Glial cells

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Abstract
The nervous system is built from two broad categories of cells, neurones and glial cells. The glial cells outnumber the neurones and the two cell types occupy a comparable amount of space in nervous tissue. The main glial cell types are, in the central nervous system, astrocytes and oligodendrocytes and, in the peripheral nervous system, Schwann cells, enteric glial cells and satellite cells. In the embryo, glial cells form a cellular framework that permits the development of the rest of the nervous system, and regulate neuronal survival and differentiation. The best known function of glia in the adult is the formation of myelin sheaths around axons thus allowing the fast conduction of signalling essential for nervous system function. Glia also maintain appropriate concentrations of ions and neurotransmitters in the neuronal environment. Increasing body of evidence indicates that glial cells are essential regulators of the formation, maintenance and function of synapses, the key functional unit of the nervous system.

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Cell facts

• Throughout the brain, spinal cord and peripheral nerves, neurones are never found except in a close association with glial cells.
• The turnover rate of mature glia is normally close to zero but most of them respond to injury by rapid proliferation.
• Glial cells come in many types and have multiple functions in the developing and mature nervous system.
• Following injury, glia are major regulators of neuronal repair and they are largely responsible for the difference in regeneration capacity between the central and peripheral nervous system.

1. Introduction: the main glial types
Two main cell types build the nervous system. These are neurones, which are directly involved in electrical transmission and information processing, and glial cells. In all parts of the nervous system, glial cells outnumber neurones by some margin, and they make up a large part of nervous tissue. For instance, glial cells occupy about half the volume of the brain. These cells carry out many indispensable functions, both in development and during the normal function of the mature system (Jessen & Richardson, 2001). They are also major players in the reaction of the nervous system to disease and trauma.

The term “glial cell” denotes in fact a broad category of cells that is made up of many sub-types.
1.1. Glia in the central nervous system

In the central nervous system (CNS), consisting of the brain and spinal cord, the major glial types are astrocytes and oligodendrocytes. The astrocytes, which are more numerous, have many radiating processes that interweave in complex and intimate ways between neuronal cell bodies and fibres. Some astrocyte processes contact blood vessels and may control the blood-brain barrier which protects the CNS from unwanted substances in the general circulation. Others form cuffs or veils around individual synapses, and synaptic transmission can be modified by signals between nerve terminals and these glial elements (Fig. 1). They also have high affinity uptake sites for major brain neurotransmitters that help to remove excess transmitter following release from nerve terminals. Together this provides compelling evidence that glial cells are directly involved in information processing in the brain. Astrocytes also help to control the levels of potassium in the extracellular space and have major roles in CNS development.

Oligodendrocytes form one of the most highly specialised cellular structures in the body, the myelin sheath, which forms electrical insulation around nerve fibres thereby making rapid transmission of electrical signals in the brain possible. The CNS also contains microglia, resident, macrophage-like cells that originate from blood monocytes rather than the neuroectoderm.

1.2. Glia in the peripheral nervous system

In the peripheral nervous system (PNS), the major glial cells are Schwann cells. They ensheathe all axons in peripheral nerves and are found in two types, myelinating and non-myelinating. The myelinating Schwann cells form insulating sheaths around axons that are comparable in structure and function to those made by oligodendrocytes in the CNS. The non-myelinating cells show similarities with astrocytes and are likely to have metabolic and mechanical support functions. There is evidence that Schwann cells are indispensable for neuronal survival during development, and in damaged nerves Schwann cells control successful regeneration and restoration of function.

Olfactory ensheathing cells represent a special category of glia that resembles non-myelinating Schwann cells and associate with both the CNS and PNS part of the primary olfactory axons. Another important category of PNS glia is the enteric glia. They are found in the autonomic ganglia of the gut (the enteric nervous system). Unlike other parts of the PNS, the enteric system has complex synaptic interactions and high integrative capacity, and the enteric glia are remarkably like astrocytes in structure and biochemistry. The cell bodies of other autonomic ganglia and sensory ganglia are enveloped by simpler satellite glial cells, while the synapses between nerve terminals and skeletal muscle are covered by terminal glia, also called teloglia or perisynaptic glia. They help to maintain a stability of the neuromuscular junction and regulate synaptic transmission.
2. Development

The glial cells and neurones of the CNS develop from neural precursor cells of a germinal layer called the ventricular zone, that lines the lumen of the developing spinal cord and the ventricles of the brain. Oligodendrocyte development is better understood in the spinal cord than in the brain. In the cord, oligodendrocytes appear to originate from a tightly restricted area of the ventricular zone in a process that depends on the transcription factors Olig 1 and 2 and the signalling molecule sonic hedgehog (Nave & Trapp, 2000). From this location, oligodendrocyte progenitor cells migrate to reach all parts of the cord while progressing through defined differentiation stages and remaining in the cell cycle. They fall out

![Diagram of oligodendrocyte and Schwann cell development](image)

Fig. 2. The diagram shows the main stages in (A) oligodendrocyte and (B) Schwann cell development, and some of the molecular markers that can be used to differentiate each stage from the preceding one. The lineages arise from multipotent cells in steps that are broadly comparable. Note that only the Schwann cell lineage generates two distinct cell types and includes a fate decision point, the immature Schwann cell stage. Also, fully differentiated Schwann cells retain an unusual plasticity throughout life and can readily de-differentiate to form cells similar to immature Schwann cells (open arrows). Basal lamina (gray line) is associated with Schwann cells but not with Schwann cell precursors or cells in the oligodendrocyte lineage. Blue: axons. Red: myelina. Olig: Olig2/2 transcription factors. PDGF-R alpha: platelet derived growth factor receptor alpha. GC: galactocerebroside. PLP: proteolipid protein. MBP: myelin basic protein. p75NTR: low-affinity p75 neurotrophin receptor. P0: protein zero. BFABP: brain fatty acid binding protein. GFAP: glial fibrillary acidic protein.
of division after they have associated with their target axons. At this point, they start to express high levels of myelin gene products and form myelin sheaths around axons (Fig. 2A). In more anterior regions of the CNS, the origin of oligodendrocytes is less clear, although also here, ventral structures are likely to be a major source of these cells, in analogy with the cord. The adult CNS retains a population of cells, the adult oligodendrocyte precursor, that is in many ways similar to early cells in the lineage. It is likely that these cells take part in myelin repair under certain circumstances, such as in early multiple sclerosis lessons (see below).

Astrocytes are generated from two sources (Goldman, 2001). Early in development, they form from elongated precursors that have their cell body in or near the ventricular zone and a process that stretches radically to terminate at the surface of the neural tube or developing brain. These cells show many molecular and morphological features that characterise astrocytes later in development and are generally known as radial glia. Later in development, astrocytes also originate from a distinct set of germinal areas, the subventricular zone. Surprisingly, recent work has shown that radial glia and another astrocyte-like cell, the subventricular zone astrocyte, are also active generators of neurones during development and even, in some cases, in the adult brain. These findings challenge traditional notions about the function of glia, since these astrocytes are acting like multipotent neural stem cells. This has caused much head-scratching, with some workers arguing that these neurogenic cells should no longer be classified as glia, but regarded as neural precursors that happen to have some glial-like features, while others are happy to embrace the new concept that some glia have the novel and exciting role of generating neurones in the developing and adult brain.

Schwann cells develop from the neural crest, which is a transient population of cells that migrates away from the dorsal aspect of the neural tube as it closes (Jessen & Mirsky, 2002; Mirsky & Jessen, 2001). Crest cells are multipotent cells that give rise not only to the neurones and glia of the PNS but also to pigment cells in the skin and to some smooth muscle and connective tissue cells. The generation of Schwann cells from crest cells requires the transcription factor Sox-10 and involves, first, the formation of Schwann cell precursors that, in turn, form immature Schwann cells. This population diverges, about half the cells forming myelin around larger diameter axons, while the others associate with smaller diameter axons and become non-myelinating cells (Fig. 2B). This last step of Schwann cell development remains reversible throughout life. The lineage is strikingly dependent on signals from axons. In early development, the most important of these signals is neuregulin-1. Myelination also depends on signals from axons but the identity of this key signal is not known. The transcription factor Krox-20 is indispensable for Schwann cell myelination, although it is not required for oligodendrocyte myelination.

3. Functions

3.1. Role in development

3.1.1. Guidance

In the developing brain, neurones are often formed at what in cellular terms is a very long way from their final site of residence. Development therefore involves a remarkable amount of neuronal migration, a process in which glial cells play a major role. This has probably been studied most thoroughly in the cerebral cortex and the cerebellum. Here, the radial glial cells mentioned before act as indispensable scaffolds for extensive neuronal migration, involving astrotactin and neuregulin-1 signalling, that establishes the layered architecture of these structures (Rakic, 2003). Glia are also implicated in directing axonal growth during development, although it can be disputed whether some of the cells that perform such early guiding functions should be classified as glial cells.

3.1.2. Survival

Some of the best evidence for the common notion that glia support neuronal survival comes from the PNS. In mice in which the transcription factor Sox-10, or neuregulin-1 signalling, have been inactivated, Schwann cell precursors and later, Schwann cells are missing. This is accompanied by the death of large numbers of motor neurones and dorsal root sensory (DRG) neurones, both of which send their axons into peripheral nerves, suggesting that these neurones depend on survival signals from developing glia, a function that is perhaps carried out via
Another example comes from the experimentally induced loss of enteric glia that leads to death of enteric neurones (Bush et al., 1998). A number of mutations in glial genes that initially cause glial malfunction eventually also lead to axonal abnormalities and neuronal death, again pointing to the trophic dependence of neurones on glia (see below; Berger, Young, & Suter, 2002).

3.1.3. Synapse formation

The synapse is the key functional unit in the nervous system and synapses are found in astonishing numbers between neurones and between neurones and other cells. Provocative evidence now indicates that not only the formation, but also the efficiency and maintenance, of synapses depends on signals from astrocytes (Barres & Smith, 2001). These observations, that come from cell culture studies, have important implications, not least for the mechanisms underlying the deterioration of synaptic transmission implicated in age-related memory loss and cognitive dysfunction.

3.2. Myelination

Myelin is made by oligodendrocytes in the CNS and myelinating Schwann cells in the PNS (Fig. 2). While each Schwann cell forms myelin around a single axon, an oligodendrocyte can myelinate up to 30–40 axons by carrying processes each of which ends in a myelin sheath. The sheath forms by spiralling movements of a flattened cellular process around the axon and involves several thousand fold increase in membrane area. Extrusion of the cytoplasm and compaction of the stacked membrane bilayers leads to the formation of a myelin segment which provides electrical insulation around the axon. Sodium and potassium channels are concentrated in the axonal membrane at the meeting points between myelin segments. This alternating arrangement of electrically excitable and insulated areas along the axon leads to a saltatory conduction of electrical signals that is about ten times faster than impulse conduction along an unmyelinated axon of a similar diameter. This difference has undoubtedly provided the evolutionary pressure for the emergence of myelinating cells (Colman, Pedraza, & Yoshida, 2001).

3.3. Control of synaptic function

Glia cells have long been known to possess neurotransmitter receptors (Porter & McCarthy, 1997). The important new idea now being established is that these receptors are activated during synaptic activity, leading to elevation of Ca$^{2+}$ and release of glial glutamate that acts back to modulate synaptic transmission and neuronal excitability (Haydon, 2001; Verkhratsky, Orkand, & Kettenmann, 1998). Because Ca$^{2+}$ elevation can be propagated between astrocytes as a Ca$^{2+}$ wave over long distances, activation of astrocytes at one site could modulate neuronal activity at a distant location. Comparable events take place at PNS synapses (Rochon, Rousse, & Robitaille, 2001). These exciting findings suggest that the synapse is best viewed as a tripartite entity, consisting of three functional parts, the pre- and post-synaptic element and the surrounding glia.

3.4. Homeostatic regulation of neurotransmitter and potassium ion concentrations

Glia cells have molecular pumping mechanisms and intracellular enzymes that enable them to take part in removing major neurotransmitters, including glutamate and GABA, from synaptic sites and metabolise them, thereby helping to terminate postsynaptic action following transmitter secretion. During electrical activity of neurones, K$^+$ is transferred from neurones to the extracellular space where, if it accumulated, it could disastrously alter the electrical excitability of neurones. Resuptake into neurones and diffusion in the extracellular space are not enough to prevent K$^+$ buildup, and it is now clear that removal of K$^+$ via carrier and channel molecules in glial membranes is an essential function of astrocytes (Walz, 2000).

4. Pathology

4.1. Multiple sclerosis (MS)

This is perhaps the most widely recognised disease associated with glial cells (Lucchinetti & Lassmann, 2001). Multiple sclerosis (MS) is a progressive disease with a significant immune involvement that primarily affects oligodendrocytes. It is characterised by...
the formation of multiple lesions in the CNS in which myelin is destroyed and oligodendrocytes die. Axons are also adversely affected. The causes of MS are not well understood and effective treatment remains to be developed.

4.2. Type 1 Charcot–Marie–Tooth disease (CMT)

CMT is a collection of inherited diseases all of which cause malfunction of peripheral nerves (Berger et al., 2002). The majority of these are due to mutations in some five Schwann cell genes coding for structural proteins of myelin or proteins related to cell-cell communication, the cytoskeleton or control of myelin gene transcription. While the direct effects of most of these mutations is instability and breakdown of Schwann cell myelin, clinical disability is thought to relate better to axonal damage resulting from this disturbance of normal Schwann cell function.

4.3. Tumours

The majority of malignant brain tumours is derived from glial cells or their progenitors (Nistér, Uhrbom, Hesselager, & Westermark, 2001). Most of these tumours have an astrocytic component, but a high degree of heterogeneity often makes it difficult to determine the cell of origin. It is not clear to what extent the frequency of glial tumours relates to the ongoing proliferative potential of adult glial cells, or whether the multipotent neural progenitors now known to persist in the adult CNS (above) are significant targets of malignant mutations.

In the PNS, Schwann cell tumours arise in the context of two diseases, neurofibromatosis (NF) type 1 and NF type 2, caused by mutations in two genes important for Schwann cell function, neurtubulin and merlin (Schwannomin), respectively (Ratner & Daston, 2001). Neurofibromin is a GTP activating protein (GAP) for Ras proteins, while the tumour suppressor merlin links the actin cytoskeleton to transmembrane proteins.

4.4. Signalling and homeostatic functions of astrocytes

Astrocytes have the potential to secrete a variety of signalling molecules including a large number of immune modulators, metalloproteases and nitric oxide. In this way, and by their ability to remove potentially cytotoxic amino acids such as glutamate (above), astrocytes are likely to be important regulators of many pathological processes, including stroke and inflammatory conditions such as Alzheimer’s disease and MS.

4.5. Injury to the nervous system

In the event of mechanical damage, such as spinal or peripheral nerve injury, glial cells act as major determinants of repair by expressing molecules that block or promote axon regrowth (Fawcett & Asher, 1999; Fu & Gordon, 1997; Houle & Tessier, 2003). In the PNS, axons have a good chance of regrowing following nerve cut or crush and many of them may reach correct targets leading to restoration of function. This is largely due to the remarkable response of Schwann cells in the distal part of injured nerves. They re-enter the cell cycle, lose their myelin sheaths and de-differentiate to adopt the phenotype of immature Schwann cells, which, due to expression of trophic factors and adhesion molecules, provide a particularly favourable environment for axonal re-growth. The situation is quite different in the CNS. There, injury prompts astrocytes to hypertrophy and reorganise to form the glial scar, that forms a barrier to regeneration, and both astrocytes and oligodendrocytes express factors that potentially block the re-growth of axons. These molecules include Nogo-A, myelin associated glycoprotein, oligodendrocyte-myelin glycoprotein, tenascin and factors associated with chondroitin heparan sulphate. As a result, the prognosis for spinal cord injury, for instance, is poor, although novel treatments, including the neutralisation of inhibitory molecules and insertion of PNS glia or other agents that promote regeneration, are starting to yield promising results.

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References


