# Astrocytes And Microglia In Homeostatic And Pathological Conditions: What Do We Know About Them?

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## Abstract

In the last century, many different studies have shown the importance of glial cells in both homeostatic and pathological situations of the CNS. These cells were first described by Rudolf Virchow as a connective tissue that joins the different elements of the Central Nervous System (CNS) together, but in 1870s, neuroglia was distinguished from connective tissue by Camillo Golgi.

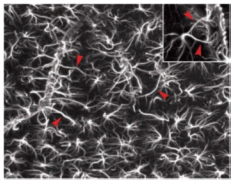
Four types of glial cells are classically considered in the adult CNS which are astrocytes, oligodendrocytes, microglial cells and ependimary cells. The following review summarize the role of astrocytes and microglia in CNS homeostatic and pathological conditions.


## Materials and Methods

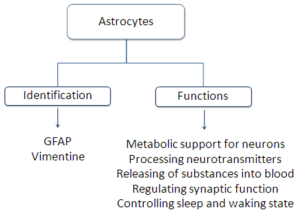
- **Scientific literature search on PubMed database:** recent papers and reviews of glial cells research were selected according to their quality and data of publication.
- **Specialized books and reviews about neuroscience:** glial cells and neuroinmmunology chapters
- **Attendance to glial cells seminars** at *Medical Histology Unit* (Faculty of Medicine, UAB)

## Astrocytes In Homeostatic Conditions: characteristics and functions

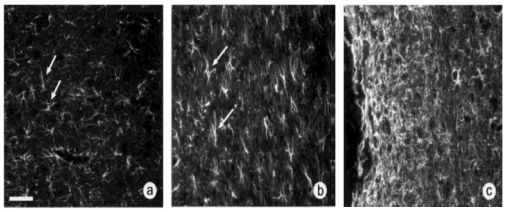
- First described by Santiago Ramón y Cajal as a spider-like cellular population which expand their processes throughout the CNS.
- Essential component of the blood brain barrier (BBB). These cells can regulate the accessibility of factors and molecules from blood (e.g. glucose via GLUT-1 transporters).
- Astrocytes regulate the maintenance or degeneration of synapses by expressing factors which trigger complement component expression in both microglia and neurons.
- They modulate neurotransmission as they present neurotransmitter receptors in their plasma membrane (e.g. AMPA, NMDA and P2X trimeric purinoceptors).



Adapted from Kimelberg *et al.* 2009



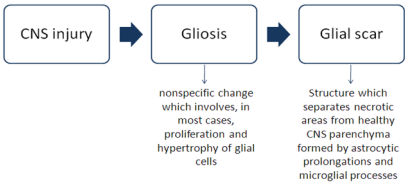

## Astrocytes In Pathological Conditions




- Astrocytes of adult rat spinal cord revealed by GFAP immunoreactivity:

a) Astrocytes in normal uninjured spinal cord.
b) Isomorphic astrogliosis after injury. This type of astrogliosis is characterized by **astrocytic hypertrophy** with preserved tissue organization.
c) Anisomorphic astrogliosis after injury. The damaged CNS region is encapsulated and is characterized by interlocking astroglial processes making a dense plexus.

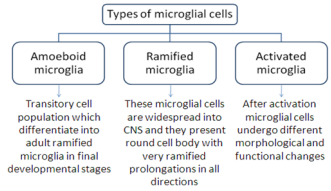
Adapted from Mc Graw *et al.* 2001

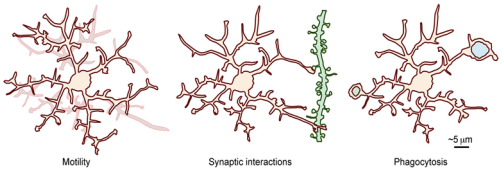



- **Astrocytic hypertrophy**: morphological changes and increasing of intermediate filaments
- **Astrocytic hyperplasia**: proliferation in response to microglia's secreted cytokines an other different factors

## Microglia In Homeostatic Conditions: characteristics and functions

- Microglia are the smallest glial cells found in the brain and spinal cord.
- They are resident macrophages in the CNS and can suffer different morphological and functional changes under changes in the CNS microenvironment.
- Types of microglial cells are usually identified by their morphological differences and by their membrane-antigen variations




- In normal healthy brain, microglial cells perform different functions such as:
  - -Check and remodel their local microenvironment.
  - - Control the state of synaptic contacts.
  - - Restructuration of neuronal circuits via phagocytosis.

Adapted from Tremblay *et al.* 2011

**Some markers of microglial cells**

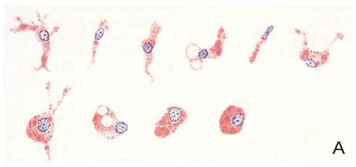
| *Molecular structure/Antigen* | *Functional relevance* |
|---|---|
| **CD11b** | Complement receptor 3 (CR3) |
| MHC-II | Antigen presentation by APC |
| **CD11c** | Cell adhesion and marker for dendritic cells |
| CD34 | Marker for precursor cells of myeloid lineage |
| **CX3CR1** | Receptor for the chemokine fractalkine implicated in microglial activity and motility |

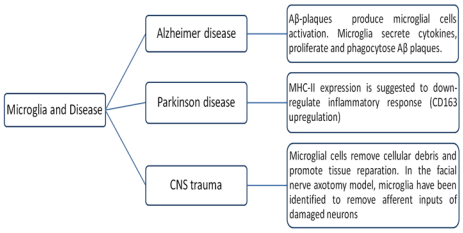
## Microglia In Pathological Conditions

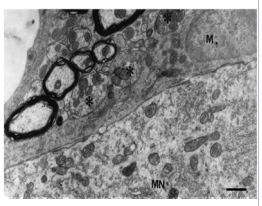
Reactive Microglial Cells Functions

| | |
|---|---|
| **Migration** | CNS injury leads to the release of chemotactic factors. β2-integrin CD11a is essential for this process |
| **Proliferation** | Promoted by cytokines (IL-1β, IL-4, IFN-γ) and neurotrophic factors (BDNF, NT-3) |
| **NO production** | Defense against pathogens and other non-infectious processes |
| **Phagocytosis** | Removal of cellular debris and apoptotic cells. Vitronectin receptor, CD36 scavenger receptor and TREM-2 are crucial in this process |
| **Secretion of diffusible factors** | Cytokines, chemokines, trophic factors and inflammation mediators |
| **Antigen presentation and regulation of immune response** | MHC-II membrane expression let microglial cells to present antigens to T-cells. They can also up-regulate other dendritic cells markers, co-stimulatory molecules and cathepsin protease. Neuroprotective effect is observed when microglial cells activate T-helper cells |

- After CNS injury, different factors can activate microglial cells.
- One of the major factors which promote microglial cells activation is **ATP** (P2X receptors).
- Activation of microglial cells results in molecular, functional and morphological changes . All these changes depend on the type of CNS insult produced.
- Figure (A): Microglial cells spectrum of morphological changes after activation (Adapted from Graeber *et al.* 2011)




**Synaptic stripping:** CCL21 and CXCR3 are crucial for this neuron-microglia interaction

Adapted from Moran *et al.* 2003

## Conclusions

This review shows that the classical view of glial cells as "passive elements" into the CNS is not valid anymore. Both astrocytes and microglia actively participate in maintaining normal functions of the CNS (e.g. neurotransmission, synapses remodeling, etc.). After injury, these cells have been demonstrated to regulate the control and monitor the consequent response. Glial response is not always a harmful process as glial cells modulate the immune response in order to minimize possible damage in the CNS.

Although many different aspects of the biology of these cells remain unknown, the crucial role that these cells play in CNS pathological process make them an interesting research area in order to develop new therapeutic targets for prevalent diseases such as Alzheimer disease, Parkinson disease or CNS traumas.

## References


- Only relevant references are cited below. A detailed references list is available upon request for the committee:
  - Kettenmann H *et al*. Physiology of microglia. Physiol Rev 2011 Apr;91(2):461-553.
  - Kettenmann *et al.* Microglia: new roles for the synaptic stripper. Neuron 2013 Jan 9;77(1):10-18.
  - Parpura V *et al*. Glial cells in (patho)physiology. J Neurochem 2012 Apr;121(1):4-27.