Glial Biology: A Historical Perspective

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Abstract

In spite of the fact that the glial cells were discovered as "neuroglia" as far back as 1854 they remained to be further designated as astrocytes, oligodendrocytes, and microglia up to 1924. Unlike neurons, the glial cells did not get serious attention for almost 100 years and these cells remained to be described as "glue," "servants of the neurons," and so on until the later part of nineteenth and early twentieth century. They gained importance only in the 1980s when neuroscientists realized the interplay between the neurons and glia particularly with the development of modern technologies in understanding cell-cell interactions. Now we understand that the formation, maturation, functioning, and maintenance of neurons are essentially dependent on the glial cells. This chapter intends to summarize the historical perspectives of these developments.

Keywords

Astrocyte · Oligodendrocyte · Microglia · Neuroinflammation

1 Introduction

First described by Virchow in 1854 (neuroglia), further defined by Cajal in 1897 (astrocytes), and better delineated by Hortega in 1919 (microglia and oligodendrocytes), the glial cells in the central nervous system were relegated to be the supporters and "servants" of the neurons, the "regal" constituents of the CNS, for more than a century. Slowly their other characteristics and functions came to be

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recognized. While during the latter part of the nineteenth and the early twentieth century pathbreaking advances were made in respect to the neuroanatomical, neurophysiological, and neurochemical features of the neurons by His (1831–1904), Meynert (1833–1892), Kraepelin (1856–1926), Sherrington (1857–1952), Langley (1852–1925), Brodmann (1868–1918), Dale (1875–1968), and Adrian (1889–1977) among many others, glial biology did not receive similar attention. Studies on neuroglia had to wait till the 1980s when cellular biology and neurosciences underwent a revolution led by the development of molecular biology, genomics, and genetic engineering and a host of new technologies. Today, one can study glial biology in vivo in real life.

1.1 Astrocytes

The morphological heterogeneity of astrocytes, their orderly arrangement covering specific territory, their participation in "tripartite" "synapses," and their control of cerebral vasculature have now been established. They are excitable in a manner different from neurons. Details of astrocyte-neuron cross-talk and their control of synaptic transmission have been elaborated. They express a wide variety of functional neurotransmitter receptors and release a variety of gliotransmitters. They not only regulate cerebral circulation in response to neuronal activity but also play an active role in brain energy production, delivery, utilization, and storage. They play an important role in brain development, neuronal differentiation, and neuritic outgrowth. Astrocytes not only regulate neurogenesis but are also the neuronal progenitors. They integrate and process synaptic information and finally regulate synaptic transmission and plasticity.

Astrocytes secrete a variety of membrane-associated molecules and participate in neuroinflammation and several other brain pathologies.

1.2 Oligodendrocytes

First clearly defined as a distinct entity by Río Hortega and Wilder Penfield in the 1920s (Penfield 1924), oligodendrocytes have been a subject of detailed studies in recent years in respect to their origin and development. They are all derived from oligodendrocyte progenitor cells (OPCs) and cannot multiply on their own. Axonal activity normally controls the production and/or release of the growth factors that are responsible for the proliferation of OPCs and hence the oligodendrocyte. Their primary function is myelination of the axons in the CNS.

It is now well established that there is a cross-talk between the neurons and oligodendrocytes for the initiation of myelination. Myelination itself is a complex process which has recently been elaborated to a great extent.

It has been shown that oligodendroglia not only myelinate the axons but also provide trophic support to neurons by the production of neurotrophic factors like GDNF, BDNF, and IGF1.

In addition to myelination, oligodendrocytes and OPCs have immunomodulatory function. Besides MS, oligodendroglia have been found to be involved in a host of other CNS pathologies like ischemia, stroke, injuries, inflammation, and infection. They are easily destroyed by antibodies in diseases like neuromyelitis optica (Devic's disease) and autoimmune encephalomyelitis. They are found to be affected in patients of Alzheimer's disease, schizophrenia, and amyotrophic lateral sclerosis.

1.3 Microglia

They were first described as "rod cell" in histopathological studies on the brain of dementia patients by Franz Nissl in 1880. Their morphological details were illustrated by Del Río-Hortega (1919, 1920, 1932), and they were designated as "microglia" to distinguish them from astrocytes and neurons. They are of mesodermal and not of ectodermal origin.

Microglia are the immunocompetent residual macrophages of the CNS responsible for innate immunity. They kill invading microorganisms in the brain, remove debris, and facilitate tissue repair after injury. When activated, microglia release a number of immunocompetent molecules and chemokines which control neuroinflammation and regulate immune response of the brain.

While the role of microglia in acute insult to the brain was well known, it is only recently that their role in neuroinflammation associated with neurodegeneration has been brought to light.

2 Biology of Glia: Part I—Astrocytes

2.1 History

The study of human glia dates back to 1854 when Virchow (1821–1902) described the cellular nature of the cerebral interstitial substance which he called "Nervenkitt." Two years later, he named it "neuroglia" (Greek word for glue) (Somjen 1988). He believed the neuroglia to be of connective tissue origin, functioning as glue between the nerve cells (Oberheim et al. 2009). Using black chrome silver reaction, Camillo Golgi (1843–1926) in 1885 (Golgi 1885) was able to illustrate these better, thus confirming these to be undoubtedly different from neurons. He later termed these as radial glia or multipolar glia. Golgi pointed out that in the brain the glia cells are interposed between blood vessels and neurons and assumed that they convey nutritive substance to the neurons. Soon after, Andriezen published a paper, "The neuroglial elements in human brain" (BMJ.2 (1700) 227–230, 1893) providing further details. A year later, Retzius using Golgi stain illustrated the morphological diversity of glial cells in the human cortex. Ramón y Cajal (1852–1934), who primarily concentrated on neurons, published two pioneering papers in 1897 and 1913 mostly dealing with the function of the glia, "Something about the physiological significance of neuroglia" (Cajal 1897) and "A contribution to the understanding

of neuroglia in the human brain" (Cajal 1913) [Quoted by Navarrete and Araque 2014]. "Algo Sobre La signification functional de la neuroglia" (1897) and "Contributional conocimante de la neuroglia del cerebro—humano" (1913). It is to his credit that Cajal along with a number of his students illustrated the relationship of glial cells, mostly astrocytes, to the neurons, synapses, and blood vessels (Newman 2017). His studies thus provided the concept of "tripartite synapse," "neurovascular coupling," and "astrocyte-neuron interaction."

Andriezen (1893) and Ritzius (1894) provided valuable information about the morphology of the astrocytes. However, Albert von Kolliker (1817–1905) has been credited to distinguish two types of astrocytes named Kurzstrahler later called protoplasmic astrocytes and Langstrahper, i.e., the fibrous astrocytes (Von Kolliker 1919) (Quoted by Sierra et al. 2016). According to Kettenmann and Verkhratsky (2008) and Matyash and Kettenmann (2010), it was von Lenhossek (1863–1937) who coined the term "astrocytes" in 1895 (Lenhossek 1895) in the second edition of his textbook on the nervous system. He classified astrocytes as protoplasmic and fibrous.

Around the same time, Franz Nissl (1860–1918) was the first to recognize microglia as a distinct entity but named them "Stabehenzellen" (rod cells) in 1899. However, it was Pio del Río Hortega (1882–1945), along with his pupil Collado, who using silver sodium carbonate stain first described the various forms of microglia—globose and amoeboid during development and actively phagocyte forms and resting mature form in adults (Penfield 1928; Barron 1995).

Working in Hortega's laboratory in Spain, Wilder Penfield (1891–1976) was able to stain the oligodendrocytes for the first time. This was published in 1924 (Penfield 1924) in *Brain* giving a detailed account of these cells. A recent paper by Kuhn et al. (2019) provides a detailed account of these cells.

While during the latter part of the nineteenth and early part of the twentieth century path-breaking advances were made in respect to neuroanatomical, neurophysiological, and neurochemical studies of the neurons, mostly in the UK and Europe, little attention was paid to neuroglia. These pioneer neuroscientists included Franz Nissl (1860–1918), Wilhelm His (1831–1904), Theodor Meynert (1833–1892), Emil Kraepelin (1856–1926), Gustav Retzius (1842–1919), Charles Sherrington (1857–1952), von Economo (1876–1931), John Langley (1851–1925), Korbinian Brodmann (1868–1918), Henry Dale (1875–1968), and Edgar Adrian (1889–1977).

According to Khakh and Sofroniew (2015), Kuffler (1967) was the first to predict the role of neuroglia in neuronal activity which initiated the emerging field of glial biology. Thus, detailed studies on neuroglia had to wait till 1980 when cellular biology and neurosciences underwent a revolution by the developments in molecular biology, genomics, and genetic engineering. This was supported by new technologies and the development of new tools such as the patch-clamp technique, fluorescence imaging, and confocal and multiphoton microscopy which allowed the detailed visualization of the structural and physiological processes of the cells. The outcomes of these investigations, some of which permit in vivo visualization of their activities, are described in respect to individual glial cell categories. It must,

however, be pointed out these cells do not function individually independently but in collaboration with each other and the neurons for a particular goal.

In short, there have been recent advances in respect to the structure, distribution, organization, and functions of astrocytes hitherto unknown (Volterra and Meldolesi 2005). Verkhratsky and Nedergaard (2018) have provided a very detailed account of "physiology of astroglia." This chapter provides an update on the current knowledge on astrocytes.

Astrocytes are the largest number of cells in the CNS. Though already recognized as a distinct entity, it took more than a century to unveil their true functions, not just as a "glue" but as essential participants in the development and functions of the neurons themselves. Interestingly, *von Lenhossek* who in 1895 coined the word "astrocytes" recognized these cells to be equivalent to the nerve cells. In short, astrocytes are highly polyvalent cells that are implicated in almost all processes that occur in the CNS such as neurogenesis, synaptogenesis, and bilateral communication with neurons and other glial cells (Yu et al. 2020). The following account highlights some of these features:

2.2 Morphology

Astrocyte's Homogeneity As mentioned earlier, initially, the morphology of astrocytes was described by Andriezen (1893), Retzius (1894), and Cajal (1897), not only in humans but also in other mammals. However, it was Emsley and Macklis (2006) who drew attention to the heterogeneity of astrocytes. They divided astrocytes in nine classes—tanycytes, radial cells, Bergmann glia, protoplasmic astrocytes, fibrous astrocytes, velate glia, marginal glia, perivascular glia, and ependymal glia. Oberheim et al. (2006, 2009) described a novel human-specific subtype of astroglia designated as varicose projection astrocyte. Matyash and Kettenmann (2010) provided a detailed account of the morphology and physiology of astrocytes. They pointed out that the morphology of astrocytes is determined by the cytoarchitecture of a given brain region. Recent studies have confirmed that astrocytic morphology is heterogeneous within and across brain regions and dynamic in both physiological and pathological states (Yu et al. 2020; Khakh and Sofroniew 2015; Khakh and Deneen 2019).

Astrocytes manifest heterogeneity of membrane currents, glutamate receptor expression, expression of other transmitter receptors, gap junction coupling, and Ca2+ signaling (Matayash and Kettenmann 2010).

Instead of being considered to be distributed haphazardly, it is now known that they exist in an orderly arrangement with minimal overlap. They cover specific territory that interfaces with the microvasculature that might include thousands of synapses. The fraction of this territory can be controlled by specialized astrocyte micro domains which allow highly dynamic interaction with surrounding synapses (Bushong et al. 2002; Oberheim et al. 2006; Khakh and Sofroniew 2015; Khakh and Deneen 2019).

Morphologically and most likely functionally human astrocytes differ from those of rodents. The human cortical astrocytes are larger and structurally more complex and more diverse than those of the rodents (Oberheim et al. 2009). One of the most distinguishing features of the adult human brain is the complexity and diversity of its cortical astrocytes. In all mammals, protoplasmic astrocytes are organized into a spatially non-overlapping domain that encompasses both neurons and vasculature. However, unique to both humans and primates are additional populations of interlaminar astrocytes that also project distinctive long process, frequently un-branched, throughout the layers of the cortex, terminating in either layer 3 or 4. They were already described by Andriezen and Retzius in 1890 (Oberheim et al. 2006).

The most important marker of astrocytes is glial fibrillary acidic protein (GFAP) which is found in almost all reactive astrocytes during central nervous system injury. Other putative markers for astrocytes are S100B. Barres (2008) has provided a list of other markers used for identification of astrocytes.

2.3 Functions

It is now well established that astrocytes have key role in brain development and functions such as neuronal metabolism, synaptogenesis, homeostasis of the extracellular milieu, and cerebral microcirculation. The biology of astrocyte-neuron interaction has emerged as a rapidly expanding field in the 1990s and has become the most exciting topic in current physiology that is changing our vision of the physiology of the nervous system (Perea et al. 2008; Verkhratsky and Nedergaard 2018). This paper by Alexei Verkhratsky and Nedergaard (2018) is an extensive review on the physiology of astroglia in *Physiology Reviews* 98, 239–389. Astrocytes are highly polyvalent cells that are implicated in almost all processes of CNS functioning including local integration, synaptic and non-synaptic communication, neurogenesis, and synaptogenesis (Yu et al. 2020).

Astrocyte Excitability

Till recently considered to be non-excitable support cells of the brain, it is now established that astrocytes are excitable, based on their distinct physiology quite different from neurons. Numerous studies performed during the past few years have established a form of cellular excitability of astrocytes based on variation of Ca2+ concentration in cytosol rather than electrical changes in the cell membrane, a characteristic of neurons. This excitability is regulated by Ca2+ levels in the cells. In the late 1980s, astrocytes were found to express voltage-gated channels and neurotransmitter receptors (Volterra and Meldosi 2005; Barres 2008; Matyash and Kettenmann 2010).

Studies performed in cultured cells, brain slices, and in vivo have firmly established the astrocyte excitability which is manifested as the elevation of cytosolic Ca2+. Fluorescence imaging techniques have shown that Ca2+ elevation occurs spontaneously as intrinsic elements in the absence of neural activity, or they can be triggered by neurotransmitters released during synaptic activity.

Astrocyte Ca2+ elevation has also been observed following physiological sensory stimuli (Perea et al. 2008). Astrocyte Ca2+ elevation stimulates the release of different gliotransmitters. Imaging of astrocytic calcium levels was the initial experimental step of the glial revolution (Haydon 2001).

Astrocyte-Neuron Interaction

Astrocytes express a wide variety of functional neurotransmitter receptors and release several neuroactive molecules such as glutamate, D-serine, ATP, adenosine, GABA, TNFX, prostaglandins, proteins, and peptides. These molecules collectively called as "gliotransmitters" control astrocyte to neuron communication and also synaptic transmission (Perea and Araque 2010; Araque et al. 2014).

It has been demonstrated that signaling between neurons and astrocytes is a reciprocal communication where astrocytes not only respond to neuronal activity but also actively regulate neuronal and synaptic activity (Zonta et al. 2003; Perea and Araque 2006; Haydon and Carmignoto 2006; Newman 2003; Araque and Navarette 2010; Yu et al. 2020).

Astrocytes have an important role in various aspects of brain development and function such as neural metabolism, synaptogenesis, homeostasis of the extracellular milieu, and cerebral circulation. They are involved in neuronal survival and differentiation, neuronal guidance, and neurite outgrowth (Zonta et al. 2003). Interestingly enough studies have produced evidence to suggest that astrocytes not only regulate neurogenesis but are also neural progenitors. It has been shown by anatomical, genetic, and functional studies on humans and other mammals that astrocytes are critical for improved cognitive abilities in humans (Robertson 2014; Zhang and Barres 2013).

There is a yet another function of neuron-astrocyte co-existence in the CNS. They support each other in a variety of ways. Recently, Farmer et al. (2016) explored the influence of neurons on two specialized types of astrocytes in the mouse cerebellar cortex. They found the neurons produced the morphogen sonic Hedgehog. Hedgehog signaling adjusted distinctive gene expression within the two astrocytic cell types. They concluded that mature neurons appear to promote and maintain specific properties of associated astrocytes.

Astrocytes and Synapses

Astrocyte processes envelop the neuronal synapse and give rise to a structure called "tripartite synapse." As mentioned earlier, Cajal (1897) had described this anatomical structure, but it is only recently its functional significance has been elaborated (Gallo and Chittajallu 2001; Perea et al. 2008).

Astrocytes are thus an integral part of the synapse and can be considered as cellular elements involved in synaptic information processing (Perea and Araque 2006, 2010). It is now established that astrocytes sense the activity of neighboring synapses responding to neurotransmitters released by synaptic terminals. Furthermore, astrocytes may in turn influence synaptic transmission (Araque et al. 2001; Haydon 2001; Carmingnoto 2000). Recently, Santello et al. (2019) have explored the role of astrocytes from information processing to cognition and cognitive

impairment. Volterra and Meldolosi (2005) have elaborated how astrocytes "listen and talk." Thus, astrocytes are part and parcel of an integrated network of brain communication, both synaptic and non-synaptic routes. The control of synaptic structure and function depends upon direct neuroglia signaling involving intracellular Ca2+ concentration which is induced by synaptic glutamate-dependent activation of AMPARS (Bezzi and Volterra 2001). Various soluble factors released by astrocytes have been shown to promote formation and maturation of excitatory and inhibitory synapses (Bolton and Eroglu 2009).

The earlier concept of "tripartite synapse" has now been extended to a "multipartite synapse" consisting of (1) the presynaptic terminals; (2) the postsynaptic compartment; (3) the perisynaptic process of neighboring microglial cell that periodically contacts the synaptic structures; and (4) the extracellular matrix (ECM), which is present in the synaptic cleft and extends extrasynaptically.

The role of astroglia in the regulation of synaptic connectivity is, however, immensely wider; astrocytes control emergence and shaping of synaptic network, regulate ionic homeostasis of the synaptic cleft, control neurotransmitter dynamics, present or allow neurotransmitter spillover, and contribute to synaptic extinction (Oliet et al. 2001). These multiple roles of astroglia in synaptic physiology were synthesized in the concept of the "astroglial cradle."

Neuron-dependent excitation of astrocytes is widespread. The transfer of information from neurons to glia occurs through the spillover helped by the existence of "tripartite synapses." Astrocytes can discriminate neuronal inputs of different origins and can integrate concomitant inputs (Volterra and Meldolesi 2005). Astrocytes integrate and process synaptic information elaborating a complex non-linear response to the incoming information from adjacent synapses.

In short, astrocytes integrate and process synaptic transmission and finally regulate synaptic transmission and plasticity, through the release of gliotransmitters (Lino et al. 2001). Astrocytes mainly signal through high-affinity slow-desensitizing receptors to modulate neurons and perform integration in spatiotemporal domains complementary to these neurons (Araque et al. 2014). According to Perea et al. (2008), astrocytes must, therefore, be considered an integral component of synaptic physiology.

2.4 Astrocytes and Neurovascular Regulation

The idea that astrocytes connect to blood vessels and neurons dates back to Camillo Golgi (1871) and beautifully illustrated by Ramón y Cajal (1895). However, the dynamic processes that complement these structural interactions, most notably the active dialogue between astrocytes and other elements of the central nervous system, have only begun to emerge recently. The functional networks of neuron, glia, and vascular cells have been termed the neurovascular unit. It is well known that neuronal activity leads to focal vasodilation, which is the basis of functional MRI (fMRI) studies (Klienfield et al. 1998; Raichle 1998). Tokano et al. (2006) are credited to be the first to demonstrate that astrocytic calcium elevation induces

vasodilation of the cortical perforating arterioles. Cajal (1895) hypothesized that constriction of astrocyte end-feet would trigger vasoconstriction and end-feet relaxation would induce vasodilation. About a century later, Paulson and Newman (1987) proposed astrocytic potassium "siphoning," i.e., influx of potassium ions into the astrocytes near active synapses and efflux of potassium from astrocyte to end-feet into the perivascular space and subsequently potassium-induced vasodilation as a mechanism of functional hyperemia.

Cellular imaging of neurons and astrocytes together with cerebral blood flow (CBF) recording in single vessels in vivo in living animals achieved only relatively recently using multiphoton microscopy of fluorescent-labeled blood vessels, and multicell bolus loading calcium indicators have helped in understanding the mechanism of functional hyperemia (Klienfield et al. 1998; Tokano et al. 2006). As a result of these studies, it has been possible to have a detailed dissection of different cellular components—blood vessels, astrocytes, pericytes, endothelium, and neurons—in vivo (Zonta et al. 2003; Haydon and Carmignoto 2006). This in turn is responsible for understanding brain energy metabolism.

2.5 Astrocytes and Brain Energy Metabolism

It is now well established that astrocytes play an active role in brain energy delivery, production, utilization, and storage (Allaman et al. 2011). While neurons consume nearly 20% of the oxygen and 25% of the glucose consumed by the human body, they generally lack mechanism for storing energy. There is close relationship between brain activity, glutamatergic neurotransmission, energy requirements, and glucose utilization (Belanger et al. 2011). As mentioned earlier, task-dependent increases in cerebral activity are accompanied by changes in local blood flow and glucose utilization. These processes are called "neurovascular" and "neurometabolic" coupling. Fox and Raichle (1986, 1988) in their PET studies established the mechanism underlying task-induced increase in glucose metabolism.

Astrocytes possess unique cytoarchitectural and phenotypic features that ideally positioned them to sense the surroundings and dynamically respond to changes in the microenvironment. They advance two different types of processes. On the one side, they constitute an essential component of the "tripartite synapse," and on the other, they are in contact with intraparenchymal microvasculature through their end-feet.

Astrocytes are thus tailored to ideally position themselves to sense neuronal activity at the synapses and respond to their appropriate metabolic supply via their end-feet (Belanger et al. 2011). Both astrocytes and neurons have a capacity to oxidize glucose and/or lactate. Enough evidence exists suggesting a role of astrocytes in coupling glutamatergic transmission and energy metabolism via a lactate shuttle (Suzuki et al. 2011). Astrocyte to neuron lactate transport is required for long-term memory formation. Astrocytes are also known to play an important role in the homeostasis of extracellular environment. They control the extracellular K+ concentration through the expression of specific channels. They play a critical

role in the clearance of glutamate from the synaptic cleft to terminate synaptic function (Araque and Navarrete 2010).

2.6 Astrocytes and Non-Neural Cells: Glia-Glia Interaction

Astrocytes also control non-neuronal brain cells. They attract cells to their territory through the release of chemokines. In this way, they coordinate the special positioning of microglia and synaptocytes during inflammation and oligodendroglia during development. They might drive reparative stem cells to lesion sites (Volterra and Meldolesi 2005). ATP releases cytokine leukemia-inhibiting factor (LIF) which promotes myelination activity of oligodendrocyte (Cohen and Fields 2008). Various factors released by astrocytes, e.g., PDGF, LIF, NT-3, NT-4, CNTF, and IGF-1, promote the differentiation, proliferation, and survival of oligodendrocyte precursor cells. These also help myelin formation and remyelination following injury (Gard et al. 1995).

2.7 Astrocytes and Neuroinflammation

Astrocytes are known to secrete membrane-associated molecules including cytokines, growth factors, and neurotransmitters (gliotransmitters) in response to physiological and pathological stimuli. It is therefore not surprising that they may have a role in nervous system disorders. Not only are they activated by these disorders, but they contribute to it (Ridet et al. 1977; Tandon 2007). One of the important roles astrocytes play in this respect is through participating in neuroinflammation. It has been known for a long time that following injury, damage, degeneration, and loss of neural tissue, there is proliferation of glial elements, particularly astrocytes, to replace it. However, their role in inflammation has been brought to light only recently (Tandon 2016; Tewari and Seth 2016). Like microglia, neuronal insult/damage also activates astroglia which then secrete a variety of cytokines and chemokines which contribute to neuroinflammation. The relative roles of microglia and astrocytes vary in different conditions. They promote angiogenesis, interaction with other extracellular molecules to regulate vascularization, and clearance of dying cells leading to a scar formation limiting the damaged area. On the other hand, scar arrests the growth of axons in the vicinity of the reactive astrocytes, thus stalling the regenerative process after injury. There is, thus, an active debate on the relative beneficial and detrimental aspect of astrocytes during neuroinflammation.

2.8 Astrocytes and Other Neuropathological Conditions

It is now known that astrocytes play an important role in the clearance of glutamate. The glutamate-induced neurotoxicity is blamed for the pathogenesis of a variety of

neurological disorders, e.g., epilepsy, trauma, stroke, and even neurodegenerative disorders. Astrocytes failing to clear excessive glutamate are responsible for their involvement in these pathologies. Tewari and Seth (2016) in their Table 3.2 have provided a summary of "astrocyte disorders" which include Alzheimer's, Huntington's, and Parkinson's diseases and also epilepsy, autism, multiple sclerosis, and others. It provides information on the nature of astrocyte response in each of these disorders and a list of important recent references. Chapters 8, 9, 10, 11 and 12 are also dealing with the role of astrocytes in brain disorders.

In their extensive review, Verkhratsky and Nedergard (2018) have provided information on some little-known functions of astroglia. These include relation to chemoreception of oxygen, CO_2, and pH and regulation of respiration and circadian rhythm. Their role in higher cognitive function has been postulated.

In summary, astrocytes are highly heterogeneous in form and function. They are intimately integrated into the neural network and control CNS homeostasis at all levels of organization from molecular to the whole organ. Astrocytes play an important role in brain development, neuronal differentiation and guidance, and neurite outgrowth. Recent studies have shown that astrocytes not only regulate neurogenesis but are also the neuronal progenitors. They play an active role in the brain energy production, delivery, utilization, and storage. Astrocytes are chemosensing elements of the brain contributing to systemic homeostasis of ions, metabolites, and energy. Till recently considered non-excitable, they are now known to be excitable primarily regulated by Ca2+ levels in the cytoplasm. They are endowed with a large number of ion channels, neurotransmitters and neuromodulator receptors, and SLC transporters. Astrocytes have been found to secrete a host of molecules (gliotransmitters) which control astrocyte to neuron communication and also synaptic transmission. It is now universally acknowledged that astrocytes modulate both the intrinsic neuronal excitability and the strength of synaptic transmission. The neurovascular unit constituted by the astrocytes provided for focal vasodilation in response to neuronal activity, i.e., the functional hyporemia and neuroinflammation. Disturbances in these diverse physiological functions of astrocytes are therefore closely related to diverse neuropathological disorders and neurodegeneration.

3 Biology of Glia: Part II—Microglia

3.1 History

First recognized by Franz Nissl (1860–1918) during his studies on the histopathology of dementia as the rod cells in 1880, it was Pio del Río Hortega (1882–1945) who along with his student Collado in 1918 using his silver staining technique illustrated the detailed morphology of microglia. According to one of Hortega's biographers, "The microglia danced to him and revealed their graceful limbs ------ under the microscope he found a world of beauty which pleased his artistic soul and satisfied his inquisitive mind." He described microglia as a unique cell type differing

in morphology from other glia and neurons (Del Río-Hortega 1919; Sierra et al. 2016).

Ramón y Cajal, who provided a detailed description of astrocytes in the late 1890s and early 1900s, found evidence for some of other cells (other than neurons and astrocytes) which did not stain as well by his famous gold chloride sublimate method and called them the "third element." Río Hortega, who considered Cajal as his mentor and master, modified the staining techniques such as the ammoniacal silver carbonate and demonstrated that the "third element" of Cajal consisted of two distinct cell types, i.e., microglia (mesoglia) and oligodendrocyte (which he first called interfascicular glia). According to Sierra et al. (2016), "Surprisingly, however, the field of microglia did not advance for decades and some neuropathologists even denied their existence for most part of the twentieth century. Only in late 1960s Georg Kreutzberg started to study these cell types again. This marked a rebirth of microglia research"

3.2 Morphology

Microglia constitute approximately 15–20% of the total glial population (Carson et al. 2006). They are not ectodermal in origin and were believed to be of mesenchymal lineage (Barron 1995). It is remarkable that Hortega in one of his papers on "Putative Origin of Microglia" in 1919 provided a detailed reasoning "to believe that microglia histogenetically differ from ordinary astrocytes and that their nature is mesodermal."

Morphologically resting and activated microglia manifest different characteristics. The former are characteristically elongated cell bodies with spine-like processes that often branch perpendicularly. Nimmerjahn et al. (2005) have demonstrated that even in the resting state, while the soma and main branches remained stable for hours, their processes were remarkably motile, undergoing cycles of formation of extension and withdrawal on time scale of minutes. In contrast, in the activated state, the cell body increases in size; there is a thickening of proximal processes. These processes were observed to directly contact astrocytes, neuronal cell bodies and blood vessels, decrease in ramification of distal branches suggesting that in healthy brain microglia serve some house-keeping function (Fetler and Amigorena 2005).

The morphological and structural evolution of microglia in pathological conditions creates a variety of cell types. When they migrate to the site of injury to perform their phagocytic function, they undergo a hypertrophic transformation and acquire multiple shapes and elongated forms becoming rod cells: when they engulf damaged elements, they become granuloadipose bodies (Del Río-Hortega 1919). This activation is believed to be preceded by molecular events like changes in their expression of cell adhesion molecules, cytoskeleton reorganization, and antigen presentation (Patro and Patro 2004).

Microglia play an important role during the development of the CNS (see below). During this period, they manifest different morphologies, i.e., the ameboid form

which originates from the yolk sac. They acquire a round or irregular shape (Pont-Lezica et al. 2011). This is in contrast to the ramified "or" resting surveillant microglia of adult CNS and the "reactive" or "activated" microglia.

3.3 Distribution

All brain regions contain microglia in varying numbers, but they are more abundant in the gray matter. Microglia interact more or less closely with neurons, both protoplasmic and fibrous astrocytes, and the blood vessels (Graber et al. 2016). Recently, a special type of microglia with close association to neurons has been described by Baalman et al. (2015).

3.4 Functions

Microglia are the immunocompetent resident macrophages of the CNS, responsible for innate immunity. They kill invading microorganisms in the brain, remove debris, and facilitate tissue repair after injury. During development of the brain, they play a major role in the developmental pruning of unnecessary synapses (Rakic and Zecevic 2000). In the adult brain, the "ramified" microglia are really not resting but continuously survey the healthy brain for any damage as shown by in vivo time-lapse video microscopy by Nayak et al. (2014). They serve an immune-surveillance function and can sense subtle changes in the microenvironment through a variety of surface receptors (Barron 1995; Nimmerjahn et al. 2005). Such microglia release various neurotrophic growth factors to promote the neuronal survival and also enhance neurogenesis. During an injury or degeneration to the brain, the microglia get activated and release neuroinflammatory molecules, growth factors, matrix proteins, chemokines, prostaglandins, and reactive free radicals (Patro et al. 2016; Streit 2005; McGeer and McGeer 2001).

Microglia in Immune Regulation

As mentioned earlier, microglia when activated provide innate immunity to the CNS. Such activated microglia release a number of immunocompetent molecules and chemokines like macrophage inflammatory protein 1α (M1P1α), monocyte chemoattractant protein 1 (MCP1), IL, 1 L/β, IL3, IL6, IL10, IL12, IL15, IL18, and tumor necrosis factor-α. These molecules not only control inflammation but also regulate immune response of the brain. At the same time, activated microglia also promote neuroprotection by releasing anti-inflammatory and growth factors like NGF, BDNF, and NT-3. The relative role of microglia in neuronal damage and protection depends upon a variety of factors like the nature of damage and pathology, the duration of insult (acute or chronic), and the age of the patient (Suzuki et al. 2004; Colton 2009).

Role of Microglia in Neuroinflammation and Diverse Neuropathologies

Microglia, the resident macrophages of the nervous system, play a dominant role in the pathophysiology of neuroinflammation, a common feature of brain pathologies, from the moment of an insult or injury, damage, or destruction to the neural tissue. Microglia invade the affected region and get activated. Even in their resting stage, they serve an immune-surveillance function. They can sense subtle changes in the microenvironment through a variety of highly conserved pattern recognition surface receptors (Barron 1995; Nimmerjahn-et al. 2005). Like all toll-like receptors (TLRs) to recognize both pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs). On the other hand, activated microglia are capable of releasing a variety of pro-inflammatory factors like NO, H_2O_2, OH, NOO, TGFX3, and PGE2 and a variety of interleukins (Streit et al. 1999; Block and Hong 2005; Tandon 2007). While the role of microglia in acute insult to the brain was well known, it is only recently that their role in neuroinflammation associated with neurodegeneration has been brought to light (Block and Hong 2005; Brown and Neher 2010). Patro et al. (2016) in their paper (Table 2.1) have summarized the neurodegenerative and neuroprotective role of microglia in various pathological conditions which include AD, PD, HD, ALS, MS, cerebral ischemia, prion disease, HIV, AIDS, brain tumor, and chronic pain.

While the neurotoxic or destructive role of microglia is well known, activated microglia also act as a defense mechanism for various insults to the brain. They kill invading microorganisms, remove debris, and facilitate tissue repair after injury. Being the immune cell of the CNS, they protect and repair the damage and also facilitate the healing process (Alosi 2001; Ekdahl et al. 2009). Apart from their conventional neuromodulatory function, they contribute to neuroendocrine regulation as well as neurogenesis (Chan et al. 2007; Ghosh and Ghosh 2016).

4 Biology of Glia: Part III—Oligodendrocytes

4.1 History

Oligodendrocytes, now well recognized as the myelinating cells of the central nervous system, were first defined by Río Hortega as a distinct entity—a constituent of the "third element" of his mentor Ramón y Cajal whose staining technique had failed to reveal them. Working in Hortega's laboratory, Penfield succeeded in developing an exquisite picture of these cells. As mentioned in his autobiography, "No Man Alone," "One morning, I was thrilled to see that 'Oligo cells' in one of my sections were especially clear, complicated and beautiful. The cells were not 'few-branching' but many branching '---------'. Then I stood up and handed a section to don Pio. Finally, he turned and said quietly-----. 'Casi mejor quo Yo' (Almost better than I could do)." On the advice of Hortega, this was published in *Brain* by Penfield (1924).

4.2 Origin and Development of Oligodendrocytes

Studies of the human fetal forebrain suggest that human oligodendrocytes have multiple origins. Simultaneous presence of three different populations which give rise to oligos has been reported (Jakovcevski and Zecevic 2005). However, it is not known whether oligodendrocytes from these different sources have different roles, myelinate different axonal pathways, or affect the outcome of CNS pathologies (Bradl and Lassmann 2010). Most of the earlier studies on oligodendrocyte development and myelin formation were on rodents. Even though there are some differences between the rodent and human oligodendrocytes, there is a great deal of similarity. They are all derived from oligodendrocyte progenitor cells (OPCs) which arise from the medial ganglionic eminence and anterior endopeduncular area of the ventral forebrain. These OPCs populate the entire embryonic telencephalon including the cerebral cortex (Bradl and Lassmann 2010). There are several waves of these cells, and they have to travel long distances in order to end up in their final place of destination. The migration is guided by regulation signals like PDGF, FGF, netrins, semaphorins, and chemokines CXL. Once located at their final destination, some OPCs persist into adulthood, while the vast majority differentiate to myelin-producing oligodendrocytes (Kuhn et al. 2019).

Rogister et al. (1999) provided a detailed account of the origin of OPCs from neural stem cells through the developing CNS. Jakovcevski and his colleagues have elaborated the sequence of oligodendrocyte development in human fetal telencephalon (Jakovcevski and Zecevic 2005; Jakovcevski et al. 2009). There are some differences between the OPCs distributed in white and gray matter, being evenly distributed in the former and being less abundant in the latter.

Recent molecular biological investigations have revealed distinct markers for various stages of development of OPCs and embryonic and adult oligodendrocytes (Kuhn et al. 2019).

4.3 Oligodendrocytes and Myelination

The key function of oligodendrocytes is myelination of the axons in the CNS. The myelin sheath is an extension of oligodendrocyte (and Schwann cell) plasma membrane that wraps around axons in concentric fashion. In the CNS, oligodendrocytes myelinate large diameter axons and provide trophic support for the underlying axons (Kuhn et al. 2019; Simons and Trajkovic 2006). Myelination is a complex and highly regulated process. Myelination occurs as a result of the upregulation of myelin protein expression which leads the number of wraps around the axon. With time, the number of wraps increases, thereby forming compact myelin internodes. Throughout the process, more oligodendrocytes are produced than necessary. The extras undergo apoptosis. The final number of oligos that survive matches the number and length of axons that need to be myelinated (Barres and Raff 1999; McTigue and Tripathi 2008). According to Barres and Raff (1993), although oligos themselves do not divide, the proliferation of oligodendrocyte precursor cells

(OPCs) that give rise to them does depending upon the electrical activation of the neighboring axons. They observed that axonal electrical activity normally controls factors that are responsible for the proliferation of OPCs and thereby helps to control the numbers of oligos that develop in the region (for details, see Gibson et al. 2014). It has been shown that axons do so through regulating astrocytes, but not OPC proliferation. Furthermore, oligos survival depends on the release of PDGF, IGF-1, CNTF, or NT-3 by astrocytes (Barre and Raff 1993, 1999; Barre et al. 1993). In addition, axonally derived neuregulin (NRG) is a likely candidate signal that mediates axonally promoted survival of mature myelinating oligodendrocytes. For all practical purposes, Schwann cells in the peripheral nervous system behave in the same manner (but this is not being discussed in any details here).

Oligodendrocytes not only ensheath axons to electrically insulate these structures but also induce a clustering of sodium channels along the axon, at the node of Ranvier, which is one important prerequisite for saltatory nerve conduction (Bradl and Lassmann 2010). Molecular signals that initiate CNS myelination are still ill understood. However, they provided evidence that the onset of CNS myelination in normal development might be determined by the degree of neuronal differentiation and not by the timing of an intrinsic oligodendrocyte differentiation program. It is now well established that there is a cross-talk between the neurons and oligodendrocytes for the initiation of myelination. Electrical activity is believed to control the release of PDGF (platelet-derived growth factor) by the neurons which enhances mitosis of OPCs. On the other hand, myelin- forming cells also send essential signal to axons. Expression of myelin genes such as myelin-associated glycoprotein (MAG) and PLP appears necessary for axonal function and survival throughout life (Rogister et al. 1999; Yin et al. 1988). Although the electrical activity of neurons in the CNS is an essential promyelinating factor, additional changes on neurons seem to be needed to drive efficient myelin formation (Barres 2008; Bradl and Lassmann 2010).

There is increasing evidence that cells of the oligodendrocyte linage are capable of responding to a variety of neurotransmitters. Glutamate released by axons of glutamatergic neurons could be a regulator of OPC numbers (Yuan et al. 1998). Similarly, expression of non-NMDA Kainate, AMPA-preferring glutamate receptors, adrenergic receptors and several others by OPC possibly regulate their proliferation and differentiation. This has been extensively reviewed by Araque et al. (1999), Rogister et al. (1999), Mc Tigue and Tripathi (2008) in their Table 1 provide a long list of positive and negative effect of different molecules on OPC proliferation and differentiation.

4.4 Non-Myelinating Functions of Oligodendrocytes and OPCs

In addition, another player in the early axon/oligodendrocyte cross-talk is Jagged, a ligand that signals notch 1 receptor on OPC and inhibits oligodendrocyte differentiation (Wang et al. 1998). Besides, the primary function of myelination oligodendrocytes and OPCs has recently been shown to have immunomodulatory

capacity. OPCs express cytokine receptors and assess their microenvironment through filopodia extension (Kuhn et al. 2019). According to Kirby et al. (2019), OPCs present antigen and are cytotoxic targets in inflammatory demyelination. In response to inflammatory cues, OPCs, like microglia, have been shown to migrate to the site of injury. Their precise role in this regard needs to be explored further (Kirby et al. 2019). In short, oligodendrocytes are now recognized as critical regulators of neuronal function in CNS development, homeostasis, and regeneration (Kuhn et al. 2019).

Oligodendrocytes and the myelin sheath metabolically support axons. According to Lee et al. (2012), there is enough evidence to suggest that oligodendroglia support axon survival through a myelin-independent mechanism. Oligodendrocytes can provide trophic support for neurons by the production of neurotrophic factors like GDNF, BDNF, and insulin-like growth factor 1 (IGF1) (Du and Dreyfus 2002). Oligos can generate lactate, which can then be transferred to axons to generate metabolic energy in the form of ATP (Bercury and Macklin 2015). This is done with the help of (monocarboxylate transporter 1) MCT 1 lactate transporter which is localized to oligodendrocytes in vivo. In addition, a number of glycolytic and Krebs cycle enzymes contribute to glucose metabolism and ATP production (Kuhn et al. 2019; Lee et al. 2012; Pierre and Pellerin 2005).

4.5 Oligodendrocytes and CNS Pathology

A combination of high metabolic rate with its toxic by-products, high intracellular iron and low concentration of the antioxidative glutathione, oligodendrocytes are particularly vulnerable to oxidative damage and mitochondrial injury. Hence, the oxidative damage is a common contribution to the oligodendrocyte loss under many pathological conditions like MS, ischemia and injury, and inflammation and infection. Oligodendrocytes also express a variety of molecules which make it susceptible to excitotoxic cell death, glutamate toxicity, and damaging effect of extracellular ATP. Oligodendrocyte loss can also occur as a result of exposure to inflammatory chemokines like tumor necrosis factor-α (TNFα) (Bradl and Lassmann 2010; Barres 2008; Jana and Pahan 2006; Jurewicz et al. 2005).

Oligodendrocytes are easily destroyed by specific autoantibodies as seen in patients with MS-like inflammatory demyelination diseases. As a matter of fact, demyelination and oligodendrocyte death are common features of inflammatory white matter lesions as Devic's disease (neuromyelitis optica) and autoimmune encephalomyelitis.

The above pathogenetic mechanisms may damage oligodendrocytes alone or in association with damage to the myelin also. It has been observed that different pathological patterns of white matter injury reflect different mechanisms of myelin and oligodendrocyte damage. Primary oligodendrocyte injury is seen in conditions of infections such as progressive multifocal encephalopathy. In contrast, combined demyelination and oligodendrocyte damage is observed in ischemic lesions of the white matter and stroke and also in severe inflammatory brain lesions as seen in

acute multiple sclerosis, virus encephalitis like herpes simplex encephalitis, and progressive multifocal encephalomyelitis (Aboul-Enein et al. 2003; Bradl and Lassmann 2010). Increased number of oligodendrocytes, unassociated with demyelination, has been reported a couple of days after spinal contusion. This remarkable amount of oligogenesis occurs in a gliogenic zone along the borders of spinal contusion lesion (Tripathi and Mc Tigue 2007; Mc Tigue and Tripathi 2008). Oligodendrocyte genesis has also been observed along the borders of ischemic lesion in the brain where the new cells are co-localized with astrocytes, microglia, and macrophages (Mabuchi et al. 2000).

In addition to the acute lesions of the CNS mentioned above, oligodendroglial pathology is also reported in several neurodegenerative disorders. Rarely genetic defects that lead to oligodendrocyte damage are reported in some leukodystrophies; this is due to the accumulation of mutated PLP1 (Torii et al. 2014). White matter pathology is a characteristic of Alzheimer's disease (AD) (Fischer et al. 2015; Desai et al. 2010). However, oligodendrocytes and demyelination are believed to occur secondary to degeneration (Xu et al. 2001). Oligodendrocyte pathology can be evident even before any neurodegenerative event materializes (Fischer et al. 2015).

A reduction of perineuronal oligodendrocytes in gray matter of prefrontal cortex has been reported in schizophrenia (SZ). This is specially so in the left CA4 region of the anterior and posterior hippocampus. This decreased number of oligodendrocytes was found to be associated with cognitive deficit. In addition, Raabe et al. (2019) have demonstrated that expression of myelin and oligodendrocyte-related genes was profoundly affected in the prefrontal, temporal, and occipital cortex, hippocampus, and basal ganglia (for further details, also see Cassoli et al. 2015; Uranova et al. 2007; Vikhreva et al. 2016; Schmitt et al. 2015). Lee et al. (2012) demonstrated that oligodendrocyte-specific MCT 1 (monocarboxylate transporter 1) loss causes axonopathy. Similarly, the reduced ability of gray and white matter oligodendroglia to support motor neurons caused by altered MCT1 expression may contribute to amyotrophic lateral sclerosis (ALS) pathogenesis.

Oligodendrocytes are the cells of origin of both oligodendrogliomas and oligoastrocytomas. On the basis of an immunohistological and electron microscopic study of 55 such tumors, Sarkar et al. (1988) observed that both these tumors arise from a common progenitor cell capable of differentiation into both oligodendrocyte and astrocyte. The nature and degree of differentiation depend probably on gene expression and/or some microenvironmental factors. Oligodendrogliomas express S100, MAP 2, and other markers; IDH1 (R132H) is uniformly positive in the majority of oligodendrogliomas. But there is no specific immunohistochemical marker for the diagnosis.

More than 90% of oligodendrogliomas harbor IDH1 mutation. Concurrent deletion of chromosomal arms 1P and 19q is the diagnostic alteration. Most common mutation in IP/19q co-deleted oligodendrogliomas is present in CIC gene on 19q.13.2 followed by FUBP1 mutation on 1p 31.1. Prognostically favorable role of IDH1 mutation and 1P/19Q co-deletion is noted in those who are treated with adjuvant radiotherapy and/or chemotherapy in contrast to those treated with surgery alone (Rao and Santosh 2018).

Advances in knowledge about the structure and function of glial cells have a major impact on our understanding of normal neural function and pathogenesis of a variety of brain diseases, specially neuroinflammation and neurodegeneration.

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