Glial Cells: The Other Cells of the Nervous System

5. Microglia – The Guardians of the CNS

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In the early part of the twentieth century, the important role played by a set of small cells under pathological conditions in the brain was recognized for the first time by De RioHortega. He developed a staining technique that could distinguish these cells from neurons and other glial cells and coined the term 'microglia' to describe them, as they were glial cells of small size. De RioHortega also reported their resemblance in structure and function to the scavenger cells of the immune system, the macrophages. Microglia have turned out to be controversial cells. They could be distinguished without doubt only much later when specific monoclonal antibodies were developed and used to label them and their progenitors. They are not considered to be true glia by many as they are seen to be originating from the monocytic lineage and not from neuroepithelium like other glial cells. Thus, microglia are often considered as an extension of immune system into the central nervous system (CNS). However, a few reports from in vitro systems keep the controversy of their origin yet unresolved. Functionally, there is no doubt that these 'other' cells of the nervous system, like the immune system, are guardians that respond immediately to infections, trauma and cell death in the neural tissue.

Structure of Microglia

Under normal conditions the microglia are difficult to identify. They are small cells, scattered all over the neural tissue. They comprise about 20% of the total glial cell population and form a network of immune cells that merge with the cellular architecture of the brain. These cells are relatively stable and functionally quiescent. Unlike their counterparts in the peripheral nervous system (the resident macrophages), about 1% of microglia undergo replacement.

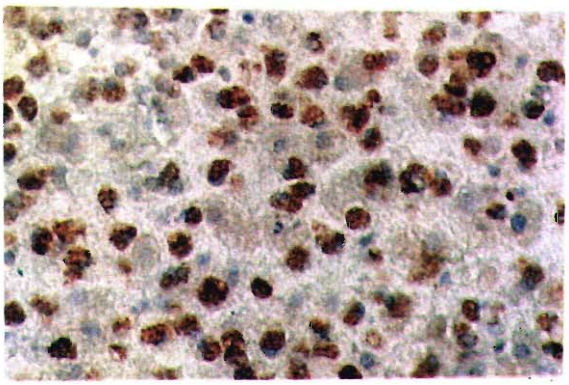

Figure 1. Immunohistochemical staining for macrophage factor shows all brain-derived macrophages positive for this staining. (PAP oxidase, magnification X 200)

Microglia can be identified distinctly as phagocytic cells under pathological conditions. Activated microglia were first described by Franz Nissl as 'rod cells'. These activated microglia can be recognized by a distinct macrophage like morphology. (*Figure* 1) They are mobile and migrate to the site of trauma or infection. The structural and functional likeness and the origin of activated microglia and macrophages are so close that they are often referred to as 'microglia derived brain macrophages'.

In the CNS, different classes of microglia can be identified on the basis of their morphology and functional maturation:

a. The amoeboid microglia, found immediately after birth.
b. The ramified, resting macrophages in the mature CNS.
c. The activated but not phagocytic microglia with protective function that appear in response to subtle brain injury.
d. The activated microglia with phagocytic or cytotoxic activity found in large numbers at the site of trauma, injury or infection.

Resting microglia have a characteristic cell surface under normal conditions. They have receptors to most CNS signal molecules such as neuro transmitters (acetylcholine and adenosine), Adenosine Triphosphate (ATP), and special proteins like Calcitonin Gene Related Protein. These receptors probably help the microglia to judge the integrity of their microenvironment. Being extremely to sensitive to chemical cues to disturbances in the normal state of neural tissues, microglia can be readily triggered to their functional mature activated form (*Figure* 2).

Part 1. An Introduction to Glial Cells, *Resonance*, Vol.7, No.1, pp.4-10, 2002.
Part 2. Astrocytes – Star Performers in the Neural Tissues, *Resonance*, Vol.7, No.4, pp.20-26, 2002.
Part 3. Oligodendrocytes Ensheathers of the CNS, *Resonance*, Vol.7, No.6, pp.6-13, 2002.
Part 4. Schwann Cells – Regulators of the Periphery, *Resonance*, Vol.7, No.8, pp.8-15, 2002.

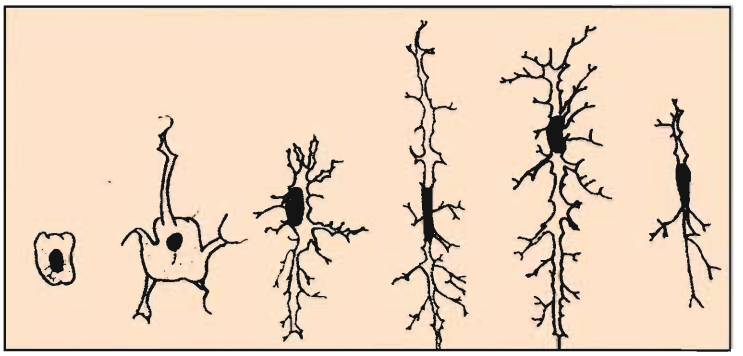

Figure 2. Diagrammatic representation of stages of a resting microglial cell being converted into an activated macrophage like phenotype.

Activated microglia develop a characteristic cell surface that makes them responsive to all chemicals involved in an inflammatory reaction. (*Table* 1) They express the Major Histocompatibility Complex proteins (MHC-I and MHC-II) that help them in immune recognition functions. A new set of adhesion molecules appears on their surface and permits greater mobility. A surface antigen that is common to all leucocytes, CD45, also appears on their surface. All these molecules, and more, equip the microglia to function as an active immune cell. These markers on the cell surface are often used to determine the class to which the microglia belong.

Role of Microglia in Developing and Healthy CNS

Microglia have been proposed to play a role in sustaining normal growth pattern in the developing CNS. They are known to secrete growth factors that act on neurons and other glial cells.

Table 1. Products formed from activated microglia.

Cytokines/Growth factors	**Reactive oxygen species:**
Interleukin 1 (IL 1)	Nitric oxide
Interleukin 2 (IL 6)	**Neurotoxic metabolites:**
Tumour Necrosis Factor-alpha (TNF-alpha)	Quinolinic acid
Transforming Growth Factor-B (TGF- B)	Arachidonic acid metabolites
Nerve Growth Factor (NGF)	Leukotriens
Fibroblast Growth Factor –2 (FGF-2)	Prostaglandins
Brain Derived Neurotrophic Factor (BDNF)	Amyloid precursor proteins
Protein Cleaving Enzymes:	
Cathepsins B and L	

The basic function of microglia in the CNS is to maintain tissue integrity under all circumstances. Under normal conditions they take care of the tissue debris generated by the wear and tear of the neurons and glia. Under pathological conditions they minimize tissue damage by performing a dual function.

The number of neurons produced in a mammalian brain far exceeds what is necessary and a majority of these neurons undergo programmed death. Young, newly formed microglia participate in cleaning the debris formed by the dying neurons. Thus, microglia are important in fine sculpturing of the CNS that takes place during development.

The basic function of microglia in the CNS is to maintain tissue integrity under all circumstances. Under normal conditions they take care of the tissue debris generated by the wear and tear of the neurons and glia. Under pathological conditions they minimize tissue damage by performing a dual function. When tissue is severely damaged and neural tissue is dying, microglia act as scavengers and remove the tissue debris and the bacterial or viral invaders. The cells in these situations are strongly cytotoxic. The cells perform this function either by active phagocytosis or by secreting chemicals (free radicals, NO, proteases) that help in scavenger activity. When the tissue injury is mild, and the damage is subtle and not necessarily resulting in cell death, the microglia play a protective role. Along with astrocytes they make an attempt to isolate the intact cells from the lesion and support regenerative processes. There is no evidence of microglia ever destroying a normal neuron.

Role of Microglia in Disease

Activated macrophages are found to be performing cytotoxic as well as protective functions under various situations. Animal models as well as human cases have been studied for microglial function. Microglia are seen to be on the scene in all neurodegenerative conditions. Increased microglia are seen in aged brains. Under normal condition the brain is not freely accessible to serum constituents and blood cells. The endothelial cells lining the blood vessels that supply the brain have tight junctions to ensure that no large protein or cells enter the brain tissue and the end feet of astrocytes further hold the endothelial cells together (see Part 2 of this series). During disease, however this blood brain barrier can be breached. The endothelial cells,

the astrocytes and the perivascular microglia, the very cells that form the blood brain barrier, instead mediate the entry of leukocytes into the brain. Once the activated immune cells are inside the brain they, in turn, activate parenchymal astrocytes and microglia and recruit them to participate in an inflammation. The specific role of microglia in some well-documented situations is enumerated below.

Microglia in HIV associated CNS damage: Microglia have been implicated in neurodegenerative damage caused during HIV infection. To begin with, they appear to help the entry of the virus into the CNS. Circulating lymphocytes or monocytes carry the virus through the blood stream and transmit it via the perivascular microglia into the CNS. As the infection settles, the parenchymal microglia also get the infection and harbour the virus for a long time. While neurons and other glia are often seen to be free of the virus, microglia appear to support the viral life cycle and are responsible for the chronic persistence of the virus in the brain. Long-lived, infected microglia are also the sites from where new mutants of the HIV originate. Microglia have been implicated as the cause of HIV associated degeneration in the CNS, and subsequent dementia. Infected microglia secrete factors that eventually cause cell death. Well-documented secretions of HIV harboring microglia are viral proteins like *gp120, tat* and *nef*. It has been proposed that *gp120* mediated injury not only causes death of neurons, but also of astrocytes and oligodendrocytes. Moreover, microglial secretions like tumor necrosis factor, cytokines (such as IL-6 and IL-1B), aracdonic acid and nitric oxide have been thought to be responsible for neurotoxicity associated with HIV infection.

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Microglia in Alzheimer's disease: Alzheimer's disease is characterized by deposition of structure called 'senile plaques', and neurofibllary tangles that are formed because of the accumulation of the protein β amyliod. Activated microglia are seen clustered around senile plaques. This clustering indicates the attempt made by the microglia to remove plaques by phagocytosis. Microglia are also seen to internalize the β amyloid fibers.

Presence of lesions causing loss of myelin is the characteristic feature of multiple sclerosis. Massive infiltration of inflammatory cells, including the activated microglia is observed at the site of MS lesions.

However, in the diseased condition the plaques are persistent and the surrounding microglia remain in a highly activated state that proves to be counter-productive. These microglia rather than offering protection appear to induce toxicity. Interestingly, microglia themselves secrete β amyloid protein in response to persistent β amyloid in the surroundings and contribute to the progression of the disease.

Microglia in multiple sclerosis (MS): Presence of lesions causing loss of myelin is the characteristic feature of multiple sclerosis. Massive infiltration of inflammatory cells, including the activated microglia is observed at the site of MS lesions. These activated microglia act like Antigen Presenting Cells (APC) and trigger the recruitment of T lymphocytes into the inflammatory reaction. These, in turn, further activate microglia that secrete potential neurotoxins that also damage oligodendrocytes and add to loss of myelin. However, there is a positive role of microglia as well. *In vitro* studies have demonstrated that microglia are the source of growth factors that help in remyelination, though whether this happens in the brain or not is yet to be ascertained. Presence of activated microglia has been also demonstrated in Parkinson's disease and prion disease.

Microglia in tissue trauma: Head injuries, direct or indirect, trauma in cerebrum, cerebellum and the brain stem appear to induce immediate local microglial accumulation. This is followed by a delayed reaction. After infarction, the microglia rush to the ischemic regions. Microglia are seen to surround the vulnerable part and appear to isolate morphologically intact neurons from further toxicity.

Microglia in cancer: Brain tumors are typically seen to be infiltrated by microglia. In gliomas and secondary brain lesions, the microglia are found in increased density in the peripheral regions. These cells are, however, only weakly cytotoxic. Their responses seem to be altered by secretions of tumor tissue and they are unable to react strongly against the transformed cells. Damage and disease of the CNS are a challenge to the tiny

microglia. The activated microglia rise to the occasion by recruiting a set of molecules that aid in their function. Like the macrophages, microglia synthesize and secrete cytokines that not only support their immune activity but also their protective action. Normally, cellular expression of cytokines in all cells of CNS is under strict regulatory control. Under pathological conditions, however, there is dysregulation of cytokine production locally, often for a short time. This triggers a train of events that may amplify the damage. The microglia secretions are a part of the molecular cross talk that decides the fate of the local tissue. There is no doubt that as alert guardians of a fragile tissue microglia perform a very delicately balanced and timely job.

Suggested Reading

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The astronomer may speak to you of his understanding of space, but he cannot give you his understanding ... . And he who is versed in the science of numbers can tell of the regions of weight and measure, but he cannot conduct you thither ...

No man can reveal to you aught but that which already lies half asleep in the dawning of your knowledge.

Kahlil Gibran
'*The Prophet*' (1926)