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ASTROCYTES, OLIGODENDROCYTES AND SCHWANN CELLS: BIOLOGY AND FUNCTION

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1. ABSTRACT

Central nervous system (CNS) is composed of two major cell types: neuron and glia. Astrocytes and oligodendrocytes belong to the latter category. Astrocytes, through an intricate network surrounding blood vessels, play an important role in supplying food, water and ions from periphery to the CNS and maintain CNS homeostasis. Astrocytes also play an active role in neurogenesis. However, under inflammatory or neurodegenerative conditions, astrocytes produce proinflammatory mediators and take active part in the ongoing events. Neurons in the CNS are covered by myelin sheath that maintains conduction of nerve impulse. Consistently, the CNS houses oligodendrocytes for myelin synthesis. On the other hand, Schwann cells are the myelinating cells in the peripheral nervous system (PNS). Balanced expression of several genes and activation of transcription factors critically regulate the entire complicated functional network of astrocytes, oligodendrocytes and Schwann cells. Keeping a birds' eye view, this chapter delineates genesis and functional aspects of astrocytes, oligodendrocytes and Schwann cells.

2. INTRODUCTION AND HISTORICAL VIEW

For decades, astrocytes and oligodendrocytes were considered as silent partners of neurons in the CNS. It was known that astrocytes, like neurons, were unable to transmit messages as they did not possess voltage and ion gated channels. With the advancement of science, it is now well accepted that astrocytes possess ion channels as well as G-protein coupled receptors necessary to sense and respond to neuronal activities. Recent advancements also reveal that oligodendrocytes, apart from myelinating neurons in the CNS, secrete some growth factors to help neuronal growth and development. On the other hand, under disease conditions, astroglia undergo proliferation and gliosis. Activated astroglia also secrete neurotoxic molecules that

may be involved in the loss of neurons in neurodegenerative disorders and the damage of oligodendroglia in neuroinflammatory demyelinating disorders.
The present chapter focuses on biology and functional aspects of astrocytes and oligodendrocytes ranging from their genesis to their enormous role in maintaining CNS homeostasis along with their role in CNS pathology. The biology and function of PNS myelinating Schwann cells has been discussed later as a separate section (Section 6).

3. DEVELOPMENT OF ASTROCYTES AND OLIGODENDROCYTES IN THE CNS

The vertebrate nervous system including neurons, astrocytes, oligodendrocytes, and other cells originates from a flat sheet of neuroepithelial cells, constituent of the inner lining of neural plate along the dorsal surface of embryo (Fujita, 2003). These neuroepithelial cells are the earliest precursors in the developing CNS.

3.1. Generation of glial precursor cells

During neurogenesis, neuroblasts are first derived from stem cells and then migrate peripherally to the mantle and marginal layers in the developing brain. After that, DNA synthesis in neurons is completely ceased and the progenitor cells enter into the phase of gliogenesis in the neural tube. These glioblasts are functionally different but morphologically indistinguishable from the multipotent stem cells and eventually differentiate first into functional astrocytes and then oligodendrocytes. The quiescent form of the glioblasts called microglia comes after these events.

Differentiation of cortical progenitor cells is being controlled by some transcription factors having basic-helix-loop-helix (bHLH) motifs. These are NeuroD, Neurogenin, Mash, Olig, Id, and Hes families of protein. The restricted and time-dependent binding of these transcription factors with corresponding DNA sequences present in the promoter of different developmental genes determines the outcome of final cell types. Recent developments (Gotz and Barde, 2005; Alvarez-Buylla et al, 2001) show that neuron and glia are generated from same progenitors/precursors.

3.2. Signaling events driving the precursors to functional cells: astrocytes and oligodendrocytes

The signaling events like hedgehog and notch regulate genesis of functionally distinguished glia and neurons from multipotent stem cells. Hedgehog (Hh) family of signaling molecules are the key organizers of tissue patterning during embryogenesis (Altaba et al., 2002). In mouse, three Hh genes have been identified. These are Desert hedgehog (Dhh), Indian hedgehog (Ihh) and Sonic hedgehog (Shh). The Shh plays a vital role in the development of CNS. In mammals and birds, Shh is the only hedgehog family member that is reported to be expressed in normal CNS.

The oligodendrocyte progenitors (OPs) in caudal as well as ventral neural tube originate under the influence of Shh protein secreted from ventral midline. At this initial stage, Shh patterns the ventral neuroepithelium by controlling the expression of a set of transcription factors PAX6, NKX 2.2, high mobility group protein SOX10, and basic helix-loop-helix proteins Olig1 and Olig2. These Olig genes and SOX10 are co-expressed in cells before the appearance of PDGF-α on OPs. These PDGF-positive OPs then proliferate and migrate away from the

ventricular surface to all parts of the CNS before differentiating into functional myelin forming mature cells.

Notch signaling (Yoon and Gaiano, 2005) first specifies glial progenitors and then functions in those cells to promote astrocytes versus oligodendrocytes fate. The ligands of the Notch signaling pathway are expressed in differentiating neurons. The receptors Notch are transmembrane proteins and are found on neural stem cells. Upon ligand binding, intracellular domain (NCID) of Notch is cleaved by γ-secretase which then enters into the nucleus to form a complex with C promoter binding factor (CBF1) and mastermind-like (MAML). Then the complex (NCID:CBF1:MAML) binds to promoter regions of target genes Hes and Herp and up-regulates corresponding HES/HERP proteins. These proteins are bHLH transcriptional regulators that antagonize proneural genes like Mash 1 and neurogenins. As a result, it blocks neuronal differentiation.

4. ASTROCYTES: BIOLOGY AND FUNCTION

In the middle of the 19th century, German anatomist and pathologist Rudolph Virchow was wondering about the group of cells in the brain that surround the neurons and fill the spaces between them. Dr. Virchow named these cells as “neuroglia” means “neural glue”. He used the term ‘glue’ to represent the gluing function of these cells to hold the neurons in place. Nowadays ‘neuroglia’ is collectively used for all glial cells in the CNS. Later on, due to “star-shaped” appearance, the major neuroglial cells were named as “Astrocytes” (Astra: star; cyte: cells).

4.1. Morphology and markers

Morphologically, astrocytes can be classified into two types: fibrous astrocytes and protoplasmic astrocytes **(**Brightman and Cheng, 1988**)**. Fibrous astrocytes are located predominantly in white matter and possess fewer but longer processes. These processes form cytoplasmic bundles of intermediate filaments (IFs). The major constituent of these filaments are glial fibrillary acidic protein (GFAP). Under light microscope, the fibrous astrocytes look like a star-shaped cell body with finer processes. These processes are extended for long distances and contain abundant IFs.

Table 1. Markers of astrocytes

Marker	Function	Cellular localization	Molecular weight
GFAP	Major constituent of intermediate filament found mostly in adult astrocytes	cytoplasm	50 kDa (predicted)
EAAT1	Transport of amino acids	cytoplasm	59.5 kDa
Glutamine synthase	In CNS, the enzyme found only in astrocytes; it catalyzes conversion of glutamate to glutamine	cytoplasm	43 kDa
S-100	Ca-binding proteins	cytoplasm/nucleus	21-24 kDa

GFAP, glial fibrillary acidic protein; EAAT1, excitatory amino acid transporter