles, would lead to neuroprotection.