Glial cells—fundamentals and alterations

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Abstract

Glial cells are interstitial cells in the central and peripheral nervous systems, playing such roles as morphological structuring, supplying nutrition, insulator of electrical conduction, and phagocytosis of foreign bodies, etc. Microglia acts as immune cells like antigen-presenting cells and is originated from myeloid cells (mesodermal) as dendritic cells fixed around the cerebral capillaries and macrophages and of multicellular origin. Astrocytes, oligodendrocytes and ependymal cells are derived from neural tube (ectodermal) and playing roles as metabolism, release of neurotransmitter, regulation of ion concentration, which directly affect neural functions. Astrocyte also relates the formation of blood-brain barrier by close attachment to endothelial cells. Oligodendrocyte in the central nervous system synthesizes myelin sheath. Neurilemmal cell synthesizes myelin sheath in the peripheral nervous system and enables saltatory conduction. Lesions of glial cells include glioma and demyelination.

Introduction

Glial cells, also called neuroglia or glia, are cells of the central or peripheral nervous system functioning with the neural cells as neurons. The name “glia” is a Greek noun, which means glue or paste. However, it is inappropriate nowadays to consider glia as “glue” in the nervous system.

Glia were discovered in 1856 by the pathologist Rudolf Virchow in his search for connective tissue in the brain. The human brain contains about ten times more glial cells than neurons.

Function

Glial cells provide support, nutrition (including oxygen) and protection for neurons, insulate neurons independently by forming myelin, to destroy external pathogens and remove dead neurons. Glia guide migration of neurons in early development, and producing molecules that modify the growth of axons and dendrites. Recent findings in the hippocampus and cerebellum have indicated that glial cells are also active participants in synaptic transmission, regulating clearance of neurotransmitters from the synaptic cleft, releasing factors such as ATP, which modulate presynaptic function, and even releasing neurotransmitters themselves. The role of glial cells as managers of communications in the synapse gap, thus modifying learning pace, has been discovered recently.

Traditionally glia were thought to lack certain features of neurons. For example, glia were not believed to have chemical synapses or to release neurotransmitters. They were considered to be the passive bystanders of neural transmission. However, recent studies disproved this. For example, astrocytes are crucial in clearance of neurotransmitter from within the synaptic cleft, which provides distinction between arrivals of action potentials and prevents toxic build up of certain neurotransmitters such as glutamate (excitotoxicity).
Furthermore, at least in vitro, astrocytes can release neurotransmitter glutamate in response to certain stimulation. Another unique type of glia, the oligodendrocyte precursor cells (OPCs), have very well defined and functional synapses from at least two major groups of neurons. The only notable differences between neurons and glia, by modern scrutiny, are the ability to generate action potentials and the polarity of neurons, namely the axons and dendrites which glia lack. They are also crucial in the development of the nervous system and in processes such as synaptic plasticity and synaptogenesis.

Glia retain the ability to undergo cell division in adulthood, while most neurons cannot. The view is based on the general deficiency of the mature nervous system in replacing neurons after an insult or injury, such as a stroke or trauma, while very often there is a profound proliferation of glia, called gliosis, near or at the site of damage. However, detailed studies found no evidence that mature glia such as astrocytes or oligodendrocytes retain the ability of mitosis. Only the resident OPCs seem to keep this ability after the nervous system matures. On the other hand, there are a few regions in the mature nervous system, such as the dentate gyrus of the hippocampus and the subventricular zone, where generation of new neurons can be observed.

Most glia are derived from ectodermal tissue of the developing embryo, particularly the neural tube and crest. In the central nervous system (CNS), glia develops from the ventricular zone of the neural tube. These glia include the oligodendrocytes, ependymal cells, and astrocytes. The exception is microglia, which are derived from hemopoietic stem cells. In the adult, microglia are largely a self-renewing population and are distinct from macrophages and monocytes, which infiltrate the injured and diseased CNS. In the peripheral nervous system (PNS), glia derive from the neural crest. These PNS glia include Schwann cells in peripheral nerves and satellite cells in ganglia.

**Microglia (not glia as defined strictly)**

Microglia are specialized macrophages capable of phagocytosis that protect neurons of the CNS. They are technically not glia because they are derived from myeloid progenitor cells (as are macrophages and dendritic cells), which come from the bone marrow rather than ectodermal tissue. During embryonic development, they migrate to the CNS to differentiate into microglia. However, they are commonly categorized as glial cells because of their supportive role to neurons. These cells comprise approximately 15% of the total cells of the CNS. They are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy CNS, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels).

Microglia, the smallest of the glial cells, act as the immune cells of the CNS and can act as phagocytes, cleaning up CNS debris. Most serve as representatives of the immune system in the brain and spinal cord. Microglia are close cousins of other phagocytic cells including macrophages and dendritic cells. Microglia are thought to be highly mobile cells that play numerous important roles in protecting the nervous system. They are also thought to play a role in degenerative disorders such as Alzheimer's disease, dementia, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). They are responsible for producing an inflammatory reaction to brain trauma and are the main HIV-1 target cells in the CNS.

In 1841, Gluge identified phagocytic cells of mesodermal origin in the damaged brain. In 1846, Virchow observed phagocytes ("foam cells" according to his nomenclature) contributing to a disease process termed congenital encephalitis. In 1890, His described ameboid mesodermic corpuscles, which entered the developing brain of human embryos in the second month, colonized both grey and white matter, and emitted protoplasmic radiation. In 1897, Babes described activation of microglia in a rabies case, but did not know what the clusters of microglia he saw were. In 1899, Nissl suggested that glial cells in the brain have similar functions to macrophages in other tissues. In 1900, Robertson distinguished neuroglia and mesoglia, the latter cells, derived from mesoderm, displaying phagocytic activity in pathological conditions such as chronic brain degeneration. In 1904, Alzheimer believed that glial cells became ameboid in certain acute infections and were destined to combat the infection. In 1913, Ramon y Cajal recognized mesoglia as the third element of the CNS. However, del Rio Hortega, a student of Ramon y Cajal, first called the cells "microglia". He conducted the first systematic studies on this cell type. He was the first to demonstrate (in 1919 to 1922) that mesoglia were composed of microglia, which are of mesodermal origin, whereas oligodendroglia, astroglia and neurons are of neuroectodermal lineage. Many of his observations are still valid.

There has been a decades-long debate about the nature and identity of microglial cells, which lasted until immunocytochemical as well as lectin markers were discovered in the 1980s. It then became clear that microglia share phenotypic characteristics (as well as lineage properties) with bone marrow–derived monocytes/macrophages. In general, the immunophenotype of microglial cells appears to be down-regulated but the cells should not be considered weak...
macrophages; microglia display a number of properties that are unique to these resident cells of the CNS, which are about as numerous as neurons. One example is their involvement in synaptic plasticity under pathological conditions called synaptic stripping. During vascularization of the CNS, cells related to the mononuclear phagocyte system appear to invade the central nervous tissue and give rise to resting microglia. Unlike neuroectodermal glias, microglial cells are not electrotonically coupled, i.e. functionally connected via gap junctions. This may explain their very localized involvement in disease processes, which is of great diagnostic use including in neuroimaging.

The presentation of antigen to lymphocytes is a likely function of microglia. Microglia are a resident CNS source of a number of immune molecules apart from MHC antigens, e.g. interleukins. There are many different names for microglia, which exhibit considerable morphological plasticity. The term “ameboid microglia” should be reserved to describe the cell’s appearance in developing (i.e. fetal) nervous tissue. Microglial rod cells representing an activated microglia phenotype are mainly found in the cerebral cortex typically in quaternary syphilis, subacute sclerosing panencephalitis (SSPE) and lead intoxication. Brain macrophages which are morphologically indistinguishable from macrophages of peripheral sources are found in early active multiple sclerosis (MS) lesions and in cerebral infarcts. Some brain tumors (especially high grade gliomas) are very rich in what appear to be phagocytic microglia but it is at present impossible to be certain about their source. In addition to microglia, there are other macrophage phenotypes present within the bony confinements of the normal CNS. These include epi-plexus and meningeal macrophages as well as perivascular macrophages (thus called perivascular cells as they lack a macrophage phenotype in normal conditions). The topic of brain macrophages and microglia is a difficult one due to historical nomenclatorial controversy and some still existing confusion. Terminological clari-

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**Fig. 1** The relations of glial cells with a neuron. Astroglia extends its processes to the dendrites of a neuron and surrounding a capillary to form blood-brain barrier. Microglia preferentially exists around a capillary as a pericyte. Oligodendroglia surrounds an axon of a neuron. (Copyright Masaru Wada, Tokyo Medical and Dental University, Japan)
ity is of utmost importance.

The term microglia refers to cells that reside within the parenchyma of the nervous system, that share many if not all the properties of macrophages in other tissues, but that in their non-activated or resting state have a characteristic ramified morphology not seen in resident macrophages of other organ systems. Resting microglia show characteristic elongated, almost bipolar cell bodies with spine-like processes that often branch perpendicularly.

Although microglia are brain macrophages, they are distinguished by their parenchymal location and certain functional differences from other types of brain macrophages such as meningeal and perivascular macrophages and perivascular cells or pericytes, which are enclosed by a perivascular basement membrane within blood vessels and are not part of the CNS parenchyma.

The origin of microglia was a matter of intense controversy in Rio-Hortega’s day. Although it is still a somewhat contentious issue, most authorities now agree on the correctness of his concept of mesodermal glial cells invading the parenchyma during embryonic development followed by the ingress of bone marrow–derived blood monocytes in the postnatal period. Thus, microglia are currently regarded as members of the mononuclear phagocyte system. Another of his concepts that has withstood the test of time is that of three phases of microglia reflecting their plasticity: an ameboid phase found in the fetus, a ramified (resting) phase found in the nervous system framework, and a third phase of recovery of ameboid properties and motility necessary for active discharge of their macrophagic function.

As Rio-Hortega recognized, the penetration and migration of microglia takes place very quickly, and postnatally, microglia are to be found in every location within the nervous system. However, what often is not appreciated is the fact that the brain is composed primarily of glial cells. While about 15% of the cells in the brain are neurons, it is estimated that microglia are found in roughly equivalent numbers. In a recent study of the local density of microglial cells in the normal adult brain, ramified microglia bearing markers such as CD68 and major histocompatibility complex (MHC) class II antigen were found to be more concentrated in white matter than in gray matter, and significant regional differences were observed, with microglia ranging from 0.5 to 16.6% of all the cells within various areas of the brain parenchyma. Grey matter of the cerebellum had the lowest density of microglia, while the highest levels of CD68-positive and MHC class II-positive cells were found in the medulla.

Ameboid (Fetal or Reactivated) Microglia

Consistent with the concept of Rio-Hortega, ameboid, ramified, and reactive microglia are currently viewed as different forms of a single cell type. Ameboid microglia are active macrophages during development and are precursors of resting or ramified cells, which can, in response to a variety of insults such as infection, traumatic injury, or ischemia, reactivate in the postnatal brain, assume an ameboid shape, and move to the site of injury. Early in human fetal brain development, microglia are mainly ameboid in appearance, whereas by 18 weeks of gestation, a ramified morphology predominates. Consistent with the ability of these cells to assume ameboid morphology, upon isolation and culture, a homogenous population of ameboid microglia can be obtained for in vitro studies.

Astrocytes are the predominant cell type within the CNS, and astroglia–microglia interactions appear to play an important role in microglial cell biology. For example, in vitro studies have shown that blood monocytes and ameboid microglia develop branching processes when layered on astrocytes, suggesting that astrocytes induce the morphology of ramified microglia. Moreover, ameboid and even fully ramified microglia have been shown to migrate rapidly when seeded on a confluent layer of astrocytes. Although astrocytes differ morphologically and functionally from microglia, the two glial cell types appear to act in concert as the intrinsic immune system of the CNS.

Kudo studied in detail on the origin of brain macrophages (gitter cells) ultrastructurally and enzyme-histochemically and revealed the brain macrophages were derived from blood monocytes, pericytes or microglia. Recent study on the origin of brain macrophages proved that CD34-positive hematopoietic progenitor cells migrate and generate phagocytic dendritic cell clusters around the brain blood vessels. Those cells differentiate into the activated macrophages under stimulation of interferon gamma. Brain macrophages are obviously multiple in their origin.

Ramified (Resting) Microglia

The term glia suggests that microglia share with astroglia and oligodendroglia the property of brain support and, more particularly, the support of neurons. However, such a supportive role in the healthy brain is more recognized in astroglia, which make important contributions to neurotransmitter metabolism, and for oligodendroglia, which are the source of myelin, than for ramified microglia. While it seems likely that ramified microglia also contribute to the well-being of neurons, this neuronocentric view may underestimate the importance of the neuronal support of microglia. Nonetheless, ameboid microglia are thought to have a crucial scavenger function in the developing brain by removing
the large number of cells in the neocortex that die in the course of normal remodeling of the fetal brain. Scavenger receptors have been identified on neonatal murine microglia, whereas this class of cell surface protein is not detected on microglia in neonatal mouse or normal human adult brain. Further evidence of a supportive role of microglia has been shown in the facial nerve axotomy paradigm, in which the recovery of injured neurons is dependent on the trophic function of activated microglia.

Activated Microglia

As mentioned previously, certain cell surface markers of importance in immune regulation, such as MHC class II molecules, are constitutively expressed on ramified microglia in the normal adult brain. However, in response to a variety of CNS insults such as microbial invasion, ramified microglia have the capacity not only to dramatically change their morphology to reactive or ameboid forms but also to rapidly up-regulate a large number of receptor types and produce a myriad of secretory products that are thought to contribute to the defense of and, potentially, damage to the infected brain. The state of microglial activation represents a continuum that is reflected by in vitro studies, with relatively minor changes being observed just in the process of preparing and culturing ameboid microglia, which express CD14, a marker not found in ramified microglia. At the far end of the activation spectrum, marked alterations are seen following stimulation with microbial products such as lipopolysaccharide (LPS). Because activated microglia are regarded as a pivotal cell in both defense against and immunopathogenesis of infections and inflammatory diseases of the CNS, numerous in vitro studies of the regulatory factors involved in microglial activation have been reported, and in recent years, techniques to identify activated microglia in vivo have been applied to studies of various pathological conditions.

Dendritic cells

Dendritic cells (DCs) (Gk dendro—tree) are major antigen presenting cells (APCs) in mammalian immune system. Their main function is to process antigen material and present it on the surface to other cells of the immune system. DCs are present in small quantities in tissues that are in contact with the external environment, mainly the skin (where they are often called Langerhans cells) and the inner lining of the nose, lungs, stomach and intestines. They can also be found at an immature state in the blood. Once activated, they migrate to the lymphoid tissues where they interact with T cells and B cells to initiate and shape the adaptive immune response. At certain development stages they grow branched projections, the dendrites, which give the cell its name. However, these do not have any special relation with neurons, which also possess similar appendages. Immature DCs (frequently found in the afferent duct of lymph nodes) are also called veiled cells, in which case they possess large cytoplasmic veils rather than dendrites.

It had been believed that the DCs do not exist in the brain, though, immature DCs exist perivascularly in the brain. Microglia differentiates to an activated macrophage under the effect of interferon–gamma and can even be a DC in the brain.

DCs were first described by Langerhans (Langerhans cells of the skin) in 1868. However, DCs were thought to be neural cells morphologically. It was not until 1973 that the term DCs was coined by Steinman and Cohn.

All DCs share the similar morphological appearances. They all possess very large contact surfaces to their surroundings compared to overall cell volume.

Three types of DCs are known among primates: myeloid DCs, plasmacytoid DCs and follicular DCs. Myeloid DCs evolve from lymphoid or myeloid precursors and thus are of hematopoietic origin. The subset named lymphoid DCs is still found among some papers, however, the distinction between myeloid and lymphoid DCs makes no sense, since both myeloid and plasmacytoid DCs are derived from both lymphoid and myeloid precursors.

Myeloid DCs are most similar to monocytes and were previously classified into two subsets, MDC-1 and MDC-2, according to the types of induced reactions of helper T-cells, Th1 and Th2 phenotypes, however, this classification is rather inappropriate because induced helper T-cell reaction changes depending upon the amount of interleukin-12 secreted from the DC, not corresponding to their DC subsets.

Plasmacytoid DCs are morphologically similar to plasmocytes, but have certain characteristics similar to myeloid DCs as they can produce high amounts of interferon–alpha and have thus become known as IPC (interferon–producing cells) prior to their nature as DCs was revealed. The difference with myeloid DCs includes plasmacytoid DCs are CD11c (−), CD11b (−), ILT1 (−), CD1a (−), while myeloid DCs are all positive and plasmacytoid DCs are CD123 (alpha chain of interleukin–3 receptor) high, while myeloid DCs are CD123 low. Consequently plasmacytoid DCs are strongly activated by interleukin–3.

Follicular DCs in the lymphatic follicles present antigens to B-cells but not to T-cells and are probably not of hematopoietic origin, but simply look similar to true DCs. The markers BDCA (blood dendritic cell antigen)–2, BDCA–3, and BDCA–4 can be used to discriminate among the types.

DCs start out as immature DCs. These cells are characterized by high endocytic activity and low T-cell
activation potential. DCs constantly sample the surroundings for pathogens such as viruses and bacteria. This is done through pattern recognition receptors (PRRs) such as the toll-like receptors (TLRs). TLRs recognize specific chemical signatures found on subsets of pathogens. Once they have come into contact with such a pathogen, they become activated into mature DCs. Immature DCs phagocytose pathogens and degrade its proteins into small fragments of peptides and upon maturation present those fragments at their cell surface using MHC class II molecules. Simultaneously, they upregulate cell-surface receptors that act as co-receptors in T-cell activation such as CD80 and CD86, greatly enhancing their ability to activate T-cells (the corresponding T-cell ligand is CD28). They also upregulate CCR7, a chemotactic receptor that induces the DC to travel through the blood stream to the spleen or through the lymphatic system to a lymph node. Here they act as APCs: they activate helper T-cells and killer T-cells as well as B-cells by presenting them with antigens derived from the pathogen, alongside non-antigen specific costimulatory signals.

Every helper T-cell is specific to one particular antigen. Only professional APCs (macrophages, B lymphocytes, and DCs) are able to activate a helper T-cell that has never encountered its antigen before. DCs are the most potent of all the APCs.

As mentioned above, myeloid DCs probably form from monocytes, and, depending on the right signal, can turn into either DCs or macrophages. Activated macrophages have a lifespan of only a few days. The lifespan of activated DCs, while somewhat varying according to type and origin, is of a similar order of magnitude, but immature DCs seem to be able to exist in an inactivated state for much longer. The monocytes in turn are formed from stem cells in the bone marrow. However, the exact genesis and development of the different types and subsets of DCs and their inter-relationship is only marginally understood at the moment, as DCs are so rare and difficult to isolate that only in recent years have they become the subject of focused research. Distinct surface antigens that characterize DCs have only become known since 2000; before that, researchers had to work with a mixture of several antigens which, used in combination, result in isolation of cells with characteristics unique to DCs.

The DCs are constantly in communication with other cells in the body. This communication can take the form of direct cell-to-cell contact based on the interaction of cell-surface proteins. An example of this includes the interaction of the receptor CD40 of the DC with CD40L present on the lymphocyte. However, the cell-cell interaction can also take place at a distance via cytokines. For example, stimulating DCs in vivo with microbial extracts causes the DCs to rapidly begin producing IL-12[20]. IL-12 is a signal that helps send naive CD4 T-cells towards a Th1 phenotype. The ultimate consequence is priming and activation of the immune system for attack against the antigens, which the DC presents on its surface. However, there are differences in the cytokines produced depending on the type of DC. The plasmacytoid DC has the ability to produce huge amounts of IFN-α, more than any other blood cell[20].

**Astrocytes**

The most abundant type of glial cell, astrocytes, or astroglia, (Gk astro = star) has numerous projections that anchor neurons to their blood supply. Besides a role in the physical structuring of the brain, they regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission. The current theory suggests that astrocytes may be the predominant reinforcement of the blood-brain barrier. The astrocyte end-feet encircling endothelial cells form part of the blood-brain barrier. Astrocytes may regulate vasoconstriction and vasodilatation by producing vasoactive substances as arachidonic acid. Calcium is used for mutual signal transmission between astrocytes. The gap junctions (electrical synapses) between astrocytes allow inositol triphosphate (IP3) to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the further production of IP3. The net effect is a calcium wave that propagates from cell to cell. Extracellular release of ATP, and consequent activation of purinergic receptors on other astrocytes, may also mediate calcium waves in some cases.

There are generally two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Proliferative astrocytes have short, thick, highly branched processes and are typically found in grey matter and have many branching processes whose endfeet envelop synapses. Fibrous astrocytes have long, thin, less branched processes whose endfeet envelop nodes of Ranvier and are more commonly found in white matter. Astrocytes can be classified to two types also by transporter/receptor classification as GluT type those express glutamate transporters (EAAT1/SLC1A3 and EAAT2/SLC1A2) and respond to synaptic release of glutamate by transporter currents and GluR type those express glutamate receptors (mostly mGluR and AMPA type) and respond to synaptic release of glutamate by channel-mediated currents and IP3-dependent Ca2+ transients. Astrocytes express glial fibrillary acidic protein (GFAP).

Other roles include providing neurons with nutrients...
such as glucose, expressing plasma membrane transporters such as glutamate transporters for several neurotransmitters, including glutamate, ATP and GABA. More recently, astrocytes were shown to release glutamate or ATP in a vesicular, Ca2+-dependent manner; regulating ion concentration in the extracellular space as astrocytes express potassium channels at a high density. When neurons are active, they release potassium, increasing its extracellular concentration. Because astrocytes are so permeable to potassium, they rapidly clear its excess accumulation in the extracellular space. If this function is interfered with, the extracellular concentration of potassium will rise, leading to neuronal depolarization. Abnormal accumulation of extracellular potassium is well known to result in epileptic neuronal activity; modulating synaptic transmission: rapid changes in astrocyte morphology have been shown to affect heterosynaptc transmission between neurons in the supraoptic nucleus of the hypothalamus; serving as intermediaries in neuronal regulation of blood flow; promoting the myelinating activity of oligodendrocytes; electrical activity in neurons causes them to release ATP, which serves as an important stimulus for myelin to form. The ATP does not act directly on oligodendrocytes; ATP causes astrocytes to secrete LIM, a regulatory protein that promotes the myelinating activity of oligodendrocytes. This suggests that astrocytes have an executive-coordinating role in the brain.

In the 1990s, following persistent study, a small fan club of scientists began to uncover evidence that astrocytes signal to neurons and influence their activity. First, cell experiments in petri dishes found that following an increase of calcium in astrocytes: there is an increase of calcium in surrounding neurons. This implied some form of communication between the two cell types. Next, scientists found that indeed the calcium increase in astrocytes directly links to changes in neuron activity. In one study of rat cells, microelectrodes measured the electrical impulses that neurons use to signal to each other. In response to the calcium increase in astrocytes, the majority of neurons tested slowed down their signaling activity. A few increased their signaling activity. Other research is uncovering key molecules that aid in communication. Several studies indicate that following the rise of calcium, astrocytes release the amino acid glutamate, which helps communication with neurons. The communication flows both ways, with neurons also being able to talk to the astrocytes through their own glutamate release. Signaling molecules, such as ATP and prostaglandins, also appear to promote the cell-to-cell communication, according to other new investigations.

Determining why the astrocyte chatting occurs and whether it actually affects the neurons' ability to process information, is another area of research. Early studies hint that some of the chatting may aid memory. Adding glutamate to cell samples of astrocytes prompts them to produce special molecules that nourish neurons, known as trophic factors. Other research has found that these molecules are key to memory function. In one recent study, injections of trophic factors into the brains of rats boosted the biological mechanisms known to relate to memory and improved the rats' performance in a memory task. This all may mean that glutamate release from neurons triggers astrocytes to produce trophic factors, which then help neurons process information for memory. Scientists currently are testing this theory.

Together the research is not only making researchers rethink how the brain operates, but also how to treat it when it malfunctions. For one, if the research on astrocytes' connection to memory pans out, then the cells may make good targets for treatment of memory disorders such as Alzheimer's disease. The relationship of astrocytes to glutamate also may make them good targets for clinical intervention since several brain disorders have been tied to glutamate problems. For example, some scientists believe that when the brain is infected by the AIDS-causing HIV virus or deprived of oxygen from lack of blood flow due to a stroke, a release of excess glutamate causes death of neurons. Agents that target astrocytes might help limit the glutamate overflow and prevent the cell death.

Furthermore, studies are underway to determine whether astrocytes play an instrumental role in depression, based on the link between diabetes and depression. Altered CNS glucose metabolism is seen in both these conditions, and the astrocytes are the only cells with insulin receptors in the brain.

**Calcium waves**

Astrocytes are linked by gap junctions, creating an electrically coupled syncytium. An increase in intracellular calcium concentration can propagate outwards through this syncytium. Mechanisms of calcium wave propagation include diffusion of IP3 through gap junctions and extracellular ATP signaling. Calcium elevations are the primary known axis of activation in astrocytes, and are necessary and sufficient for some types of astrocytic glutamate release.

**Bergmann glia**

Bergmann glia also known as “radial epithelial cells” (named by Golgi) are astrocytes in the cerebellum that have their cell bodies in the Purkinje cell layer and processes that extend into the molecular layer, terminating with bulbous endfeet at the pial surface. Bergmann glia expresses high densities of glutamate transporters that limit diffusion of the neurotransmitter glutamate.
during its release from synaptic terminals. Besides their role in early development of the cerebellum, Bergmann glia are also required for the pruning or addition of synapses.

**Blood-brain barrier**

The blood–brain barrier (abbreviated BBB) is a membranous structure that acts primarily to protect the brain from chemicals in the blood, while still allowing essential metabolic function. It is composed of endothelial cells, which are packed very tightly in brain capillaries. The BBB restricts passage of substances from the bloodstream much more than endothelial cells in capillaries elsewhere in the body. Processes from astrocytes surround the endothelial cells of the BBB, providing biochemical support to those cells. The BBB is distinct from the similar blood-cerebrospinal fluid barrier, which is a function of the choroid plexus with which it is often confused.

The existence of such a barrier was first noticed in experiments by Ehrlich in the late 19th century. Ehrlich was a bacteriologist who was studying staining, which is used for many studies to make fine structures visible. When injected, some of these dyes, notably the aniline dyes, would stain all of the organs of an animal except the brain. At the time, Ehrlich attributed this to the brain simply not picking up as much of the dye. In a later experiment in 1913, one of Ehrlich's students, Goldmann injected the dye into the spinal fluid of the brain directly. He found that in this case the brain would become dyed, but the rest of the body would not. This clearly demonstrated the existence of some sort of barrier between the two. At the time, it was thought that the blood vessels themselves were responsible for the barrier, as no obvious membrane could be found. The concept of the blood–brain (then termed hematoencephalic) barrier was proposed by Stern in 1921. Its proof was not established until the observation using the scanning electron microscope in the 1960s showed the actual membrane. It was once believed that astrocytes rather than epithelial cells were the basis of the BBB because of the densely packed astrocyte processes that surround the epithelial cells of the BBB.

Throughout the body, the walls of capillary vessels are made up of endothelial cells, separated by small gaps. Soluble chemicals within the various tissues pass through these gaps into the blood stream, to be carried throughout the body and into different tissues. However, these endothelial cells are packed more tightly together in the brain, due to the existence of zonulae occludentes (tight junctions) between them. This blocks the passage of most molecules. The BBB blocks all molecules except those that cross cell membranes by means of lipid solubility (such as oxygen, carbon dioxide, ethanol, and steroid hormones) and those that are allowed in by specific transport systems (such as glucose and some amino acids). Substances with a molecular weight higher than 500 Daltons generally cannot cross the BBB, while smaller molecules often can. In addition, the endothelial cells metabolize certain molecules to prevent their entry into the CNS. For example, L-DOPA, the precursor to dopamine, can cross the BBB, whereas dopamine itself cannot. (As a result, L-DOPA is administered for dopamine deficiencies (e.g., Parkinson's disease) rather than dopamine).

In addition to tight junctions acting to prevent transport in between epithelial cells, there are two mechanisms to prevent passive diffusion through the cell membranes. Glial cells surrounding capillaries in the brain pose a secondary hindrance to hydrophilic molecules, and the low concentration of interstitial proteins in the brain prevent access by hydrophilic molecules.

The BBB protects the brain from the many chemicals flowing within the blood. However, many bodily functions are controlled by hormones in the blood, and while the secretion of many hormones is controlled by the brain, these hormones generally do not penetrate the brain from the blood. This would prevent the brain from directly monitoring hormone levels. In order to control the rate of hormone secretion effectively, there are specialized sites where neurons can sample the composition of the circulating blood. At these sites, the BBB is leaky; these sites include three important circumventricular organs, those three are the subfornical

![Fig. 2 Schematic of a 3-cell archetype for the blood-brain barrier comprising brain capillary endothelial cell (E), the astrocyte (A) and the pericyte (P). (Copyright Mark Gumbleton, Cardiff University, UK)]
organ, the area postrema, and the organum vasculosum of the lamina terminalis (OVLT).

The BBB acts very effectively to protect the brain from many common infections. Thus, infections of the brain are very rare. However, since antibodies are too large to cross the BBB, infections of the brain, which do occur, are often very serious and difficult to treat. Antibiotics of large molecules are incorporated to the brain at insufficient therapeutic concentration. The blood-cerebrospinal fluid barrier also proposes similar difficulty in the treatment of meningitis. Overcoming the difficulty of delivering therapeutic agents to specific regions of the brain presents a major challenge to treatment of most brain disorders. In its neuroprotective role, the BBB functions to hinder the delivery of many potentially important diagnostic and therapeutic agents to the brain. Therapeutic molecules and genes that might otherwise be effective in diagnosis and therapy do not cross the BBB in adequate amounts.

Mechanisms for drug targeting in the brain involve going either through or behind the BBB. Modalities for drug delivery through the BBB entail its disruption by osmotic means, biochemically by the use of vasoactive substances such as bradykinin, or even by localized exposure to high intensity focused ultrasound (HIFU). Other strategies to go through the BBB may entail the use of endogenous transport systems, including carrier-mediated transporters such as glucose and amino acid carriers; receptor-mediated transcytosis for insulin or transferrin; and blocking of active efflux transporters such as p-glycoprotein. Strategies for drug delivery behind the BBB include intracerebral implantation and convection-enhanced distribution.

Nanotechnology may also help in the transfer of drugs across the BBB. Recently, researchers have been trying to build nanoparticles loaded with liposomes to gain access through the BBB. More research is needed to determine which strategies will be most effective and how they can be improved for patients with brain tumors. The potential for using BBB opening to target specific agents to brain tumors has just begun to be explored.

**Diseases influencing BBB functions**

Meningitis disrupts the BBB. This disruption may increase the penetration of various substances (including antibodies) into the brain.

Multiple sclerosis (MS) is considered an autoimmune disorder in which anti-myelin antibody attacks the nerves in the CNS. Normally, a person’s nervous system would be inaccessible for the lymphocytes due to the BBB. However, it has been shown using magnetic resonance imaging (MRI) that, when a person is undergoing an MS attack, the BBB has broken down in a section of the patient's brain or spinal cord, allowing T lymphocytes to cross over and destroy. It has been suggested that, rather than being a disease of the immune system, MS is a disease of the BBB. However, no conclusive evidence has been found so far. There are currently active investigations into treatments for a compromised BBB. It is believed that oxidative stress plays an important role in the breakdown of the barrier; anti-oxidants such as lipoic acid may be able to stabilize a weakening BBB.

Neuromyelitis optica (Devic’s disease) is similar and is often confused with MS. Among other differences from MS, the target of the autoimmune response has been identified. Patients with neuromyelitis optica have high levels of antibodies against a protein called aquaporin 4, which is a component of the astrocytic foot processes in the BBB.

Late-stage neurological trypanosomiasis, or sleeping sickness, is a condition in which trypanosoma protozoa are found in brain tissue. It is not yet known how the parasites infect the brain from the blood, but it is suspected that they cross through the choroid plexus, a circumventricular organ.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS caused by reactivation of a latent papovavirus (the JC polyomavirus) infection, which can cross the BBB. It affects immunocompromised patients and is usually seen in AIDS patients.

De Vivo disease (also known as GLUT1 deficiency syndrome) is a rare condition caused by inadequate transport of glucose across the barrier, resulting in mental retardation and other neurological problems. Genetic defects in glucose transporter type 1 (GLUT1) appear to be the main cause of De Vivo disease38-39.

New evidence indicates that disruption of the blood brain barrier in Alzheimer’s disease patients allows β-amyloid containing blood plasma to enter the brain where the Aβ adheres preferentially to the surface of astrocytes. These findings have led to the hypothesis that breakdown of the BBB allows access of neuron-binding autoantibodies and soluble exogenous Aβ42 to brain neurons and binding of these autoantibodies to neurons triggers and/or facilitates the internalization and accumulation of cell surfaces-bound Aβ42 in vulnerable neurons through their natural tendency to clear surface-bound autoantibodies via endocytosis. Eventually the astrocyte is overwhelmed, dies, ruptures, and disintegrates, leaving behind the insoluble Aβ42 plaque. Thus, in some patients, Alzheimer’s disease may be caused by (or more likely, is aggravated) by a breakdown in the BBB.

**Glioma**

A glioma is a type of primary CNS tumor that arises from glial cells. The most common site of involvement...
of gliomas is the brain, but they can also affect the spinal cord or any other part of the CNS, such as the optic nerves\(^{19}\). Chlorotoxin is the peptide isolated from the venom of the Leirus quinquestratus scorpion (Israeli yellow scorpion) by means of gel filtration chromatography. The peptide appears to bind with glioma-specific chloride ion channels with a high affinity.

Gliomas do not metastasize via the bloodstream, but they can spread via cerebrospinal fluid (CSF) and cause drop metastases to the spinal cord.

High-grade gliomas are highly vascular tumors and have a tendency to infiltrate. They have extensive areas of necrosis and hypoxia. Often tumor growth causes a breakdown of the BBB in the vicinity of the tumor. As a rule, high-grade gliomas almost always grow back even after complete surgical excision.

**Astrocytoma**

Astrocytomas are primary intracranial tumors derived from astrocytes cells of the brain. They may arise in the cerebral hemispheres, in the posterior fossa, in the optic nerve, and rarely, the spinal cord. In children, the tumor is usually located in the cerebellum.

Well-differentiated astrocytomas constitute about 25 to 30% of cerebral gliomas and have a predilection for the cerebrum, cerebellum, hypothalamus, optic nerve and chiasm, andpons. Although astrocytomas have many different histological characteristics, the most common is the well-differentiated fibrillary astrocytomas. These tumors contain GFAP, which is a useful diagnostic marker in a tissue biopsy.

Astrocytomas have great variation in their presentation. The World Health Organization recognizes the following grading system for astrocytomas\(^{19}\):

- Grade 1 pilocytic astrocytoma
- Grade 2 diffuse astrocytoma
- Grade 3 anaplastic astrocytoma
- Grade 4 glioblastoma multiforme

In addition to these four tumor grades, astrocytomas may combine with oligodendrocytes to produce oligoastrocytoma. Unique astrocytoma variants have also been reported.

Histological diagnosis with tissue biopsy will normally reveal an infiltrative character suggestive of the slow growing nature of the tumor. The tumor may be cavitating, pseudocyst forming, or noncavitating. The appearance is usually white-gray, firm, and almost indistinguishable from normal white matter.

**Pilocytic astrocytoma**

Pilocytic astrocytoma (Gk pilo = hair), classified as grade 1 astrocytoma, is a brain tumor that occurs predominantly in children, primarily pediatric tumor, with median age of diagnosis at 12 and involves the midline basal and posterior fossa structures. It is generally considered a benign tumor of childhood. It is often cystic and if solid, it tends to be well circumscribed. It is characteristically a contrast-enhancing tumor by current imaging investigations (e.g. CT scan, MRI). Microscopically, the tumor is composed of bipolar cells with long hairlike GFAP-positive processes. Rosenthal fibers, eosinophilic granular bodies and microcysts are often present.

**Glioblastoma multiforme**

Glioblastoma multiforme (GBM), classified as grade 4 astrocytoma, is the most common and aggressive type of primary brain tumor, accounting for 52 percent of all primary brain tumor cases and 20% of all intracranial tumors. Despite being the most prevalent form of primary brain tumor, the incidence of GBM is only 2–3 cases per 100,000 people in Europe and North America.

A normal glioblast is an immature cell derived from neuroectoderm and with the ability to differentiate into several different types of neuroglia. It is considered by some to be equivalent to a spongioblast, while others consider them to be distinct entities.

Treatment can involve chemotherapy, radiotherapy and surgery; all of which are acknowledged as palliative measures, meaning that they do not provide a cure. The five-year survival rate of the disease has remained unchanged over the past 30 years, and stands at less than three percent. Even with complete surgical resection of the tumor, combined with the best available treatment, the survival rate for GBM remains very low.

Almost all cases of GBM are sporadic, without a familial predilection, although chromosomal aberrations such as PTEN mutation, MDM2 mutation, and p53 mutation are commonly seen in these tumors. Growth factor aberrant signaling associated with EGFR, and PDGF are also seen.

GBMs are characterized by the presence of small areas of necrotizing tissue that is surrounded by highly anaplastic cells. This characteristic differentiates the tumor from Grade 3 astrocytomas, which do not have necrotic tissue regions. Although GBM can be formed from lower grade astrocytomas, post-mortem autopsies have revealed that most GBMs are not caused by previous lesions in the brain.

Unlike oligodendrogliomas, GBMs can form in either the gray matter or white matter of the brain, but most GBM arises from the deep white matter and quickly infiltrate the brain, often becoming very large before producing symptoms. The tumor may extend to the meningeal or ventricular wall, leading to the high protein content of CSF (>100 mg/dL), as well as an occasional pleocytosis of 10 to 100 cells, mostly lymphocytes. Malignant cells carried in the CSF may spread to the spinal cord or cause meningeal gliomatosis. However, metastasis of GBM beyond the CNS is
extremely rare. About 50% of GBM occupy more than one lobe of a hemisphere or are bilateral. Tumors of this type usually arise from the cerebrum, and may exhibit the classic infiltrate across the corpus callosum, producing a butterfly (bilateral) glioma.

**Medulloblastoma**

Medulloblastoma is a highly malignant primary brain tumor that originates in the cerebellum or posterior fossa. Although it is thought that medulloblastomas originate from immature or embryonal cells at their earliest stage of development, the exact cell of origin, or “medulloblast” has yet to be identified.

It is currently thought that medulloblastoma arises from cerebellar “stem cells” that have been prevented from dividing and differentiating into their normal cell types. This accounts for the varying histological variants seen on biopsy. Rosette formation is highly characteristic of medulloblastoma and is seen in up to half of cases.

Originally considered to be a glioma, medulloblastoma is known to be of the family of cranial primitive neuroectodermal tumors (PNET). Tumors that originate in the cerebellum are referred to as infratentorial because they occur below the tentorium, a thick membrane that separates the cerebral hemispheres of the brain from the cerebellum. Another term for medulloblastoma is infratentorial PNET. Medulloblastoma is the most common PNET originating in the brain. All PNET tumors of the brain are invasive and rapidly growing tumors that, unlike most brain tumors, spread through the CSF and frequently metastasize to different locations in the brain and spine. Brain tumors are the second most common malignancy among children less than 20 years of age. Medulloblastoma is the most common malignant brain tumor, comprising 14.5% of newly diagnosed cases. In adults, medulloblastoma is rare, comprising less than 2% of CNS malignancies. The incidence of childhood medulloblastoma is higher in males (62%) than females (38%). Medulloblastoma and other PNET tumors are more prevalent in younger children than older children. 40% of medulloblastoma patients are diagnosed before the age of 5, 31% are between the ages of 5 and 9, 18.3% are between the ages of 10 and 14, and 12.7% are between the ages of 15 and 19.

Medulloblastomas usually form in the fourth ventricle, between the brainstem and the cerebellum. Tumors with similar appearance and characteristics originate in other parts of the brain, but they are not identical to medulloblastoma.

Molecular genetics reveal a loss of genetic information on the distal part of chromosome 17, distal to the p53 gene, possibly accounting for the neoplastic transformation of the undifferentiated cerebellar cells. Medulloblastomas are also seen in Gorlin syndrome as well as Turcot syndrome. Another research has strongly implicated the JC virus, the virus that causes multifocal leukoencephalopathy. Histologically, the tumor is solid, pink-gray in color, and is well circumscribed. The tumor is very cellular, the cells have many mitoses, little cytoplasm, and has the tendency to form clusters and rosettes.

**Oligodendrocytes**

Oligodendrocytes, or oligodendroglia, are a variety of neuroglia. Their main function is the myelination of axons exclusively in the CNS of the higher vertebrates, a function performed by Schwann cells in the PNS. A single oligodendrocyte can extend to up to 50 axons, wrapping around approximately 1 mm of each and forming the myelin sheath. The myelin sheath provides

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**Fig. 3** Three-dimensional drawings of an astrocyte and an oligodendrocyte. (Copyright Robert Grossfeld, North Carolina State University, USA)
insurance the axon that allows electrical signals to propagate more efficiently.

**Myelin**

The main consequence of a myelin sheath is an increase in the speed at which impulses propagate along the myelinated fiber. Along unmyelinated fibers, impulses move continuously as waves, but, in myelinated fibers, they hop or propagate by saltation. Myelin increases resistance across the cell membrane by a factor of 5,000 and decreases capacitance by a factor of 50. Myelination also helps prevent leakage of the electrical current from the axon. When a peripheral fiber is severed, the myelin sheath provides a track along which regrowth can occur. Unmyelinated fibers and myelinated axons of the mammalian CNS do not regenerate.

Oligodendroglia arise during development from an oligodendrocyte precursor cell which can be identified by its expression of a number of antigens, including the ganglioside GD3, the NG2 chondroitin sulfate proteoglycan, and the platelet derived growth factor-alpha receptor subunit. In the rat forebrain the majority of oligodendroglial progenitors arise during late embryogenesis and early postnatal development from cells of the subventricular zones (SVZ) of the lateral ventricles. SVZ cells migrate away from these germinal zones to populate both developing white and gray matter, where they differentiate and mature into myelin-forming oligodendroglia. However, it is not clear whether all oligodendroglial progenitors undergo this sequence of events. It has been suggested that some undergo apoptosis and that some fail to differentiate into oligodendroglia but persist into maturity as adult oligodendroglial progenitors.

The nervous system of mammals depends crucially on the myelin sheath for insulation as it results in decreased ion leakage and lower capacitance of the cell membrane. There is also an overall increase in impulse speed as saltatory propagation of action potentials occurs at the nodes of Ranvier in between Schwann cells (of the PNS) and oligodendrocytes (of the CNS); furthermore miniaturization occurs, whereby impulse speed of myelinated axons increases linearly with the axon diameter, whereas the impulse speed of unmyelinated cells increases only with the square root of the diameter. As part of the nervous system they are closely related to nerve cells and like all other glial cells the oligodendrocytes have a supporting role towards neurons. They are intimately involved in signal propagation, providing the same functionality as the insulation on a household electrical wire. Diseases that result in injury to the oligodendroglial cells include demyelinating diseases such as multiple sclerosis (MS) and leukodystrophies. Oligodendroglia is also susceptible to infection by the JC virus, which causes progressive multifocal leukoencephalopathy (PML), a condition that specifically affects white matter, typically in immunocompromised patients. Tumors of oligodendroglia are called oligodendrogliomas.

**Demyelination**

Demyelination is the act of demyelinating, or the loss of the myelin sheath insulating the nerves, and is the hallmark of some neurodegenerative autoimmune diseases, including multiple sclerosis, transverse myelitis, chronic inflammatory demyelinating polyneuropathy, Guillain–Barre Syndrome, and adrenoleukodystrophy. When myelin degrades, conduction of signals along the nerve can be impaired or lost, and the nerve eventually withers. The immune system may play a role in demyelination associated with such diseases, including inflammation causing demyelination by overproduction of cytokines via upregulation of tumor necrosis factor (TNF) or interferon. Heavy metal poisoning may also lead to demyelination. Even very small amounts of mercury have been shown to be particularly destructive to nerve sheaths.

Research to repair damaged myelin sheaths is ongoing. Techniques include surgically implanting oligodendrocyte precursor cells in the CNS and inducing myelin repair with certain antibodies. While there have been some encouraging results in mice (via stem cell implants), it is still unknown whether this technique can be effective in humans. Demyelination destruction or loss of the myelin sheath typically results in diverse symptoms. The symptoms are determined by the functions normally contributed by the affected neurons. Damage to the myelin sheath disrupts signals between the brain and other parts of the body producing a range of symptoms. Symptoms are often heterogeneous—dependent on pathophysiology of demyelination—differing from patient to patient, and have different presentations upon clinical observation and in laboratory studies.

**Oligodendroglioma**

Oligodendrogliomas are a type of glioma that is believed to originate from the oligodendrocytes of the brain or from a glial precursor cell. They occur primarily in adults (9.4% of all primary brain and CNS tumors) and are only rarely found in children (4% of all primary brain tumors). The median age of diagnosis for oligodendroglioma is 41 years of age. The etiology of oligodendrogliomas is unknown. Some studies have linked oligodendroglioma with a viral cause; a single case report has linked oligodendroglioma to irradiation of pituitary adenoma.

Oligodendrogliomas cannot currently be differentiated from other brain lesions solely by their clinical or radiographic appearance. As such, a brain biopsy is the only method of definitive diagnosis.
Oligodendrogliomas recapitulate the appearance of the normal resident oligodendroglia of the brain. They are generally composed of cells with small to slightly enlarged round nuclei with dark, compact nuclei and a small amount of eosinophilic cytoplasm. They are often referred to as fried egg cells due to their histological appearance. It should be noted that the characteristic histological appearance with perinuclear halo is lacking when frozen section is observed, easily leads to misdiagnosis. They appear as a monotonous population of mildly enlarged round cells infiltrating normal brain parenchyma and producing vague nodules. Although they may behave either like glioblastoma or grade III oligodendrogliomas. As such, this is an exceptionally unusual diagnosis.

By far, the most common structural deformity found is co-deletion of chromosomal arms 1p and 19q. The high frequency of co-deletion (~70%) is a striking feature of this glial tumor, and is considered as a genetic signature of oligodendroglioma. 1p/19q deletion has been correlated with both chemosensitivity to PCV regimen using procarbazine, lomustine (CCNU) and vincristine and improved prognosis (95% of survival rate after 5 years) in oligodendrogliomas. A t (1 ; 19) (q10 ; p10) translocation mediates the combined deletions of 1p and 19q. Precise differential diagnosis with astrocytoma is required. Specific markers OLIG1 and OLIG2 (basic helix loop helix transcription factor), which are expressed only among oligodendroglioma, not among astrocytoma, have been reported to be efficient for differential diagnosis. Though, some argue that those markers are expressed also among astrocytomas. Those controversies may reflect the difficulty in the definition of glioma.

**Dysembryoplastic neuroepithelial tumor**

Dysembryoplastic neuroepithelial tumor, commonly abbreviated as DNT, is a type of brain tumor that arises from the oligodendrocyte. It falls into Grade I of the WHO classification of brain tumors and, generally, has a good prognosis. DNT is a multinodular lesion with mild myxomatoid change, which localizes in the cerebral cortex. Specific glioneuronal element (SGNE) is a characteristic appearance, which is composed of alveolus-like structures containing myxomatoid substance, surrounded by fascicles (bundles) of neurofilament protein (NFP)-positive, synaptophysin-positive filaments. The internal surface of the alveolus-like structure is lined by oligodendrocyte-like cell (OLC). Floating neuron is found spotlighted. Surgical resection of the tumor often yields good outcome.

**Oligoastrocytoma**

Oligoastrocytomas are a subset of brain tumor that present with an appearance of mixed glial cell origin, astrocytoma and oligodendroglioma. Often called a "mixed glioma", about 2% of all reported brain tumors are diagnosed as oligoastrocytoma. The median age of
diagnosis is 42 years of age. Oligoastrocytomas, like astrocytomas and oligodendrogliomas, can have malignant (anaplastic) histology. However, lower grades can have less aggressive biology.

**Ependymal cells**

Ependymal cells, also named ependymocytes, line the cavities of the CNS and make up the walls of the ventricles. These cells create and secrete CSF and beat their cilia to help circulate that CSF. Ependyma is the thin epithelial membrane lining the ventricular system of the brain and the spinal cord canal. Ependyma is one of four types of neuroglia, and is itself lined with epithelial cilia of the CNS. Within the brain’s ventricles, ependymal cells are involved in the production of the CSF.

**Stem cells**

Frisén and his colleagues at the Karolinska Institute in Stockholm believe that ependyma is the prime candidate for the location of neural stem cells.

**Ependymoma**

Ependymoma is a tumor arising from the inner lining of the cerebral ventricles and the remnants of the central canal in the spinal cord. Intracranial ependymomas are usually seen in children. Spinal ependymomas arise more often in adults. The most common location of intracranial ependymomas is the fourth ventricle. Syringomyelia can be caused by an ependymoma. Ependymomas are also seen with neurofibromatosis type II. Ependymomas are composed of cells with regular, round to oval nuclei. There is a variably dense fibrillary background. Tumor cells may form gland-like round or elongated structures that resemble the embryologic ependymal canal, with long, delicate processes extending into the lumen; more frequently present are perivascular pseudorosettes in which tumor cells are arranged around vessels with an intervening zone consisting of thin ependymal processes directed toward the wall of the vessel.

Ependymomas make up about 5% of adult intracranial gliomas and up to 10% of childhood tumors of the CNS. Their occurrence seems to peak at age 5 years and then again at age 34. About 85% of ependymomas are benign. The subependymal giant-cell astrocytoma, also called giant-cell glioma, is typically associated with tuberous sclerosis (Bourneville-Pringle’s disease) but can occur independent of that condition. Arising in the walls of the lateral ventricles over the basal ganglia, this tumor tends to cause obstruction when it becomes large.

**Radial glia (Bergman glia)**

Radial glia cells, also called Bergman glia, arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the principal glial cell, and participates in a bi-directional communication with neurons.

Radial glial cells are a pivotal cell type in the developing CNS involved in key developmental processes, ranging from patterning and neuronal migration to their newly described role as precursors during neurogenesis. The term ‘radial glial cell’ refers to their two major characteristics, their long radial processes extending from the ventricular zone to the pial surface and their glial properties, such as the content of glycogen granules or the expression of the astrocyte-specific glutamate transporter or the GFAP. Notably, recent evidence demonstrates that radial glial cells characterized by long radial processes and astroglial properties constitute the majority of precursors during neurogenesis. Indeed, all radial glial cells divide throughout neurogenesis and give rise to the majority of projection neurons in the cerebral cortex.

**Schwann cells (found in peripheral nerves)**

Similar in function to oligodendrocytes, Schwann cells provide myelination to axons in the PNS. They also have phagocytic activity and clear cellular debris that allows for regrowth of PNS neurons.

Named after the German physiologist Theodor Schwann, Schwann cells are a variety of neuroglia that mainly provide myelin insulation to axons in the PNS of jawed vertebrates. The vertebrate nervous system relies on this myelin sheath for insulation and as a method of decreasing membrane capacitance in the axon, thus allowing for saltatory conduction to occur and for an increase in impulse speed, without an increase in axonal diameter. Non-myelinating Schwann cells is involved in maintenance of axons and are crucial for neuronal survival. Some group around smaller axons and form Remak bundles. Schwann cells are the PNS’s analogues of the CNS oligodendrocytes.

**Saltatory conduction**

Saltatory conduction (from the Latin verb saltare, which means to hop or leap) is a means by which action potentials are transmitted along myelinated nerve fibers. Because the cytoplasm of the axon is electrically conductive, and because the myelin inhibits charge leakage through the membrane, depolarization at one node of Ranvier is sufficient to elevate the voltage at a neighboring node to the threshold for action potential initiation. Thus in myelinated axons, action potentials do not propagate as waves, but recur at successive nodes and in effect hop along the axon, by which process they travel faster than they would otherwise. This process is
outlined as the charge will passively spread to the next node of Ranvier to depolarize it to threshold which will then trigger an action potential in this region which will then passively spread to the next node and so on. This phenomenon was discovered by Tasaki \cite{51} and Huxley\cite{52} and their colleagues.

Apart from increasing the speed of the nerve impulse, the myelin sheath helps in reducing energy expenditure as the area of depolarization and hence the amount of sodium/potassium ions that need to be pumped to bring the concentration back to normal, is decreased. Schwann cells begin to form the myelin sheath in mammals during fetal development and work by spiraling around the axon, sometimes with as many as 100 revolutions. A well-developed Schwann cell is shaped like a rolled-up sheet of paper, with layers of myelin in between each coil. The inner layers of the wrapping, which are predominantly membrane material, form the myelin sheath while the outermost layer of nucleated cytoplasm forms the neurolemma. Only a small volume of residual cytoplasm communicates the inner from the outer layers. This is recognized histologically as the Schmidt–Lanternmann incisure. Since each Schwann cell can cover about a millimeter along the axon, hundreds and often thousands are needed to completely cover an axon. The gaps between the Schwann cell covered segments are the Nodes of Ranvier, important sites of ionic and other exchanges of the axon with the extracellular liquid. Unlike oligodendrocytes, myelinating Schwann cells provide insulation to only one axon. This arrangement permits saltatory conduction of action potentials, which greatly speeds it and saves energy.

**Nodes of Ranvier**

Nodes of Ranvier are regularly spaced gaps in the myelin sheath around an axon or nerve fiber. About one micrometer in length, these gaps expose the axonal membrane to the extracellular fluid. (The myelin sheath is the fatty tissue layer coating the axon.) The myelin sheath helps speed the neural impulse by insulating the electrical current and making it possible for the impulse to jump from node to node, a process known as saltatory conduction, as opposed to traveling down the axon in tiny increments. An action potential is the sharp electrochemical response of a stimulated neuron, a neuron whose membrane potential has been changed by a nearby cell, cells, or an experimenter. In an action potential, the cell membrane potential changes drastically and quickly as ions flow in or out of the cell. The action potential travels from one place in the cell to another, but ion flow occurs only at the nodes of Ranvier. Therefore, the action potential signal jumps along the axon, from node to node, rather than propagating smoothly, as they do in axons that lack a

> **An Oligodendrocyte**

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**Fig. 4** An oligodendrocyte myelinating axons. (Copyright Juan Salinas, University of Texas at Austin, USA)
myelin sheath. This is due to clustering of voltage-gated Na+ and K+ ion channels at the nodes of Ranvier. Unmyelinated axons do not have Nodes of Ranvier; voltage gated ion channels in these axons are considerably less ordered and spread over the entire membrane surface. The myelin sheath and the nodes were discovered by French pathologist and anatomist Ranvier (1835–1922). A number of experimental studies since 2001 have implanted Schwann cells in an attempt to induce remyelination in multiple sclerosis-afflicted patients. Indeed, Schwann cells are known for their role in supporting nerve regeneration. Schwann cells possess S–100 protein.

Charcot–Marie–Tooth disease and Dejerine–Sottas disease result from a deletion and point mutation, respectively, of the gene peripheral myelin protein–22 or myelin protein zero on chromosome 17 that results in episodic, recurrent demyelination.

Satellite cells (found in peripheral nerves and ganglia)

Satellite cells are small glial cells that line the exterior surface of PNS neurons and help regulate the external chemical environment. Satellite cells also surround neuron cell bodies within ganglia.

Conclusion

Glia cells have been considered to be merely interstitial cells in the nervous system, though; recent studies revealed that they have numerous important roles in neuronal cell regulation and maintenance. Various diseases may relate to alterations of the glial cells. Deepening the knowledge on glial cells is essential for understanding of nerve functions.

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神経膠細胞—基礎と病変

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【要旨】神経膠細胞は中枢・末梢神経系での神経細胞の間質であり、形態の保持、栄養の供給、絶縁体、異物処理など様々な役割をもつ。小膠細胞は脳内にあるものの、胎生期に脳血管周囲に定着した棒状細胞やマクロファージなど複数の種類の骨髄系細胞（中胚葉）から由来し、その役割も抗原提示など免疫系細胞としての機能が多い。星状膠細胞や斜突起細胞や上皮細胞は神経管（外胚葉）から由来で代謝、神経伝達物質の放出、イオン濃度調整など神経機能に直接に関わる。星状膠細胞は血管内皮細胞に密に付着して血液脳関門の形成に関与する。斜突起細胞は中枢神経内での髓鞘の形成も行う。末梢神経では神経鞘細胞が髓鞘の形成を行い、跳躍伝導に関与する。神経鞘細胞の異常としては神経障害や脱髄がある。

〈キーワード〉 神経膠細胞、樹状細胞、神経膠細胞、髓鞘、跳躍伝導