***Role of microglia in physiological and pathological conditions***

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Microglia are the resident immune cells of the central nervous system (CNS) and sustain normal brain functions continuously monitoring cerebral parenchyma to detect neuronal activities and alteration of homeostatic processes. Depending on the brain region, they can represent from 5 to 12% of total cell population ([1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B1)). Microglial cells continuously monitor the surrounding parenchyma to sense alteration of brain functions ([2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B2), [3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B3)) and are involved in controlling neuronal excitability, synaptic activity, neurogenesis, and clearance of apoptotic cells in the healthy adult brain ([4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B4)). Microglia interact with the cerebral microenvironment through different molecules such as chemokines, cytokines, and trophic factors which, in turn, modulate microglia activities converting the homeostatic microglia into reactive microglia and viceversa ([5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B5)).

Furthermore, we focused the attention on the role of microglia in sleep. Sleep is a naturally occurring physiological state defined by behavioral criteria that include the absence of voluntary movement and increase in arousal threshold. In particular, we reported that Microglia display circadian and sleep-wake cycle variations depending on ATP and Catepsine-S molecules (6).

Alterations of functional microglial phenotype are accompanied by dynamic changes of shape of cell body and processes, although no unique correlation among microglial cell morphology and functional phenotype has been identified ([7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099404/#B6)). It was shown that an aberrant microglia activation may result in a loss or alteration of their physiological functions with possible implications on the emergence or maintenance of pathological conditions; moreover, neuro-inflammation caused by microglia hyperactivity has been associated with several neurodegenerative diseases (8).

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons (MN). Motor neuron degeneration in ALS has been correlated with the presence of an uncontrolled inflammatory environment(9) or with an inappropriate microglia activity, which impairs axonal regeneration(10, 11). We demonstrated that NK cells invading ALS affected regions in ALS patients and ALS mouse models. Furthermore, Interferon- (IFN)-g released by NK cells switch microglial phenotype toward a pro-inflammatory state. Our results point toward the importance of re-educating microglia toward a homeostatic phenotype to reduce motor neuron loss and identify NK cells as possible therapeutic targets. While microglia modulation correlates with disease progression in mutant SOD1 mice and ALS patients, we show that NK cell-mediated modulation of these cell types only affects survival and onset time, possibly due to specific or partial alteration of microglia phenotype in the different experimental settings (12).

Altogether, our results identify a central role of microglia in orchestrating CNS functions in healthy brain and in neurodegenerative diseases.

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