Glial Cells: The Other Cells of the Nervous System

1. An Introduction to Glial Cells

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Carl Ludwig Schleich (1859-1922) was an anaesthetist and a surgeon who for the first time emphasized the role of neuroglia in brain function. In an era that was dominated by the idea that neurons alone were functional units of the nervous system and that glial cells were a mere glue holding neurons in place, Schleich insisted that glia had a prominent functional role to play. He suggested that interactions between neurons and glia were so strong that it is necessary to consider brain as a neuron-glia system whose performance is dependent on both the cell types. Today Carl Ludwig Schleich is considered the forgotten ancestor to a new breed of neurobiologists, the gliologists, who specialize in working on these neglected cells of the nervous system. Though outnumbering the neurons and occupying almost half the volume of the brain, glial cells have been given little importance in textbooks of neurobiology and are very often cursorily mentioned in discussions related to brain function. Glial cells deserve a better deal, for over the years a lot of evidence has accumulated to prove that they perform a wide spectrum of functions. This is the first of a series of articles that aims to update students on what is known about glia today. It provides an overview of the various types of glia and their origins. The following articles will deal with each of the glial sub-types and their functions.

In the early 19th century, Camillo Golgi developed an extraordinary technique of silver staining to visualize neurons. Glia too were, for the first time, seen as distinct morphological units. Rudolf Virchow called them the *'nerven kitt'* (nerve-glue), clearly relegating them to a non-neuronal status with limited role. The

fact that these cells did not show any electrical activity like neurons or muscles reinforced these ideas. Neuroanatomists and pathologists, however, had sustained interest in glia as they appeared to be the most common cause of brain tumors. In the years to come several important functions were attributed to glia: they not only provided packaging for neurons, but acted like a scaffold to migrating neurons, and formed scar tissue during repair of injury. It is now known that glia have far more say in the brain function than previously thought. Glial cells maintain the integrity of the neurons in health, disease and injury. They enhance conductivity of the nerves by providing the myelin sheath and help in initiating, sustaining and, if required, strengthening the synaptic connections. They help decide whether neurons will live or die. Following damage, they support regeneration of neurons in peripheral nervous system but not in the brain where precise wiring is obligatory. Continuously engaged in a chemical dialogue amongst themselves, the neurons and the micro-milieu of the nervous system, the glial cells have liaison functions to perform. As predicted by Schleich, who was ahead of his times, the glia are turning out to be as important as the neurons for normal brain and body function.

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General Properties of Glial Cells

Glial cells are observed to be metabolically active, very like any other cell of the body, with the usual array of organelles. Deposits of fats and glycogen are often seen in their cytoplasm. Microscopically they can be distinguished from the neurons on the basis of the absence of an axon. Glial cells also have a resting membrane potential higher than that of the surrounding neurons. Unlike neurons, action potentials cannot be initiated in glial cells, yet some of them do get depolarized or hyperpolarized when exposed to neurotransmitters. Adjacent glial cells are often electrically coupled, such that ions can be exchanged amongst these cells without passing through extracellular spaces. The glial cells manage to produce large enough currents that can be measured by external electrodes, and the EEG and ERG are the sum of electrical activity of neurons and glia. Several

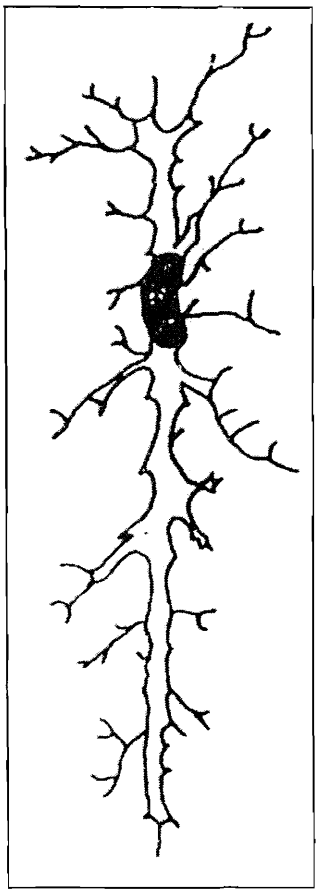


Figure 1. Diagrammatic representation of an activated microglia.

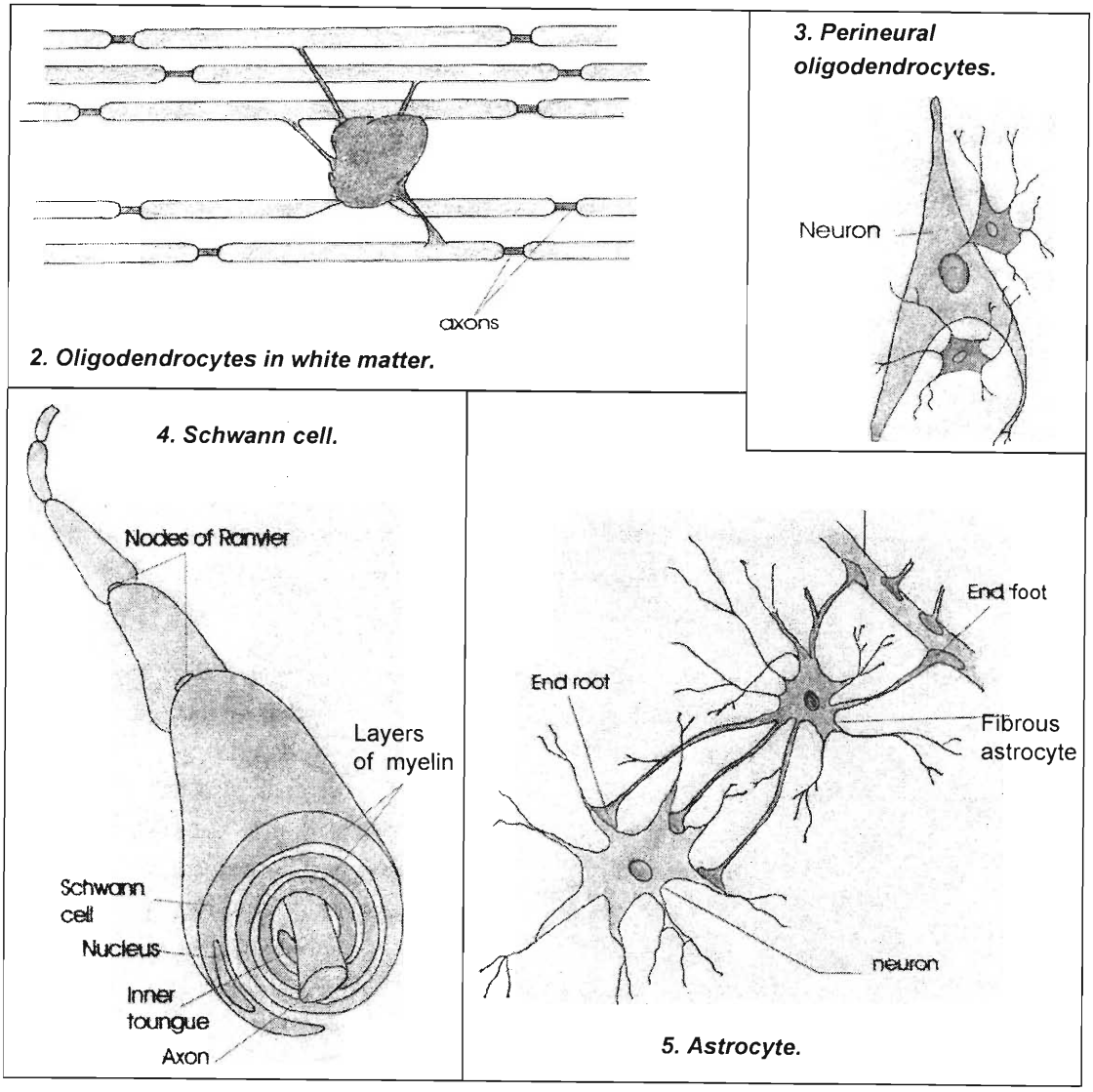
specific antibodies have been developed that can not only be used to distinguish glia from neurons, but can also be used to classify various subtypes of the glia.

Types of Glial Cells

Broadly, two distinct classes of glia have been recognized in the vertebrate nervous system. The first are the microglia (*Figure* 1), the tiny cells that act like scavengers and clean up the tissue debris formed following an injury. Resembling the cells of the immune system these cells are often considered non-glial. This is also so because, unlike the other type of glial cells, microglia originate from blood forming cells. The second major class of cells is the macroglia, the cells that predominate in the nervous system. Three distinct types of cells belong to this class of glia. The oligodendrocytes (*Figures* 2 and 3) are the cells that form myelin sheath around the neurons in the brain and spinal cord. The Schwann cells myelinate the neurons in the peripheral nervous system. (*Figure* 4) Both oligodendrocytes and Schwann cells, though apparently performing similar functions, have many more specific responsibilities that they take up which makes them distinct in form. The third cell type classified as macroglia are the astrocytes (*Figure* 5), the multifaceted star like cells of the central nervous system. All these cells can now be distinctly identified and classified on the basis of the specialized proteins each of them synthesize. Often displayed on the cell surface, these proteins serve as markers not only to give a distinct identity, but can also be used in tracing the embryonic origin of these cells.

Origin of Glial Cells

In a vertebrate embryo, one of the three germ layers, the ectoderm, in response to local factors, folds into a tubular structure that gives rise to the central nervous system (CNS). This is the neural tube that has sub-regions destined to become the spinal cord, the hindbrain, the midbrain and the forebrain. Within each of these regions are self renewing populations of progenitor



Figures 2-5. Diagrammatic representation of the microglia depicting their relation with the neurons.

cells that give rise to neurons as well as to glial cells. Local factors and specific genes have been identified that commit cells to either the neuronal or the glial lineage.

In the dorsal part of the neural tube are a set of cells, the neural crest cells, that give rise to the neurons, the glia and the melanocytes depending on the stimuli each cell receives from their immediate environment. These cells have been used extensively to understand how glial cells originate in the peripheral

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nervous system. Schwann cells, the predominant glia of the peripheral nervous system, originate from neural crest cells. Schwann cells are of two types, myelin forming and non-myelin forming. Both the cell types originate from common precursor cells and can be easily identified as they synthesize a characteristic protein, 'major peripheral myelin protein', (P0). Development of Schwann cells is initiated by signals from an axon in the neighborhood. The Schwann cell lineage involves three transition steps. The neural crest cells divide and differentiate to form Schwann precursor cells. These cells in turn give rise to immature Schwann cells that can synthesize myelin. These immature cells then further differentiate and either continue to synthesize myelin or differentiate into non-myelin forming Schwann cells. Both myelinating and non-myelinating Schwann cells are abundant and present in almost equal numbers throughout the peripheral nervous system (PNS).

In the CNS, astrocytes and oligodendrocytes originate from a common precursor cell The factors that govern the formation of these two types of glia have been studied using rat optic nerve as a model system. The precursor cells also called the O2A precursors divide in presence of a growth factor called the platelet derived growth factor (PDGF). The number of progenitor cells builds up as long as they are exposed to PDGF. Oligodendrocytes develop from these precursors in presence of PDGF and thyroid hormone. However, if these precursor cells are treated with another growth factor called ciliary neurotrophic factor, they differentiate into astrocytes. Interestingly, the growth factor, PDGF, that controls oligodendrocyte differentiation is formed and secreted by astrocytes themselves. In other words, the two macroglia self-regulate their numbers to ensure that optimal number of each subtype is present in the CNS. Astrocytes (Type I), especially in the gray matter, are known to be formed out of another set of independent precursor cells (*Figure* 6).

Functions of Glial Cells

Some glial phenotypes play a transient but important role in

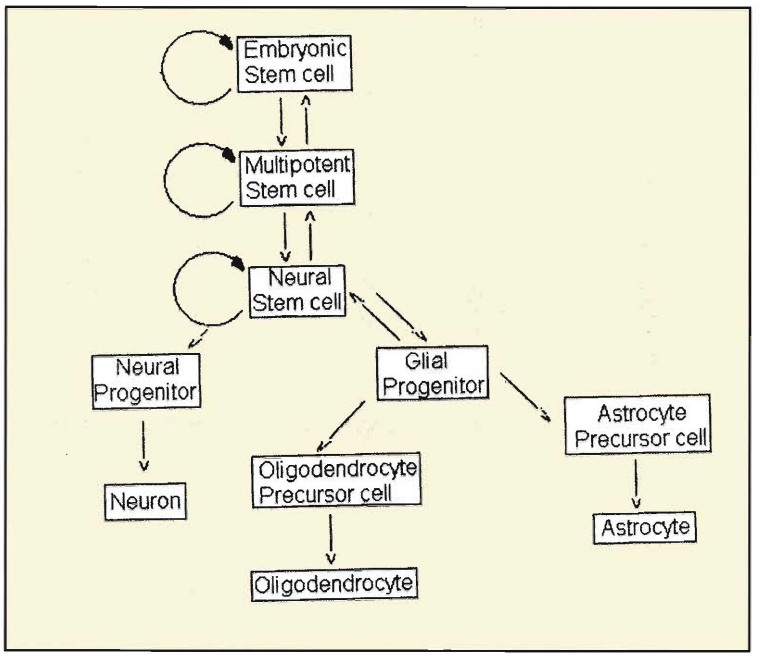

Figure 6. Diagrammatic representation of origins of glial cells in the CNS.

embryonic development of the vertebrate brain. The neurons undergo well-regulated cycles of divisions, migrate to their positions and form connections. As the number of neurons produced far exceeds the number required, some of them are induced to commit suicide or apoptosis (see *Resonance*,Vol. 5, No. 4, p. 74, 2000). Glial cells provide support during all these cellular events. A specialized set of glial cells called the radial glia appears transiently to act as scaffold to migrating neurons. Dense network of radial fibers are formed along which neurons align themselves and move to the outer layers. Adhesion molecules, such as astrotactin, on the glial cell surface and the surrounding matrix provide binding sites for the axon as the neurons wind up along the radial cells. These radial glia are formed in response to the factors (such as glial growth factor) secreted by the young newly formed neurons. Once the embryonic neuronal migration is over, the radial glia transform into smaller, star shaped astrocytes.

A set of glial cells with radial phenotype called the Muller cells persist in the neural retina. These cells, functionally astrocytes and oligodendrocytes rolled into one, maintain the retinal microenvironment. Muller cells modulate neuronal activity by

croenvironment. Muller cells modulate neuronal activity by controlling concentration of neuroactive substances in the retinal extracellular milieu. They mop up the potassium ions released because of neuronal activity and remove neurotransmitters released at the synaptic termini. Re-uptake of glutamate and gamma amino butyric acid (GABA) for recycling is also initiated by Muller cells. These cells also provide metabolic support to retinal neurons.

Conclusions

The glial cells, formed embryonically along with the neurons, become a pool of cells with diverse phenotypes and functions. Each glial cell type performs a specialized function in a specific location in the nervous system. Well integrated into the tissue, each cell type caters to local needs to ensure normal function of the neurons. Modifying their function to meet the emergencies during injury and disease, glial cells are indispensable for CNS repair and cell survival. The advancement in glial cell biology in the recent years has been immense. In the following four articles some aspects of each of the glial cell types will be reviewed.

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Suggested Reading

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'Dignity consists not in possessing honours, but in the conviction that we deserve them'.

– Aristotle