

Glial Cells: The Other Cells of the Nervous System

2. Astrocytes – Star Performers in the Neural Tissue

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In 1846 Rudolf Virchow recognized for the first time that the vertebrate brain had a large population of cells other than the neurons, collectively called the neuroglia. Much later, various types of glial cells were identified and described (see Part 1) While pathologists studied glia extensively in normal and injured or diseased brains, most textbooks mentioned glia only cursorily. In the last decade, however, new techniques of identification of specific glial cells have given an impetus to the study of their role in the central nervous system (CNS). In this series, we aim to update students about these important other cells of the nervous system. The present article highlights some aspects of the structure and function of astrocytes, the major macroglia in the CNS. Other glial cell types will be discussed in subsequent articles.

Structure of Astrocytes

Astrocytes, as the name suggests, are star shaped cells. With cytoplasmic extensions of varying length, they make contacts with neurons, other astrocytes and with endothelial cells. Their extensions end on the surface of the other cells in knob like structures called the end feet, and give rise to the glial membrane or the limiting sheath that surrounds the brain and the spinal cord. The end feet on the surface of the endothelial cells of the blood vessels are so intimate that they almost seal off the walls of the blood vessel and are considered to be responsible for limiting free flow of molecules from the plasma to the brain.

Most astrocytes of the CNS make specialized contacts with each other called gap junctions that are channels allowing relatively free movement of ions and small molecules. Thus, the astrocytes

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in the CNS almost behave like astrocytes. The gap junctions between astrocytes are rich in a protein called connexin 43, which is often used as a marker to identify these junctions. The amount and distribution of connexin 43 in astrocytes may vary with the region of the brain and the neuronal activity in the vicinity of the cell. Other markers used to identify the astrocytes are glial fibrillary acidic proteins (GFAP) and vimentin, a protein that indicates the presence of glial specific intermediate filaments in the cell (Figure 1). Astrocytes are also recognized by presence of protein S100B. Specific fluorescent-tagged antibodies against such proteins are used in precise identification and localization of astrocytes. Presence of the enzyme glutamate synthetase is also considered to be a marker for astrocytes. However, the presence of this enzyme has been reported recently in oligodendrocytes as well. Some other molecules detected in astrocytes are listed in Table 1. Some of these molecules are seen only in astrocytes while others (growth factors and adhesion molecules) are found in other cell types as well.

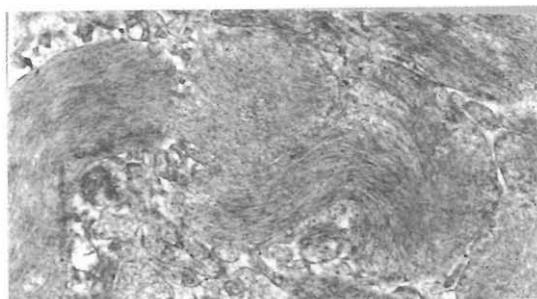


Figure 1. Electronmicrograph showing bundles made up of thin filaments representing astrocytic processes. (Uranyl acetate and lead citrate stain, magnification X12000)

Table 1. Some important molecules detected in normal astrocytes.

Adhesion /recognition molecules:	Enzymes
Integrin	Glutamate synthetase
N-Cadherin	Protein kinase C
Laminin	Cathepsin B, D
Proteoglycans	Neuron specific enolase (NSE)
CD 44	
Glial hyaluronate binding protein	Cytoskeletal constituents
Interleukin 1 (IL1)	Glial fibrillary acidic proteins (GFAP)
Clusterin	Vimentin
Glial cell adhesion molecule (G-CAM)	
Growth factors/Cytokines	Other markers
Nerve growth factor (NGF)	S 100 B
Tumor necrosis factor (TNF)	
Fibroblast growth factor (FGF)	
Ciliary neurotrophic factor (CNTF)	
Platelet derived growth factor (PDGF)	

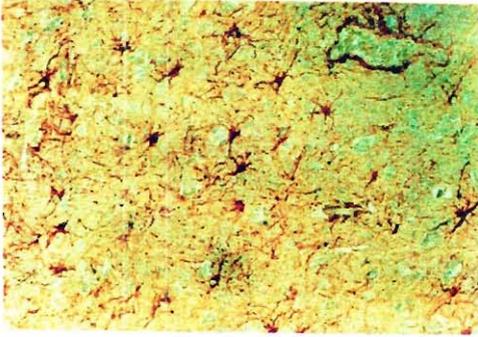


Figure 2. Astrocytes seen as star shaped cells when stained with enzyme labeled antibodies against glial fibrillary acidic proteins (GFAP). (Magnification 40 X)

Types of Astrocytes

Astrocytes have been classified according to various criteria such as structure, location, origin, antigenic profile and function. On the basis of structure and function two types of astrocytes can be identified: (a) Fibrous astrocytes – these are predominantly present in the white matter and have small cell bodies with numerous extensions.

A large number of microfilaments are characteristically present in the cytoplasm of these cells. (Figure 2) (b) Protoplasmic astrocytes – these are predominantly present in the gray matter and have fewer microfilaments in their cytoplasm. Two types of astrocytes (Type 1 and Type 2) have been reported in cultures of developing optic nerves. These two types of astrocytes express different antigens and originate from two distinct precursor cells. A unique type of astrocyte, called the radial cells, appear transiently during embryogenesis of the cerebral cortex. A functionally distinct class of astrocytes called the reactive astrocytes can be identified at the site of injury in CNS.

Functions of Astrocytes

Astrocytes Provide Support During Neural Development

In the vertebrate nervous system, special types of cells called radial glia appear during early embryogenesis of the cortex. A subset of the early neuroepithelial cells are positive for GFAP, the marker protein for astrocytes. These cells form the radial glia, while cells that do not contain GFAP give rise to the neurons. The neuronal population builds up by proliferation and cells migrate to eventually form the laminar architecture of the cortex. The radial glia have a guiding role to play in neuronal migrations as they form the scaffold along which the neurons move to reach their destinations. Most neurons appear to climb on to individual radial cells; some also migrate laterally across the radial cells. However, it appears that glia do not have a decisive role to play in guiding the neurons, acting only as



scaffolds. In other words, they provide a permissive substratum for migration of neurons but no instructive signals.

Astrocytes Aid in Maintaining Ionic Homeostasis

Astrocytes in the CNS are permeable to ions. Following electrical activity, the neuronal microenvironment undergoes a dramatic change. A sudden increase in K^+ concentration takes place. Repeated neuronal stimulations may result in K^+ accumulation that could eventually lead to depolarization of adjacent neurons. Such a situation is prevented by astrocytes as they effectively mop up the extracellular K^+ . Moreover, astrocytes being well connected by gap junctions, K^+ ions gained at one site are rapidly spread to others. Often K^+ ions are extruded at the end feet juxtaposed to the endothelial cells of the blood vessels. Increased K^+ concentration at the end feet dilates the blood vessel wall leading to increased blood flow. Thus astrocytes not only maintain the local extracellular ionic milieu, but help link heightened neuronal activity to improved local vasculature which is essential for meeting the oxygen demand of the activated neurons.

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Ion Channels on Astrocyte Membrane Play a Special Role

Since astrocytes were not excitable, it was assumed that they had no voltage gated channels. However, in the last decade, voltage gated Na^+ , K^+ and Ca^+ channels have been found on astrocytes. Na^+ channels in astrocytes closely apposed to the nodes of Ranvier have been reported. Sodium currents across these channels have been recorded in astrocytes in the rat optic nerve. It has been observed that Na^+ channels in astrocytes are influenced by neuronal activity in their vicinity. Since astrocytes lack excitability, the role of these channels has been a topic for speculation. It has been proposed that when a nearby neuron depolarizes, Na^+ enters into astrocytes through these channels and feeds the Na^+-K^+ pump, thereby enhancing the K^+ uptake of the astrocyte. In different subsets of astrocytes, variable number of Na^+ channels are expressed. It is possible that astro-

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cytes perform various transport operations linked to Na^+ exchange, and Na^+ channels are expressed transiently as per their requirements. As Na^+ channels expressed on astrocyte membrane are similar to neuronal channels, it has also been proposed that astrocytes, especially those associated with nodes of Ranvier, may be synthesizing Na^+ channels and donating them to neurons.

Astrocytes Provide Nutritional Support to Neurons

Astrocytes in the brain are rich in glycogen. Increased neuronal activity and subsequent increase in K^+ and ATPase activity depletes ATP in the astrocytes. Reduced concentration of ATP, in turn, disinhibits the enzyme phospho-fructokinase and thus increases glycolysis. The lactate produced through this pathway may be available for neuronal use as well.

Astrocytes Modulate Neuronal Function

Astrocytes contain receptors for a number of cytokines, growth factors, neurotransmitters (such as glutamate) and other neuro-active molecules. Binding of the appropriate ligands to these receptors can cause ionic changes or activation of a secondary messenger system. In this context, changes in Ca^{++} levels in astrocytes have been studied extensively. Astrocyte membranes have voltage gated as well as ligand gated calcium channels. Elevation of K^+ concentration extracellularly can depolarize astrocyte enough to open voltage gated Ca^{++} channels. Similarly, glutamate or gamma amino butyric acid (GABA) mediated depolarization can result in opening of ligand gated channels. Thus neuronal activity in the vicinity can be perceived by astrocytes through heightened intracellular Ca^{++} ion concentration. Such calcium signals are known to propagate to other astrocytes via gap junctions creating a wave of Ca^+ signals. Various responses (change in shape, volume and gene expression) of astrocytes due to increased intracellular calcium have been reported. It has also been proposed that glial calcium signaling may induce neuronal calcium increase via the gap



junctions between neurons and astrocytes or via release of glutamate by glial cells that act on neurons. This mode of neuronal modulation is currently under investigation.

Astrocytes Help Maintain the Blood Brain Barrier

The neurons and the glia in the brain and spinal cord are bathed in cerebrospinal fluid that maintains a regulated ionic milieu in the tissue. In most areas of the brain, blood components such as cells and large proteins are not allowed to freely permeate the brain tissue. This barrier is called the 'blood brain barrier' (BBB) and is formed early in development as endothelial cells of a special kind line the walls of the capillary supplying the brain. These endothelial cells overlap each other, almost fusing in regions due to 'tight junctions' between their membranes. As mentioned earlier, astrocytes extend a 'foot process' (Figure 3) that may almost completely surround the brain capillaries. So intimate is the contact between the astrocytes and the brain capillaries that for a long time it was thought that these cells alone (and not endothelial cells) were responsible for the BBB. The BBB can be breached during injury or disease. Astrocytes along with microglia have a different role to play.

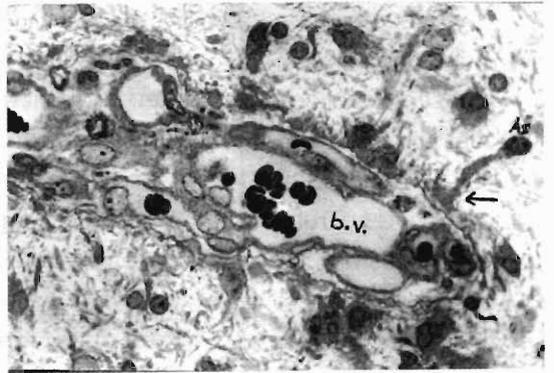


Figure 3. Astrocyte end feet seen in semi-thin section of neural tissue. Note the blood vessel (bv) and the contact of astrocytes made on the endothelial cells.

Astrocytes Preserve Host Tissue Following Injury

An injury or a lesion in the brain causes a reaction in the surrounding tissue. This eventually leads to formation of a barrier by the glial cells isolating the injured part from the rest of the tissue. This is called reactive gliosis, and the glial cells activated to participate in glial barrier are known as the reactive astrocytes. This warding off of damaged tissue by reactive gliosis helps avoid secondary lesion formation and reduces further tissue damage. Recently it has been suggested that reactive astrocytes express receptors for various growth factors and respond to them. Such astrocytes secrete neurotrophic factors that



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protect neurons from degenerating. They also secrete several proteases and protease inhibitors that modulate growth of neurites. Reactive astrocytes express increased cell surface molecules, including cell adhesion and matrix adhesion molecules. It has been proposed that under certain circumstances these may provide a permissive microenvironment for axonal regeneration. On the other hand, it has also been suggested that reactive gliosis and formation of the glial barrier may obstruct axon regeneration. Responses of astrocytes are variable and depend upon the local factors such as the signals emanating from the damaged tissue. Astrocytes have been thought to play a major role following an injury in deciding whether neurons will survive or die or whether axons will regenerate or not. These aspects of astrocyte function are of immense clinical importance and the topic of much current research.

Conclusions

Studies over the last two decades have demonstrated that astrocytes are indispensable for normal growth, function and maintenance of the CNS. The efficient function of the brain requires a precise ionic milieu. And the astrocytes ensure this by various mechanisms. Trauma in the brain can unleash a host of reactions that are contained because of astrocytes. Truly, astrocytes are the star performers of the neural tissues.

Suggested Reading

- [1] Glial Signaling, Special issue, *Trends in Neurosciences*, Vol.19, No.8 p.218, August 1999.
- [2] J L Ridet, S K Malhotra, A Privat and F H Gage, Reactive Astrocytes: cellular and molecular cues to biological function, *Trends in Neurosciences*, Vol. 20, No. 12, 1997.
- [3] E M Powell and H M Geller, Dissection of Astrocyte-mediated cues in neuronal guidance and process extension, *Glia*, Vol. 26, No. 1, 1999.

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