Review

Astrocyte, the star *avatar*: redefined

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Until recently, the neuroscience community held the belief that glial cells such as astrocytes and oligodendrocytes functioned solely as "support" cells of the brain. In this role, glial cells simply provide physical support and housekeeping functions for the more important cells of the brain, the neurons. However, this view has changed radically in recent years with the discovery of previously unrecognized and surprising functions for this underappreciated cell type. In the past decade or so, emerging evidence has provided new insights into novel glial cell activities such as control of synapse formation and function, communication, cerebrovascular tone regulation, immune regulation and adult neurogenesis. Such advances in knowledge have effectively elevated the role of the astrocyte to one that is more important than previously realized. This review summarizes the past and present knowledge of glial cell functions that has evolved over the years, and has resulted in a new appreciation of astrocytes and their value in studying the neurobiology of human brain cells and their functions. In this review, we highlight recent advances in the role of glial cells in physiology, pathophysiology and, most importantly, in adult neurogenesis and "stemness", with special emphasis on astrocytes.

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1. Introduction

The term "glial cell" traditionally refers to three main categories of cells. The first two categories are Schwann cells and oligodendrocytes, which are the myelin-forming cells of the peripheral and central nervous systems, respectively. These cell types surround the neuronal axons with a myelin sheath for insulation and facilitation of fast and efficient transmission of nerve impulses. The third main category of glial cells comprises the stellate cells called astrocytes. Although astrocytes do not provide a myelin sheath for axons, they do provide critical support for neuronal function. In addition to these, there is one more type of "glial" cell, called the microglial cell. Microglial cells are the immune effector brain cells that originate from myeloid progenitor cells mostly found in the bone marrow, a non-central nervous system (CNS) tissue, due to which they are often thought of as non-neural cells.

Keywords. Astrocytes; glia; neural stem cells; neurodegeneration; neurogenesis; neuron

Abbreviations used: ACT, α-antichymotrypsin; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APC, antigen-presenting cell; APP, amyloid precursor protein; ATP, adenosine triphosphate; BBB, blood–brain barrier; BchE, butyrylcholinesterase; BDNF, brain derived neurotrophic factor; BLBP, basic lipid-binding protein; CNS, central nervous system; CNTF, ciliary neurotrophic factor; COX-2, cyclooxygenase-2; CXCL, chemokine CXC ligand; EDGF, epidermal-derived growth factor; FGF, fibroblast-derived growth factor; FGFR, fibroblast growth factor receptor; GABA, gamma amino butyric acid, GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; IGFBP6, insulin-like growth factor-binding protein-6; IL, interleukin; iNOS, inducible nitric oxide synthase; LIF, leukaemia inhibitory factor; LTP, long-term potentiation; MBP, myelin basic protein; MCP, monocyte chemoattractant protein; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMDAR, N-methyl-D-aspartate receptor; NGF, nerve growth factor; NSC, neural stem cell; PLP, proteolipid protein; RMS, rostral migratory stream; SDF, stromal derived factor; SIC, small inward current; SOD, superoxide dismutase; SVZ, subventricular zone; TH, tyrosine hydroxylase; TNF, tumour necrosis factor; VM, ventral mesencephalic; VZ, ventricular zone

This review focuses on the astrocyte, since several recent developments have challenged the traditional view that these cells are mere passive support cells. The focus of this review is centred on understanding how new knowledge of these important glial cells relates to the functioning of the human CNS.

For decades, glial cells were regarded simply as "padding cells" of the brain and were largely overshadowed by the more overt complexity and functional importance of neuronal cells in the human CNS. However, astrocytes have become the focus of recent attention due to the recognition of some previously unknown functions (Svendsen 2002; Volterra and Steinhauser 2004; Volterra and Meldolesi 2005; Diamond 2006; Jagasia *et al* 2006). The word "glia", derived from the Greek word that commonly refers to glue, was coined by Virchow in 1846 to describe a cell type whose function was to fasten the nerve cells together in the brain. Astrocytes are classically identified histologically by the expression of glial fibrillary acidic protein (GFAP), which has been regarded as the cell-specific marker for these star-shaped cells (Eng *et al* 2000). It is also known, however, that S-100 beta is widely recognized as another astrocytic marker, though not universally (Steiner *et al* 2007). Differentiated astrocytes are also characterized by the presence of the enzyme glutamine synthetase, which converts glutamate into glutamine, and is specifically present on astrocytes (Loo *et al* 1995; Norenberg 1979). Astrocytes usually outnumber neurons in the human brain and constitute up to 20–50% of brain volume. They are known for their highly fibrous make-up and great structural intricacy. These cells are also uniquely characterized by a dense array of processes interposed between neuronal entities, some of which contact and envelop local vascular walls that help in forming an important component of the brain called the blood–brain barrier (BBB). Furthermore, astrocytes are also involved in the regulation of cerebral blood flow and neurovascular coupling, as well as supporting immune defence mechanisms by producing various immunoactive cytokines (Benveniste 1992; Anderson and Nedergaard 2003; Iadecola 2004; Haydon and Carmignoto 2006; Kim *et al* 2006; Koehler *et al* 2006).

Traditionally, astrocytes are believed to be responsible for the regulation and optimization of the functional environment of neurons in the brain. Astrocytes maintain tight control of extracellular ion concentration, pH homeostasis, glucose levels and provide metabolic substrates in addition to the secretion of neuroactive substances (Gee and Keller 2005). As efficient caretakers, astrocytes scavenge neuronal waste products, including metabolic byproducts and neurotransmitters released during synaptic transmission at the synaptic cleft. These compounds are sequestered through active uptake. In short, astrocytes are multifunctional, efficient housekeeping cells that help neurons become progressively specialized for the tasks of information processing and encoding. As such, they are often regarded as masters of communication in the mammalian brain. Astrocytes function structurally and functionally as ideal sensors and regulators of the local microenvironment (Nedergaard *et al* 2003) in the human CNS. They also play a prominent role in the regulation of glutamate homeostasis in the brain by well-balanced release, uptake and metabolism of glutamate, as they are equipped with a powerful battery of glutamate transporters (Schousboe and Waagepetersen 2005). Such studies draw attention to the previously unrecognized, versatile role of astrocytes in mammalian brain functions.

Emerging evidence suggests that astrocytes perform a much wider range of functions than was previously appreciated. These functions include neuronal differentiation, regulation of axonal guidance, formation of synapses, brain plasticity, homeostasis and even communication. Recent studies have found that astrocytes may be important mediators of thyroid hormone in neuronal development (Trentin 2006; Ullian *et al* 2004). Several reports strongly suggest that astrocytes may be important in neurogenesis and may even serve as neural stem cells (NSCs) (Wozniak 1999; Heins *et al* 2002; Joannides *et al* 2004; Ma *et al* 2005; Givogri *et al* 2006; Pillai *et al* 2006; Ihrie and Alvarez-Buylla 2008). It has been demonstrated that astrocytes from the neonatal brain increase neurogenesis from cultured adult subventricular zone NSCs (Lim and Alvarez-Buylla 1999). In addition, astrocytes derived from the adult hippocampus, but not from the adult spinal cord, promote neurogenesis from adult hippocampal NSCs in co-culture by increasing proliferation and instructing neuronal fate specification (Song *et al* 2002). The addition of these new properties to the known repertoire of glial functions has significantly enhanced our appreciation of astrocytes in the normal functioning of the adult brain.

In this review, the conventional concepts of astrocyte functions have been revisited to emphasize that astrocytes are not simply cells that pack the neuronal network of the brain, but in fact perform highly specialized functions that provide new insights into the importance of this subtype of glial cells. A detailed summary of recent advances in our understanding of the novel functions of astrocytes as dynamic regulators of neurogenesis, neuron–glia cross-talk, neuronal networking, phenotype and functional activity, as well as their role in various neurodegenerative diseases is also provided.

2. Neuron–glia cross-talk during synaptic transmission and integration

Until recently, the generation of action potentials was considered unique to the neurons. The idea that glial cells may possess similar properties of information processing

did not receive much attention, possibly because the membrane of glial cells lacked the physical properties that were considered essential for the generation of action potentials. For decades, glial cells were regarded as passive participants in synaptic functions. However, several recent reports have suggested the existence of a more dynamic, two-way cross-talk between the glia and neurons. Astrocytes have been shown to efficiently perform some very important functions such as capturing of neurotransmitters from the synaptic cleft and release of energetic substrates which are essential to metabolically sustain high synaptic activities (Magistretti and Pellerin 1996), thereby revealing closer neuron–glia interactions. Astrocytes are closely associated with synaptic structure. For example, synapses in the cortex are ensheathed by astrocytic processes (Ventura and Harris 1999). Similar ensheathing of the synapse is also found in the cerebellum by specialized astrocytes called Bergmann glia (Grosche *et al* 1999, 2002). In the retina, synapses are similarly supported by Muller cells (Newman 2001). There are reports as far back as 1966 that glial cells actually respond to neuronal activity with membrane potential depolarization (Kuffler *et al* 1966; Orkand *et al* 1966). In the past twenty years, it has been demonstrated that astrocytes possess a battery of neurotransmitter and neurohormone receptors (Verkhratsky and Kettenmann 1996). These findings suggest that astrocytes sense neuronal activity and are actively involved in signal transmission, based largely on calcium mobilization studies (Deitmer *et al* 1998; Verkhratsky and Toescu 1998). In response to neurotransmitters such as glutamate, gamma amino butyric acid (GABA), adrenaline, adenosine triphosphate (ATP), serotonin and acetylcholine, among others, astrocytes demonstrate an increase in the intracellular concentration of calcium (Finkbeiner 1993; Porter and McCarthy 1997; Perea and Araque 2007).

The N-methyl-D-aspartate receptors (NMDARs) (Dingledine *et al* 1999) play key roles in synaptic transmission, long-term potentiation (LTP) (Bliss and Collingridge 1993), activity-dependent refinement of synaptic connections (Constantine-Paton 1990; Constantine-Paton *et al* 1990; Bourne and Nicoll 1993) and excitotoxic neuronal damage (Choi and Rothman 1990). More recently, it has been highlighted that the NMDAR is a key player in excitatory transmission and synaptic plasticity in the CNS. NMDARs are heteromeric complexes comprising NR1 and different NR2 subunits. The subunit composition of NMDARs varies with their subcellular distribution; for example, the NR1/NR2A complex dominates at the synapse, whereas the NR1/NR2B complex is predominant in extrasynaptic membranes. Extrasynaptic NMDARs are activated by the glutamate escaping from the synaptic cleft following rapid synaptic action. The same extrasynaptic NMDARs are also responsible for uptake from non-synaptic glutamate sources, from neighbouring cells, the astrocytes. The calcium ion-dependent release of glutamate from astrocytes has been recently shown to act on the extrasynaptic NMDARs to promote a coordinated or synchronized activity of distinct subsets of neurons in the CA1 hippocampal region, thereby suggesting the important role astrocytes may play in brain information processing (Fellin *et al* 2004). Astrocytes respond to the synaptic release of the neurotransmitter glutamate with significant increase in intracellular calcium ion concentration and, in turn, modulate neuronal excitability and synaptic transmission by releasing neuroactive substances called gliotransmitters (Araque *et al* 1999; Beattie *et al* 2002; Perea and Araque 2007) that signal back to the neurons. Studies on the assessment of the functional consequence of increased calcium ion concentrations in astrocytes on co-cultured neurons have revealed that small inward currents (SIC) can be generated in associated neurons, which are glutamate-mediated and act via the NMDARs (Araque *et al* 1998). Such studies signify a highly plastic signalling mechanism that underlies the bi-directional communication between neurons and astrocytes (Porter and McCarthy 1996; Pasti *et al* 1997), and highlight the importance of glutamate in neural tissue. While the role of gliotransmitters in modulating synaptic transmission has been demonstrated, their role in synaptic networks had not been clearly defined until recently. The intricate role of astrocytes in ATP-mediated regulation of synaptic strength and plasticity has been recently explained using a transgenic animal model (Pascual *et al* 2005). Astrocytes tonically suppress synaptic transmission via the A1 receptors following adenosine accumulation inside them. Thus, the kinetics of ATP hydrolysis and adenosine accumulation provides a synaptic network with unique spatiotemporal conditions to control synaptic transmission.

The intracellular calcium ion concentration signal triggered in astrocytes by the synaptic release of glutamate can prompt the release of signalling molecules far from the site of initial excitation. Such signals may be disseminated to astrocyte end-feet that are in contact with cerebral arterioles and may play a role in regulation of cerebral blood flow (Zonta *et al* 2003). Activated astrocytes could be mediators of a neuronal activity-dependent event in cerebral blood flow regulation and may also be involved in controlling the permeability of the BBB. The consequences of astrocyte activation following high neuronal activity can thus be considerable in the functioning of the brain.

Several investigators have described augmentation of blood flow in brain areas with enhanced neural activity, which may perhaps be due to increased energy demand by the neural cells in that region. Recently, the role of astrocytes in controlling the microcirculation of the brain has been documented (Takano *et al* 2006). Cortical astrocytes have been shown to be equipped with mechanisms for rapid

vasodilatation, which is mediated through alterations in their intracellular calcium ion concentrations in response to rapid neural activity.

It has been reported that NMDARs, previously believed to be present exclusively on neurons, are also expressed in microglial cells, astrocytes and oligodendrocytes. This suggests that these receptors may be important for neuron–glial cross-talk. In fact, cortical astrocytes also express functional NMDARs which are important for neuronal–glial signal transmission (Lalo *et al* 2006; Verkhratsky and Kirchhoff 2007) and astrocytes boost synaptic functions via interaction with pre-synaptic NMDARs (Jourdain *et al* 2007). Recently, the role of astrocytes in synaptic transmission has been discussed in great detail (Vesce *et al* 1999; Fields and Stevens-Graham 2002; Newman 2003; Haydon and Carmignoto 2006; Kozlov *et al* 2006; Martin *et al* 2007).

Astrocytes in culture as well as *in situ* generate calcium waves in response to electrical and chemical stimuli, following strong synaptic stimulation or exposure to neurotransmitters via neurons. In the astrocytes, elevations in intracellular calcium ion concentration occur mostly following neuronal activity. However, the pioneering work by Parri and his colleagues demonstrated that astrocytes by themselves are capable of generating changes in intracellular calcium ion concentration, independent of neurons. Their experiments with freshly prepared slices of rat ventrobasal thalamus demonstrated that astrocytes *in situ* spontaneously display oscillations in intracellular calcium ion concentration and can cause NMDAR-mediated neuronal excitation in the mammalian CNS (Parri *et al* 2001).

Neuron–astrocyte cross-talk is based on the expression of different neurotransmitter receptors by the astrocytes. The endocannabinoid (endogenous transmitter) system is an important intercellular signalling system involved in a wide variety of physiological processes including those in the brain. Cannabinoid receptors play key roles in brain function, and cannabinoid effects on brain physiology and drug-related behaviour are mediated by receptors present in the neurons. Recently, it has been shown that endocannabinoids released from the neurons activate cannabinoid receptors, which facilitate the mobilization of calcium stores in the astrocytes via a phospholipase-C dependent mechanism. This defines a new role for astrocytes in non-synaptic interneuronal communication in the endocannabinoid–glutamate system (Navarrete and Araque 2008).

Glia–neuron communication is generally considered to be glutamate-mediated; however, the amino acid D-serine has been categorized as another important gliotransmitter (Mothet *et al* 2000). Exclusively synthesized in the astrocytes (Stevens *et al* 2003; Wolosker *et al* 1999), D-serine is considered an endogenous ligand for NMDARs in the brain. Recently, astrocyte-derived D-serine has been shown to play an important role in controlling NMDAR activity and modulates synaptic plasticity (Panatier *et al* 2006). This further substantiates the importance of astrocytes in synaptic transmission and neuron–glia communication.

Integration of new neurons into the existing neuronal circuitry is mandatory for functionality and contribution to brain function (Doetsch and Hen 2005; Ming and Song 2005). It is of great interest, therefore, that astrocytes have also been cited as being important for the synaptic integration of neuronal cells. In fact, synaptic integration of newly formed neurons derived from adult hippocampal NSCs is promoted by co-culturing them with adult hippocampal astrocytes (Song *et al* 2002). Glia-derived factors such as the extracellular matrix protein thrombospondin-1 and -2, as well as -4, all secreted during brain development, have been found to be important for synapse formation by promoting synaptogenesis and neurite outgrowth (Arber and Caroni 1995; Christopherson *et al* 2005). Further, it has been recently demonstrated that glutamate exocytosis from astrocytes in the hippocampal dentate molecular layer enhances the synaptic strength of excitatory synapses on the dentate granule cells (Jourdain *et al* 2007).

The recent revelations about the role of astrocytes in neuron–glia interplay have been astonishing and help in better understanding mammalian brain functions. Several landmark discoveries in the past decade on the role of calcium ions in astrocytes have opened up avenues for bolder and newer research initiatives to look at neuron–glia communication from a closer angle. This may help in the identification of novel cellular and molecular targets for designing drugs to treat neurological disorders.

3. Glial cells as neural precursor cells and their role in neurogenesis

3.1 *Radial glial cells as neural precursor cells*

The idea that glial cells could function as neuronal precursor cells dates back to the late nineteenth century. Renowned histologists such as Golgi, Magini and His observed for the first time that mitotic activity in the developing cortex, as well as throughout the nervous system, occurred mainly at the apical or ventricular surface of the neuroepithelium. Although it was believed that the ventricular zone (VZ) was the main histological compartment harbouring neuronal and glial progenitor cells, the debate continued over the actual morphological features of neuronal and glial progenitors in the VZ (Rakic 2003a,b). Histologists Rauber and Merk were the first to report that mitosis was not limited to the VZs only, but also occurred in areas just outside the ventricular regions. Several other investigators later confirmed these findings (Boulder Committee 1970; Smart 1973). It is generally believed that adult neurogenesis in most of

the mammalian species occurs in two distinct regions of the brain: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus (Alvarez-Buylla *et al* 2002, 2004; Ming and Song 2005) and, recently, the presence of astrocytic cells in this region has been discussed (Ihrie and Alvarez-Buylla 2008).

In the developing as well as adult CNS, neurons typically differentiate from NSCs via an intermediate fate-restricted, precursor cell stage, rather than directly from NSCs. The inclusion of this intermediate stage is necessary in order to better explain the process of neurogenesis during CNS development, considering the complexities involved in the process of differentiation and regionalization. Distinct cell types are generated in a coordinated manner via a common pool of CNS precursor cells that involve radial glial cells, astroglial cells and, most likely, other yet unidentified precursor cell populations.

Radial glial cells were identified in the brain approximately 100 years ago, but were not termed as such for several more years. Although radial glial cells arise from the neuroepithelial cells, their capacity for differentiation is more restricted than that of neuroepithelial cells. Radial glial cells were initially considered important in the developing nervous system, serving not only as glial progenitors, but also as the physical scaffold upon which newborn neurons migrate. However, it has since been reported that radial glial cells can also function as neuronal precursors which contribute substantially to the process of neurogenesis (Parnavelas and Nadarajah 2001; Campbell and Gotz 2002; Ever and Gaiano 2005; Gotz and Barde 2005; Malatesta *et al* 2008). Radial glial cells have been shown to generate neurons in slice cultures and *in vitro* (Malatesta *et al* 2000; Noctor *et al* 2001).

It is now believed that radial glial cells constitute the majority of precursor cells in the VZ of the cortex during neurogenesis (Hartfuss *et al* 2001; Malatesta *et al* 2003). However, this does not appear to be the case for radial glial cells present in the basal ganglion region, where they mostly generate glial cells (Malatesta *et al* 2003). In the basal ganglia, new neurons are generated from a distinct set of precursors derived from the SVZ located on top of the VZ (Smart 1976). Thus, it can be suggested that neurons originate in two main ways: from radial glial cells, as seen in the developing CNS, or from precursor cells in the SVZ, as observed in the developing basal ganglia (Malatesta *et al* 2003). Interestingly, Cre/*loxP* fate mapping and clonal analysis has recently demonstrated that radial glial cells serve as neuronal precursor cells not only in the cortex region, but also throughout the CNS. This is based on the observation that radial glial cells in all regions of the brain pass through a neurogenic stage of development (Anthony *et al* 2004). A detailed account of the cascades of transcription factors that may be critical for the generation of neurons from radial glial cells, as well as the cellular and molecular mechanisms involved in cortical neurogenesis, have been recently reviewed elsewhere (Hevner 2006; Hevner *et al* 2006).

3.2 *Signalling cascades in radial glial cells*

Neural precursor cells can be maintained in cultures in the undifferentated state as floating neurospheres (Palmer *et al* 1999; Richards *et al* 1992) or adherent to the surfaces (Reynolds and Weiss 1992; Richards *et al* 1992). Fibroblast-derived growth factor (FGF) and epidermal-derived growth factor (EDGF) seem to play an important role in maintaining these cells in an undifferentiated state (Craig *et al* 1996; Kuhn *et al* 1997; Palmer *et al* 1999). The rapidly developing field of neural precursor cells may help to unravel the role of many known and unknown factors that may be crucial for regulating neurogenesis.

Notch signalling is important in maintaining cells in the progenitor stage and for radial glial morphology, as well as determining the fate of NSCs in the developing brain (Gaiano and Fishell 2002; Gaiano *et al* 2000). Notch-1 activation upregulates the radial glial cell marker basic lipid-binding protein (BLBP) and promotes radial glial morphology during embryogenesis (Yoon *et al* 2004). Similarly, neuregulin-ErbB signalling is necessary for the promotion of radial glial characteristics. Reduction of ErbB signalling by either expressing a dominant negative form of ErbB2 or using a mutant of neuregulin in slice cultures promotes transformation of the radial glial cells into astrocytes (Schmid *et al* 2003). In addition to the Notch and neuregulin-ErbB signalling pathways, radial glial cell characteristics are also defined by yet another signalling pathway, the fibroblast growth factor receptor (FGFR) pathway. Lack of FGFR1 leads to significant reduction in radial glial cells suggesting that it is crucial for maintaining the progenitor nature of the radial glial cells. Further, the neurosphere-forming property of radial glial cells is completely lost by the deletion of FGFR1 in these cells (Ohkubo *et al* 2004). It has recently been shown that ezrin plays a role in adult neurogenesis. *In situ* experiments have shown high-level expression of mRNA for ezrin in the SVZ and rostral migratory stream (RMS). Ezrin-positive cells strongly colabel with GFAP and S100 beta (Cleary *et al* 2006; Gronholm *et al* 2005) indicating their astrocytic origin. Beta-catenin, a membrane cytoskeleton protein that is involved in the regulation and proliferation of these neuronal cells, colocalizes with ezrin in the SVZ (Cleary *et al* 2006). Beta-catenin is the downstream effector of the wnt signalling pathway, which functions in the inhibiton of neurogenesis in embryonic stem cells (Haegele *et al* 2003; Logan and Nusse 2004).

Mouse foetal hippocampus studies by Yanagasawa *et al* (2005) reveal the "fate redirection" of the astrocytes to neuronal lineage. Various neuroinductive helix loop helix transcription factors such as NeuroD, Mash-1 and Ngn were upregulated, which was concurrent with downregulation of the repressor molecule id-3 (Yanagisawa *et al* 2005).

The fact that primary astrocytes isolated from newborn and adult hippocampus, as well as newborn spinal cord promote neuronal differentiation of adult NSCs better than astrocytes isolated from other regions of the nervous system indicates that certain unique factors may be expressed by these astrocytes. Gene expression profiling analysis using rat genome arrays demonstrates that astrocytes from regions with higher neuroplasticity had distinct gene expression profiles. Detailed investigations of the functional effects of these factors that are differentially expressed in neurogenesis-promoting and -inhibiting astrocytes indicate that two interleukins, IL-1beta and IL-6, and a combination of factors that included these two interleukins promote neuronal differentiation, whereas insulin-like growth factor-binding protein-6 (IGFBP6) and decorin inhibit neuronal differentiation of adult NSCs (Barkho *et al* 2006). In fact, astrocyte-derived signals can induce neuronal differentiation from even lineage-restricted oligodendrocyte precursor cells through a Noggin-independent mechanism (Gaughwin *et al* 2006).

These findings have generated much excitement among neurobiologists about the potential role of glial cells in the nervous system. This wave of new information about the stem cell-like properties of astrocytes as well as the role of astrocytes in neurogenesis has brought astrocytes into the limelight of stem cell research. They are one of the newer, favourite cell types of developmental neurobiologists. It is thus warranted that astrocytes should be considered an important cell type that may be significant in the recovery process following various insults to the CNS.

4. Astrocytes secrete neurotrophins and modulate neuronal functions

Astrocytes secrete various soluble factors known as neurotrophins. Neurotrophins have a pleotropic effect on the neurons; they are involved in the survival, maturation, differentiation and development of neuronal cells. Evidence is accumulating which suggests that they play a role in neurodegeneration as well (Siegel and Chauhan 2000). Neurotrophins have been categorized into various families such as the nerve growth factor (NGF) superfamily, glial cell line-derived neurotrophic factor (GDNF), neurokine superfamily and non-neural growth factor superfamily. Three types of neurotrophin receptors (tyrosine receptor kinase; *Trk-A*, *Trk-B, Trk-c*) are specifically acted upon by these neurotrophic ligands where NGF acts on *Trk-A,* brain derived neurotrophic factor (BDNF) and NT-4/5 on *Trk B,* and NT-3 on *Trk-c*. NGF acting on *Trk-A* and *p75NTR* mediates downstream action via the MAP kinase pathway. This pathway is involved in the regulation of gene expression and cell survival. Similarly, BDNF, which is mediated via *Trk-B* and *p75NTR*, possesses diverse biological activities in neuronal survival, learning and memory, synaptic plasticity and induction of LTP. Although p75 augments Trk signalling as a co-receptor in cell survival, it is a potent inducer of apoptosis both *in vitro* and *in vivo* (Lad *et al* 2003). A recent work demonstrated the involvement of NGF in amyotrophic lateral sclerosis (ALS). NGF secreted by reactive astrocytes promotes motor neuron loss via *p75NTR* activation (Saez *et al* 2006).

Neurotrophins are synthesized as precursors known as proneurotrophins, which are cleaved to yield the mature forms. Earlier, it was thought that most of the functions could be attributed to this cleaved form but recent studies on proneurotrophins have produced interesting findings. Proneurotrophins are secreted in response to various pathological conditions in the brain (Harrington *et al* 2004). Several pieces of evidence point to increased secretion of pro-NGF in patients with Alzheimer disease (Peng *et al* 2004) and subsequent tissue damage via *p75NTR* activation (Pedraza *et al* 2005)**.** Cell culture studies using hippocampal neurons have shown increased production of NGF by activated astrocytes and subsequent *p75NTR*-mediated tau hyperphosphorylation and neuronal death (Saez *et al* 2006). In motor neuron disease, astrocytes secrete pro-NGF (Domeniconi *et al* 2007). Similarly, pro-BDNF acts preferentially via *p75NTR* and induces neuronal apoptosis through multiple pathways via JNK activation, cytochrome c release, and caspases -9, -6 and -3. It has been shown recently that mice null for *p75NTR* are more resistant to proneurotrophin-induced cell death than wild-type genotypes (Greferath *et al* 2000; Naumann *et al* 2006). *In vivo* studies using kainic acid for seizure induction in mice leads to the local production of proneurotrophins by astrocytes and neuronal loss (Volosin *et al* 2006). Thus, there seems to be a competitive environment between the *Trk* and *p75NTR* pathways that determines cell death or cell survival.

GDNF is known to provide trophic support to the dopaminergic neurons. *In vitro* ventral mesencephalic (VM) primary culture studies have shown GDNF to increase the number of tyrosine hydroxylase (TH)-positive cells, morphological complexity, and neuronal and functional maturation (Schaller *et al* 2005). In animal models of Parkinson disease, *in vivo* delivery of GDNF rescues the nigrostriatal neurons from 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity (Hou *et al* 1996; Cunningham and Su 2002). Similar protection has been observed in rats treated with 6-hydroxydopamine (Kozlowski *et al* 2000; Akerud *et al* 2001). Furthermore, the interplay among different neurotrophins such as GDNF, BDNF and NT-4/5 has been shown to have an additive role

in the survival of dopaminergic neurons (Espejo *et al* 2000; Onyango *et al* 2005; Ducray *et al* 2006).

Ciliary neurotrophic factor (CNTF) and related species such as leukaemia inhibitory factor (LIF), cardiolipins, oncostatins belong to the neurokine superfamily. CNTF has recently attracted the attention of many investigators possibly because of its prominent role in ameliorating neuronal degeneration in neuronal and glial cells following neuronal axotomy (Lee *et al* 1997; Ye *et al* 2004). Astrocytic activation ensues following any trauma or insult to the CNS. CNTF is a potent activator of astrocytes both in culture and *in vivo* (Hudgins and Levison 1998) and increased CNTF expression provides an index for this astrocytic activity. Likewise, CNTF plays a prominent role in glutamate homeostasis during stressful conditions in the brain. It has been shown that redistribution of glutamate transporters such as GLAST and GLT-1 takes place in CNTF-activated astrocytes and this redistribution modulates glutamate excitotoxicity in a positive way (Semkova *et al* 1999; Escartin *et al* 2006). CNTF acts in autocrine and paracrine fashion on astrocytes following insult to the spinal cord (Albrecht*, et al* 2002, 2003, 2006). A similar pattern of increased immunoreactivity is seen in experimental models of intracerebral haemorrhage (Lin *et al* 1998; Yokota *et al* 2005) and neuronal rescue (Del Bigio *et al* 2001; Hermann *et al* 2001). Knock-out models of CNTF have shown that CNTF-null mice have enhanced neuronal degeneration compared to the wild phenotype (Naumann *et al* 2006). Thus, as knowledge is accumulating on glial cells being a source of neurotrophins, they will have a promising role to play in the treatment of various neurodegenerative diseases in the near future.

5. Astrocytes in neurodegenerative diseases

It is now realized that astrocytes have diverse functions; these include their roles as efficient housekeeping cells, signalling cells, in synaptic transmission and, most importantly, as neural precursors. These findings suggest that impairment of these cells even at minor levels may contribute to various neurodegenerative disorders. In fact, astrocytes have been associated with several neurodegenerative disorders. While a detailed discussion of all the disorders associated with glial cells and astrocytes is beyond the scope of this review, some important ones have been discussed here in detail, while others have been summarized in table 1.

5.1 *Role of astrocytes in amyotrophic lateral sclerosis*

ALS, a neurodegenerative disease originally described by Charcot in 1869, is characterized by the selective degeneration of motor neurons from the cortex, brainstem and spinal cord leading to progressive paralysis and muscle atrophy. About 10% of ALS cases show a familial inheritance, 20% of which are caused by mutations in the gene encoding copper, zinc superoxide dismutase (SOD-1) (Rosen *et al* 1993).

A strong glial reaction typically surrounds both the upper and lower motor neurons in patients with ALS. Activated astrocytes, also called reactive astrocytes, play an important role following a CNS insult by undergoing enhanced proliferation. Phenotypically, they exhibit hypertrophic nuclei and cell bodies as well as a distinct pattern of long and thick cell processes, and enhanced expression of cellular markers (Ridet *et al* 1997). Reactive astrocytes in ALS show increased immunoreactivity for GFAP and the calcium-binding protein S100 beta, and express inflammatory makers such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and neuronal NOS (Migheli *et al* 1999). A similar pattern of astrocytic changes has been described in different animal models of ALS, including mice and rats carrying different SOD-1 mutations. In mice expressing the G85R SOD-1 mutation, astrocytes display major morphological and functional changes characterized by the appearance of SOD-1-containing aggregates and decreased expression of the glial glutamate transporter GLT-1 (Bruijn *et al* 1997). Oxidative stress caused by increased production of nitric oxide and peroxynitrite by damaged motor neurons constitutes a potential mechanism for astrocyte activation in ALS. Cultured spinal cord astrocytes briefly exposed to peroxynitrite undergo reactive morphological changes characterized by the appearance of process-bearing cells displaying intense GFAP, iNOS and nitrotyrosine immunoreactivity (Cassina *et al* 2002).

The role of FGF-1 has been recently documented (Cassina *et al* 2005). FGF-1 is secreted in response to oxidative stress, which activates the FGFR1 in the astrocyte nuclei and stimulates the expression of NGF and its secretion. NGF produced by astrocytes induces apoptosis in the motor neurons under specific conditions (Pehar *et al* 2004).

Many ALS patients have elevated glutamate levels in the cerebrospinal fluid and a selective reduction of the astrocytic glutamate transporter EAAT2 (GLT-1), providing support to the excitotoxic hypothesis of motor neuron degeneration. Increased internalization and degradation of GLT-1 has been recently documented in cell culture models (Vanoni *et al* 2004). Excitatory amino acid transmission is dependent upon rapid clearance of released glutamate from the extracellular space by high-affinity glutamate transporters in the astrocytes. In patients with ALS, EAAT2 transporters are decreased or defective, and caspase-3 mediated cleavage of EAAT2 results in the drastic and selective inhibition of this transporter (Sasaki *et al* 2000; Boston-Howes *et al* 2006). Significant loss of EAAT2 transporters has also been

Table 1. Role of astrocytes in neurodegenerative diseases

Disease	Role of astrocyte	Reference
Epilepsy	• Altered glutamate and GABA transporter expression; downregulation of glutamine synthase and glutamate dehydrogenase expression	(Gorter *et al* 2002; Kang *et al* 2006)
	• Decreased glutamate reuptake	(Collignon *et al* 2006)
	• Altered expression of connexin in gap junctions between astrocytes and neurons	
Multiple sclerosis	• Production of chemokines such as monocyte chemoattractant protein-1 (MCP-1)/CCL2 and IP-10/CXCL10	(Tanuma *et al* 2006)
	• Expression of major histocompatibility complex (MHC) class II molecules to function as antigen-presenting cells (APCs) to cytotoxic T cells	(Zeinstra *et al* 2000)
	• Extracellular matrix degradation by the production of matrix metalloproteinases (MMP)	(Ulrich *et al* 2006)
	• Myelin degradation by neutral protease calpain production	(Shields *et al* 1999)
	• Loss of beta-2 adrenergic receptor results in loss of protection and support to neurons, inflammatory injury through the production of pro-inflammatory cytokines and reactive oxygen species	(De Keyser *et al* 2004)
	• Possible role in the remission phase	(Albrecht *et al* 2003)
Huntington disease	• Intranuclear deposition of mutant htt protein leading to glial dysfunction and consequent neuronal disturbances	(Hermel *et al* 2004; Landles and Bates 2004; Shin *et al* 2005)
	• Glutamate exitotoxicity due to decreased glutamate reuptake; decreased expression of glutamate transporter (GLT)-1	
	• Caspase-3 and -6 activation and subsequent neuronal death	
Alzheimer disease	• Caspase-mediated neuronal dysfunction and death	(Mouser *et al* 2006)
	• Enhances fragmented Apo-E4 mediated neuronal death due to excitotoxic accumulation	(Roskams *et al* 2004)
	• Calcineurin-induced activation of astrocytes and subsequent pro-inflammatory and cytokine release	(Norris *et al* 2005)
	• Inflammatory cell recruitment and, chemokine and cytokine activation	(Tuppo *et al* 2005)
	• Decreased intercellular communication in astroglial cells induced by β-amyloid and consequent decreased neuronal survival	(Meme *et al* 2006)
Stroke/hypoxic–ischaemic episode	• Production of pro-inflammatory molecules nitric oxide (NO), interleukin-1 beta (IL-1beta), and tumour necrosis factor alpha (TNF-alpha) in response to hypoxia	(Lai and Todd 2006) (Benjelloun *et al* 2003)
	Induction of apoptosis and excitotoxicit mediated neuronal death	(Lazovic *et al* 2005; Yamashita *et al* 2006)
HIV-associated dementia	• Production of MCP-1/CCL2 and subsequent leukocyte transmigration and infiltration across the blood–brain barrier	(Eugenin *et al* 2006)
	• Enhanced expression of adhesion molecules: recruitment of cellular infiltrate in the CNS	(Woodman *et al* 1999)
	• Upregulation and increased production of various pro-inflammatory chemokines and cytokines: implication in neuronal apoptosis and death	(Kutsch *et al* 2000)

documented in the spinal cord of SOD-1 G85R transgenic mice and G93A transgenic rats (Howland *et al* 2002). Reactive astrocytes in ALS express COX-2, an enzyme that catalyses the synthesis of the inflammatory prostaglandin E2, which in turn stimulates glutamate release from the astrocytes.

Ubiquitin–proteasome has been implicated to play a role in ALS (Mendonca *et al* 2006). This pathway has been shown to be active in the motor neurons and astrocytes, which points to an underlying cellular abnormality. Dysfunction of these astrocytes alters neuronal survival and hence, directly or indirectly, they are involved in progression of the disease. Thus, astrocytes have multiple roles in the disease progression of ALS and it has recently been suggested that they are the determinants of ALS disease progression (Yamanaka *et al* 2008). It is thus important to further investigate the role of astrocytes in the pathogenesis of ALS and to develop potential therapeutic agents against the disease.

5.2 *Role of astrocytes in Alzheimer disease*

Alzheimer disease (AD) is a neurodegenerative disorder characterized by the presence of neuritic plaques in the cortical grey matter, which are predominantly composed of the 4 kDa β-amyloid peptide. It is the most prevalent cause of progressive dementia. A common feature of AD is the abundance of reactive astrocytes and activated microglia in close proximity to neuritic plaques containing amyloid-beta protein.

Astrocytes make extensive contact with the surfaces of adjacent neurons, ensure normal neuronal excitability, cause glutamate and potassium reuptake from the region of synapses, and participate in synaptic plasticity. Under pathological conditions, astrocytes respond vigorously, and undergo a series of structural and functional changes collectively referred to as astrogliosis. Activated astrocytes are readily identifiable by virtue of their dramatically elevated expression of GFAP compared with their more quiescent counterparts. Astrocytosis, one of the neuropathological hallmarks of AD, always accompanies the senile plaques and neurofibrillary tangles, and contributes to neurodegeneration. Amyloid β-peptide (A-β), the proteolytic fragment of the amyloid precursor protein (APP), plays an important role in astrocyte stimulation. *In vitro* studies reveal that A-β causes dramatic changes in the mitochrondial membrane potential restricted to astrocytes, which results in the generation of free radicals via activation of NADPH oxidase and, subsequently, neuronal death (Abramov *et al* 2004). A rise in intracellular calcium levels in the astrocytes has been attributed to pore formation in the plasma membrane, which leads to depletion of glutathione stores and subsequent neuronal death (Abramov *et al* 2004). Calcineurin, a calcium-dependent phosphatase, directly activates the astrocytes and increased calcineurin expression upregulates the cellular events eventually leading to astroglial activation and neuronal death (Norris *et al* 2005).

Astrocytes secrete various chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL-2), RANTES/CCL-5, and contribute to neuronal damage by recruiting microglia and monocyte/macrophages to plaques with the concomitant release of neurotoxins (Blasko *et al* 2004). MCP-1 stimulation of monocytes is associated with increased expression of pro-inflammatory mediators, including IL-1β, IL-6, arachidonate and superoxide radicals, which act in concert in the degenerative process.

Various glial proteins are found in the neuritic plaque; some of these proteins such as α-antichymotrypsin (ACT), IL-1β, S100β and butyrylcholinesterase (BchE) play an important role in the progression of the disease. These proteins are mainly secreted by activated astrocytes and, synergistically with the A-β peptide, cause further glial activation. Thus, a positive vicious cycle ensues in which further activation of these astrocytes recruits more inflammatory cells thereby causing damage at the site of cellular recruitment (Meda *et al* 2001). Caspase activity has also been seen in astrocytes which leads to cellular degeneration and indirectly plays a role in progression of the disease (Mouser *et al* 2006).

5.3 *Role of astrocytes in multiple sclerosis*

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disorder characterized by demyelination of the CNS. Demyelination causes sensory loss, muscle weakness and difficulties in speech and coordination. Both autoimmune and inflammatory mechanisms contribute to the pathogenesis of MS (Sospedra and Martin 2005).

Autoreactive T-cells directed against the components of central myelin are regarded as important mediators of the pathophysiological process in MS. Although the initial event leading to generation of these activated T-cells is unknown, once generated, these cells traffic to and from the CNS to the periphery. These activated T-cells act on the myelin antigens including myelin basic protein (MBP), myelin proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) resulting in myelin breakdown (Steinman 1996).

Astrocytes express a wide array of neurotransmitter receptors including β-adrenergic receptors (Kimelberg 1995; Porter and McCarthy 1997). These adrenergic receptors play important roles in a variety of protective and supportive functions such as regulation of immune–inflammatory responses, glutamate uptake, inhibition of astrocyte proliferation, trophic support to oligodendrocytes and neurons, and energy metabolism of axons (De Keyser *et al* 2004). Somehow, these β-adrenergic receptors are

lost in MS, which contributes to major histocompatibility complex (MHC) class II expression in these cells (De Keyser *et al* 1999). MHC class II molecules expressed on the membrane of antigen-presenting cells (APCs) are required for the processing and recognition of these antigens by activated T-cells (Steinman 1996). Astrocytes do not constitutively express these MHC class II molecules because of β-adrenergic receptor suppression (Frohman *et al* 1988a, b). Lack of β-adrenergic receptors allows the astrocytes in MS to function as immunocompetent APCs (Frohman *et al* 2001). *In vitro* studies have shown that astrocytes are capable of processing and presenting MBP and PLP epitopes to T-cells, and immunohistochemical studies have shown that reactive astrocytes in active MS plaques express the necessary attributes to act as APCs (Ransohoff and Estes 1991; Zeinstra *et al* 2003). In addition, activation of β2-adrenergic receptors normally inhibits the astrocytic expression of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α) and IL-1β (Nakamura *et al* 1998). Lack of β2-adrenergic receptors facilitates the release of these cytokines from activated astrocytes. These cytokines play an essential role in the inflammatory process through the induction of chemokines and adhesion molecules, recruitment and activation of T-cells, B-cells and microglia, leading to myelin and oligodendrocyte destruction.

Astrocytes play an important role in the integrity of the BBB and one of the pathological findings during relapse of MS is the disruption of this barrier. *In vivo*, it has been shown that astrocytes induce BBB properties in non-endothelial cells (Janzer and Raff 1987). This BBB helps in maintaining a relatively constant internal milieu of the brain which is inaccessible to extrinsic agents. Astrocytes secrete various cytokines and chemokines which influence BBB activity both in the normal (Ballabh *et al* 2004) and pathological state (Abbott 2002; Ballabh *et al* 2004).

Activated astrocytes provide a strong chemoattractant signal with subsequent infiltration and activation of the inflammatory cells (Barnes *et al* 1996). These mediators upregulate various adhesion molecules in the endothelial and inflammatory cells resulting in increased cellular recruitment (Bernardes-Silva *et al* 2001; Librizzi *et al* 2006). In that context, increase in chemokine CXC ligand (CXCL)-12 (stromal derived factor [SDF]-1α) expression in the astrocytes has been implicated in cellular trafficking of inflammatory cells into the brain, both in the early and late stages of MS (Calderon *et al* 2006). A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-1, -4 and -5 proteases are involved in the extracellular matrix changes in the brain of MS patients. ADAMTS-4 has shown to be predominantly expressed in astrocytes within the MS lesions (Haddock *et al* 2006).

Excitotoxic mechanisms also contribute to tissue injury though their effects are secondary to abnormal glutamate mechanisms. During inflammation, lymphocytes, microglia and macrophages release excessive amounts of glutamate which, by overactivation of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, can cause damage to the oligodendrocytes. The expression of iNOS in the astrocytes is inhibited by norepinephrine, and the lack of astrocytic β2-adrenergic receptors explains why astrocytes in MS plaques express high levels of iNOS (Liu *et al* 2001). The iNOS isoform produces high amounts of NO as well as superoxide radicals, two reactive species which directly or indirectly promote oligodendrocyte injury, demyelination, impairment of axonal dysfunction and axonal damage. Recently, the role of the inducible isoform of COX-2 in astrocytes has been documented (Molina-Holgado *et al* 2002). Both COX-2 and iNOS are expressed abundantly in MS lesions (Rose *et al* 2004) and act in concert, resulting in elevated amounts of local glutamate by enhancing its release and decreasing uptake (Rose *et al* 2004).

6. Concluding remarks and future perspectives

Recent findings on the identity and function of astroglial cells in the developing and adult CNS have prompted an important change in concepts. Recent advances in our understanding of astrocytic structure and functions have helped us expand our appreciation for these important cells of the CNS and, most importantly, their role in neurogenesis. In the past two decades, astrocytes have emerged as an important component of the neurogenic potential of the CNS at various stages of life and have been demonstrated to be adult NSCs that support the functions of neurons and adult neurogenesis. These recent advances in our understanding of the previously unrecognized functions of astrocytes have laid the foundation for numerous research studies to investigate the developmental potential and heterogeneity of the developing and adult CNS. Detailed investigations into the glial–neuronal interplay during adult neurogenesis and following trauma to the brain are warranted to exploit the potential of this important phenomenon. This may help in better management of various neurodegenerative diseases by promoting neurogenesis through the manipulation of astrocytic cells from within. The growing interest in astrocyte research by various neuroscience laboratories around the globe illustrates the importance of this evolving field of glial functions in the mammalian CNS.

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