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- 464-3** Perimedullary Fistula of Filum Terminale: Microsurgical Obliteration

to stain a cultured neuron from the mouse cerebral cortex. The first antibody was raised against MAP-2, one of the major cytoskeletal components of neuronal dendrite. It is revealed with a green fluorophore and shows five major dendrites emanating from a cell body, which is also labeled. The second antibody is against ankyrin G, a component of the axon initial segment. This is revealed with a red fluorophore. Note that the axonal process labeled by ankyrin G (indicated by the *white arrow*) is devoid of MAP-2, confirming the identity of this process as an axon.

In the 1980s and 1990s, advances in molecular biology enabled the detection of messenger RNA (mRNA) for specific proteins through a technique known as *in situ hybridization*. Medium- to high-abundance mRNAs can be localized to the cell body (where they await translation into protein). Rather than detection with an antibody, a specific mRNA is labeled by hybridizing one or more nucleotide probes that are uniquely complementary (antisense) to it. The labeled probes are then detected by any of several means, most of which amplify the signal by tagging custom-designed secondary probes or through an antibody reaction against such derivatized nucleotides incorporated into the probe. Commonly used derivatives include biotin or digoxigenin added to a uracil (uridine 5'-triphosphate) to mimic a cytosine that is then incorporated during the synthesis of the probe. The tissue is treated with proteinase to remove bound proteins and then hybridized at temperatures that ensure the specificity of the probe-message interaction. A digoxigenin-labeled probe hybridized to the message for the Purkinje cell-specific RAR-related orphan nuclear receptor ROR α is shown in Fig. 65.7C. An important aspect of the interpretation of such images is that the location of the message marks the mRNA, not the protein. In most cases, the *in situ* hybridization signal is seen in the cell body, although a small number of mRNA molecules are transported into the dendrite. The image shown in Fig. 65.7C could thus be the result of labeling the mRNA for a protein found in the nucleus, the cell body, or the synapse. The strong (purple) signal tells us that the cell is capable of synthesizing the protein (the mRNA is there), but we do not learn anything about where the protein, once synthesized, will be located.

Dendritic Structure

The dendrite represents a smooth, tapered extension of the neuronal cell body.⁵ The main tapered dendritic shafts have many of the same organelles as the cell body, including mitochondria, microtubules, neurofilaments, smooth endoplasmic reticulum, and ribosomes. The existence of ribosomes is correlated with clear evidence of local protein synthesis,⁷ and while this activity usually occurs in the cell body, studies have illustrated that a unique subset of the total population of mRNA is transported into the dendrites⁸ based on specific sequences contained within the message. Despite the similarity of its organelles to those found in the cell body, the dendritic domain has several unique features that make it identifiable with both light and electron microscopy. Biochemically, the dendrite contains several proteins that are not localized anywhere else in the nerve cell. These proteins include MAP-2, as shown in Fig. 65.7D, as well as several specific receptor species and channel proteins that differ from cell to cell.

The ultrastructure of the typical dendrite includes a relatively electron-lucent cytoplasm, an ordered parallel array of neurofilaments, and a gently tapering caliber. The branch points of large dendrites have their own unique structures. Specialized channel proteins are localized there, and detailed electrophysiologic studies have shown that the consequences of this occasionally include the cell's ability to generate a self-propagating action potential there.⁹

As outlined earlier, the most typical site of contact between a postsynaptic cell and a presynaptic axon is a dendritic spine. Spines can be found on the cell body (although this is rare in adults) or

on the main dendritic branches, but they are most common on the fine terminal branches of the dendrites. The development of a dendritic spine is heavily influenced by the presence of a presynaptic afferent but does not require it. Studies of several pathologic conditions have shown that well-proportioned spines and their associated ultrastructure can be maintained (and possibly developed) in the absence of any presynaptic element. In this case, the structure is usually ensheathed by a glial cell.

Cell Body Structure

Neurons are synthetically active cells. Although the brain typically makes up only 2% of the weight of the human body, it consumes as much as 25% of the oxygen used by the organism (see Chapter 66). It has been estimated that more than 50% of human genes are either highly enriched in, or unique to, the nervous system. Alternative splicing of transcripts is also more prevalent in the brain than in any other tissue.¹⁰ The ultrastructure of the nerve cell body reflects the high level of protein translation that goes on there. When there is a main apical dendrite, the Golgi apparatus and rough endoplasmic reticulum are prominent features that are located between the nucleus and the emanation point of the dendrite. The concentration of rough endoplasmic reticulum is sufficiently great that the term *Nissl substance* is used to describe its prominent, dark, floccular appearance in light microscopic images of basophilic dye preparations (see Fig. 65.7A). Mitochondria are also in abundance, as might be expected given the high aerobic activity of the neuron. Primary and secondary lysosomes are present, and with aging, these tend to accumulate large quantities of a waxy substance known as *lipofuscin*.¹¹ The nucleus of most neurons is oval or spherical in shape. Its nucleoplasm is relatively clear. In most large neurons there is a single prominent nucleolus, whereas in small neurons, such as the granule cells of the olfactory bulb, hippocampus, and cerebral or cerebellar cortex, there are scattered clumps of heterochromatic material with no nucleolus visible in classically stained material.

Axonal Structure

The axon leaves the cell body and forms a specialized structure known as the *axon hillock*. This specialized region has a higher density of proteins such as ankyrin G as well as voltage-dependent potassium and sodium ion channels. The high density of sodium channels results in a lower threshold for firing an axon potential.¹² Also due to the problems inherent in passive current spread through the narrow axon, the further the initial segment begins from the cell body, the more difficult it is for the neuron to fire an action potential. The axonal process then continues without tapering to the target area. Occasionally, the axon branches locally, forming an axon collateral, en route to or at the site of termination. Terminal branching is a common occurrence in the nervous system. As discussed previously, the axoplasm is filled with ordered parallel arrays of microtubules. These appear in the electron microscope to be linked to each other and to a collection of small vesicles by wispy cross-bridges. Neurofilaments are also prominent features of the axoplasm. Mitochondria and smooth endoplasmic reticulum are commonly observed, but ribosomes and Golgi membranes are absent.

Recent work has shown that protein synthesis can also be detected in the axon, although it is less prominent than in dendrites.¹³ Even with this local synthetic source, the topology of the nerve cell presents a significant maintenance problem to neurons when the synaptic terminal is more than a meter away from the cell body. To achieve effective translocation between the protein synthetic machinery in the perikaryon and the axon terminal, the axon uses several mechanisms of transport. In the orthograde direction (cell body to axon terminal), bulk materials tend to flow at a pace of about 0.5 mm/day. Organelles and some

proteins, however, are transported by rapid axonal transport that can achieve rates of 400 mm/day. Material also moves from axon terminal to cell body, in the retrograde direction, at half the speed of fast orthograde transport.

Synaptic Structure

Underlying the details of ionic fluxes during synaptic transmission are a number of crucial elements in the cell biologic structure of the neuron. On the presynaptic side, the axon terminates in a highly specialized presynaptic structure (see Fig. 65.3). The shaft of the axon broadens in diameter and assumes a shallow cup-like form. Although microtubules are a prominent feature of the central axon domain, few extend into the terminal area. Instead, the major structural elements of the presynaptic terminal include neurofilaments and actin filaments. Mitochondria are more abundant than in the axon shaft, and a collection of small vesicles appears near the synaptic cleft itself. These vesicles contain the neurotransmitter substances that will be released upon invasion of the terminal by an action potential. The vesicles are polymorphic in appearance. Those at excitatory synapses tend to be round, whereas those at inhibitory synapses are more ovoid or flattened in appearance. Synapses that release peptides contain larger vesicles with electron-dense material in their centers. These dense core vesicles are typical of neurosecretory cells. Well over a dozen proteins have been identified as crucial to this process, which involves filling of the vesicle with transmitter, docking, fusion of the vesicle with cellular membranes, release, and finally, recycling. The significance of these processes was recognized in the awarding of the 2013 Nobel Prize in Physiology or Medicine.

Neurotransmitters are packaged and released from synaptic vesicles. The vesicles have been found to cluster in the vicinity of the synapse, where modern electron microscopic techniques suggest that they are interconnected with a meshwork of fine filaments. Vesicles must first be filled with neurotransmitter, a function accomplished by a variety of transport proteins. In an active synapse, the filled vesicles are then moved to a region near to the active zone—a region of about $0.1 \mu\text{m}^2$ where release occurs. As conditions demand, the vesicles dock on the plasma membrane of the active zone. An adenosine triphosphate (ATP)-dependent process then “primes” the vesicle. In this state, the influx of Ca^{2+} ions that accompanies the invasion of the action potential into the nerve terminal triggers a process of vesicle-plasma membrane fusion that releases the contents of the vesicle into the synaptic cleft. Vesicle recycling then occurs, although the precise mechanism of this process is still debated and may be dependent on the specific synapse. In general, an endocytic process recycles the fused vesicular membrane back into the cell. The vesicular and plasma membrane proteins that accomplish this process have been well studied, but a full listing of their identities and functions is beyond the scope of this volume.

The Cell Biology of Neuronal Death

Included among the important physiologic functions of a brain cell is its program of cell death. Cell death was once viewed as a passive process, but our understanding of its biology has advanced to the point where we now appreciate that most cell loss is an active process that involves a well-orchestrated program of gene expression, proteolysis, and rearrangement of cellular organelles.^{14–16} The programs of cell death are generally divided into the more active form of cell death known as *apoptosis* and the more passive form known as *necrosis*. This duality is oversimplified since a more nuanced and probably more accurate characterization is that there are many processes that contribute to cell death. It is the summation of these processes along with the internal protective mechanisms that usually come into play in a neuron under stress that ultimately determine whether a neuron will live or die. Some of the basic forms of cell death are summarized in Table 65.1.

Apoptosis is also referred to as *programmed cell death* or *nuclear cell death*. During this process, a sequence of genetic transcription and translation is initiated. At the morphologic level, apoptosis is a process that appears to package the cell for removal without initiating an inflammatory response. The cell membrane blebs as the cell shrinks in size. The nucleus condenses and fragments; the cell dumps its water as it shrinks, with a consequent darkening of the cytoplasm. In the end, there remains only a small, round, membrane-bound corpse that is easily ingested by a local microglial cell. Different pathways have been found that produce apoptosis. The *intrinsic pathway* begins with the breakdown of mitochondrial integrity and the massive release of cytochrome *c* from the mitochondria to the cytoplasm of the cell. This catalyzes the formation of the protein complex known as the *apoptosome*. This in turn activates one or more members of a group of cysteine-aspartate proteases known as *caspases* by proteolytically cleaving their “pro” (inactive) form to the activated form of the caspase. There are currently nearly a dozen known caspase enzymes. Their substrates range from other caspases to many important cellular targets where cleavage can either activate a zymogen or destroy a crucial component of cellular homeostasis.

A second apoptotic pathway is known as the *extrinsic pathway*. It is triggered by the binding of a ligand to any of several death receptors such as tumor necrosis factor or Fas. The receptors trimerize and position pro forms of caspase-8 or caspase-10 to be proteolytically activated. In virtually every situation that has been studied, adult neurons that are lost to cell death cannot be replaced from endogenous stem cells or other sources. It is not surprising, therefore, that the progress of apoptosis—in both the intrinsic and extrinsic pathways—is tightly regulated.¹⁷ Mitochondrial integrity is regulated by a family of small peptides known as the *B-cell lymphoma 2 (Bcl-2) family*, including Bcl-2, Bax, Bad, and others. These proteins bind to each other, and the dimers can either promote or inhibit cell death. Other factors that work against the completion of the final apoptotic pathway include such proteins as inhibitors of apoptosis.

Necrosis is often referred to as cytoplasmic cell death and is the opposite of apoptosis. The process is believed to be a largely passive one that is not dependent on the participation of the synthetic processes of the cell such as transcription or translation. The ATP stores of the cell drop, starving the cell for the energy it needs for normal homeostasis. As a result, the cell takes on water and swells, as do the constituent organelles. The mitochondria swell, and the cytoplasm takes on a dilute appearance. Eventually, the surface membrane of the cell loses its integrity and the cellular contents are dumped into the extracellular space. This process is most common in the immediate aftermath of brain trauma or during certain types of metabolic imbalance.

Recently autophagy, a process of bulk cellular waste removal, has been proposed as a distinct mechanism of cell death. The normal function of autophagy is to enable the cell to remove large particles of debris such as aggregates of misfolded proteins from the cytoplasm. It is now suspected that this process can become overactive, overwhelming the protective devices of the cell and thus causing it to literally eat itself. The morphology of autophagic cell death includes swelling of organelles, loss of cytoplasmic membrane integrity, and vacuolization of the cytoplasm. A role for this form of cell death has been proposed in neurodegenerative disease.

The triggers for these cell death programs are diverse. A common example is that of excitotoxic cell death. If a neuron becomes hyperactive, one unavoidable consequence is the accumulation of abnormally high concentrations of intracellular calcium. This calcium activates a variety of calcium-activated proteases, channels, and pumps that will ultimately initiate a caspase cascade, leading to an apoptotic crisis. This type of nerve cell death is common following a seizure (hyperactivity of a neuronal network) or a vascular insult (local

TABLE 65.1 Cell Death

	Apoptosis	Necrosis	Autophagy
Morphology	Blebbing of membranes Packaging of cytoplasm Condensation and fragmentation of nucleus Engulfment of “corpse” by microglia	Rupture of membranes Dilation of organelles Lysosomal rupture	Nucleation of autophagosome Enwrapping of contents Fusion with lysosome Degradation of contents
Biochemistry	Mitochondrial release of cytochrome c Formation of apoptosome Activation of caspase proteases	Poorly defined Failure to maintain ATP levels Loss of calcium balance Increase in reactive oxygen species	mTOR as master regulator Autophagosome construction using Atg-family proteins Lysosomal fusion controlled by LAMP

ATP, Adenosine triphosphate; LAMP, lysosome-associated membrane protein; mTOR, mammalian target of rapamycin.

depolarization-inducing concentrations of various ions). While excitotoxic cell death appears to be largely apoptotic in nature, it has been suggested that it may in fact represent a fourth uniquely neuronal form of cell death.

Another emerging association with neuronal cell death is the loss of cell cycle regulation. This represents an odd situation since most adult neurons exit the cell cycle during embryogenesis and do not return. Nonetheless, in a variety of neurodegenerative conditions, including Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, ataxia-telangiectasia, stroke, and HIV-associated dementia, neurons that are known to be at risk for death are found to reexpress proteins that are normally found only in cells that are actively engaged in a cell cycle. These include such cell cycle components as Ki-67, cdk4, cyclins B and D, p16, proliferating cell nuclear antigen, and cdc2.¹⁸⁻²¹ Curiously, the cycle is not a productive one; it is never completed. DNA replication is involved, as studies with DNA hybridization techniques have shown, but both Alzheimer and Parkinson diseases, the chromosome copy number increases, as would be expected during a normal S phase of the cell cycle.²²⁻²⁴ The actual mitotic process, however, does not occur; chromosomes do not condense and mitotic spindles are not observed, nor are any forms of cytokinesis. Studies in tissue culture suggest that cell cycle initiation is an early part of the death pathway, as blocking the cycle blocks the death. In the adult brain, however, the linkage between the two processes is not direct; it is estimated that it can be many months to a year from the time a neuron initiates a cycle until it finally dies. Whether this is a new type of cell death, or merely a precursor or trigger to apoptosis or necrosis, is not known.

The idea that entrance into a cell cycle might be lethal for a neuron, even while it is restorative for other cells in other tissues, highlights the fact that neurons, because of their highly specialized form and function, are vulnerable to a variety of insults. Thus because they are postmitotic and highly differentiated, they cannot tolerate the reinitiation of the cell cycle.²⁵ Similarly, because they are in a nonmitotic state, repair of DNA damage is a crucial neuroprotective activity. Syndromes that involve disruptions of genes that encode elements of the DNA repair pathways almost always include neurodegeneration as part of their phenotype.²⁶ Excitotoxicity also reflects unique neuronal vulnerability. Because the neuron's internal calcium concentration is exquisitely sensitive to neurotransmitters, it is highly susceptible to damage from excessive synaptic activity. Oxidative damage is also a common trigger for neurodegenerative disease, and failure of antioxidant strategies of the cell can result in death. In truth, both the triggers of neuronal cell death and the death pathways themselves probably have significant overlap and may represent a continuum rather than distinct and wholly separate events. For example, a regular target of oxidative damage is DNA; thus a lesion would trigger both DNA repair and antioxidant responses. Similarly, the processes usually associated with apoptosis can be found in cells that have lost their ATP stores and thus would be considered to be undergoing necrosis.

Neurodegenerative Diseases

There are many types of neurodegenerative disorders that afflict humans. These disorders vary in their age of onset and the specificity of the affected cell populations. Alzheimer disease is an example of these conditions. Its disease process not only highlights several features of neuronal cell death, but also emphasizes the importance of interactions among the various nervous system cell types. Alzheimer disease is a progressive dementia that affects millions of individuals in the United States alone.²⁷ Clinically the disease manifests as a loss of short-term memory, a failure of executive function, and a variety of behavioral disorders such as depression and apathy. The disease is defined by the presence of two pathologic features: an extracellular deposit of a peptide fragment known as β -amyloid in a largely insoluble aggregate known as a *plaque* and a twisted configuration of fibrils (made up largely of neurofilaments and filament-associated proteins) known as a *neurofibrillary tangle*. The course of the illness involves not only neurons but also several non-neuronal cells. In the vicinity of the plaque are reactive astrocytes, as well as activated microglial cells^{28,29} (discussed later in this chapter). The astrocytes appear to surround the plaque, as if trying to wall it off from the brain. The microglial cells appear to invade the plaque, as if trying to digest it. Associated with the dementia is a loss of the majority of the neurons in several discrete neuronal populations: the hippocampus and entorhinal cortex,^{30,31} the nucleus basalis of Meynert,³² the dorsal raphe, and the locus caeruleus.³³ As the disease progresses, a more diffuse loss of neurons is observed, affecting many regions of frontal cortex and leading to significant atrophy of the brain at later stages.

As of this writing, the exact mechanism of neuronal death is controversial. At the disease process itself can be many years in duration, only a tiny fraction of 1% of the cells in even the most effected population would be expected to be undergoing cell death at any one time. This slow loss of neurons makes it difficult to find the precise cells that are actively engaged in the process of dying. Perhaps as a consequence of this protracted disease course, no consistent evidence for either apoptosis or necrosis can be found in any of the affected populations. Like many other diseases, it is a condition that affects all of the cells of the brain—neurons and nonneurons alike. For example, one pathogenic scenario is that the aggregates of the β -amyloid peptide trigger a reaction in astrocytes and microglial cells. This produces a complex inflammatory cascade that induces the release of numerous cytokines into the brain environment.^{34,35} Vascular deposits of amyloid are also found during the disease, and a role of vascular endothelial cells has also been proposed.³⁶ Thus this common neurodegenerative condition of the elderly highlights the severe consequences for the individual of losing neurons in large numbers and emphasizes the integrated nature of the cellular functions of the brain. Neurons may be the long-distance carriers of information in the brain, but in both health and disease, the brain works as an ensemble of multiple different cell types.

NEUROGLIA

The term *neuroglia*, or “nerve glue,” was coined by Virchow in 1846 to describe an inactive connective tissue or cement that held neurons of the CNS in place.³⁷ Although neuronal support is the major if not the only function of neuroglia, they are not passive caretakers of neurons. Neuroglia consist of morphologically and functionally distinct cell populations with irreplaceable structural and metabolic roles during brain development, neuronal function, and brain repair. In the human brain, neuroglia are as numerous as neurons and actively participate in information processing.³⁸

How many neuroglial cell types are there? The classic metallic impregnation techniques developed by Cajal initially identified two neuroglial cell components: astrocytes and the “third element of the CNS.”³⁹ Subsequently, del Río-Hortega divided Cajal’s third element into the myelin-forming oligodendrocytes and the CNS resident innate immune cells, the microglia.⁴⁰ Recently, a fourth population of glial cells has been identified in the adult human brain that appears to be as abundant as microglia and oligodendrocytes.⁴¹ These cells can give rise to oligodendrocytes during brain development and following demyelination in the adult brain and are referred to as oligodendrocyte progenitor cells (OPCs). As discussed later, all or some OPCs in the adult brain may have additional functions. A fifth glial cell population in the CNS is the ependymal cells, which line the ventricular system and central canal. In the peripheral nervous system (PNS), the Schwann cell is the major neuroglial component. With the exception of the ependymal cells, most CNS neuroglia extend multiple processes. The distribution and morphology of neuroglial cells in the adult brain are dictated by the functional requirements of these processes. Although many of these functions are understood, further characterization of the molecular properties of glial cells is needed to fully understand their functions.

Neuroglia are significant players in neurosurgery-based therapies, including axonal regeneration in spinal cord injury (see Chapter 67), neuronal survival in stroke, diagnosis and treatment of gliomas, glial cell transplantation, and gene therapy. Neuroglia also regulate neurotransmitter and glucose levels in the brain and may contribute to psychopathology. Microglia and astrocytes invariably react to CNS damage, and this reactivity may be beneficial or detrimental to brain function or intended procedures. Thus understanding the role of neuroglia in the nervous system is as important to the neurosurgeon as understanding the neuron. The following sections describe the morphology, distribution, and function of each neuroglial cell population. Other chapters in this volume describe, in more detail, the role of astrocytes and other neuroglia in nervous system development, function, and disease.

Astrocytes

Astrocytes are the most abundant cell within the CNS. It has been estimated that astrocytes constitute 20% to 50% of the volume of many brain areas. Astrocytes mediate many functions through physical contact between their processes and other CNS components. Therefore astrocyte distribution, shape, and function reflect in part the distribution of the CNS components they contact. Many astrocyte functions occur ubiquitously throughout the CNS, whereas others are restricted by location. Astrocyte morphologies are complex and variable. The terms *fibrous astrocyte* and *protoplasmic astrocyte* are often used to describe astrocytes in white and gray matter. This classification reflects a higher intermediate filament content in white matter and reactive astrocytes, but it provides little information regarding specificity of function. As a major cytoskeletal component, intermediate filaments provide structural stability and rigidity to cells and their processes. White matter astrocytes project long processes to stable structures (i.e., pial surface, nodes, and vessels) and thus have more intermediate

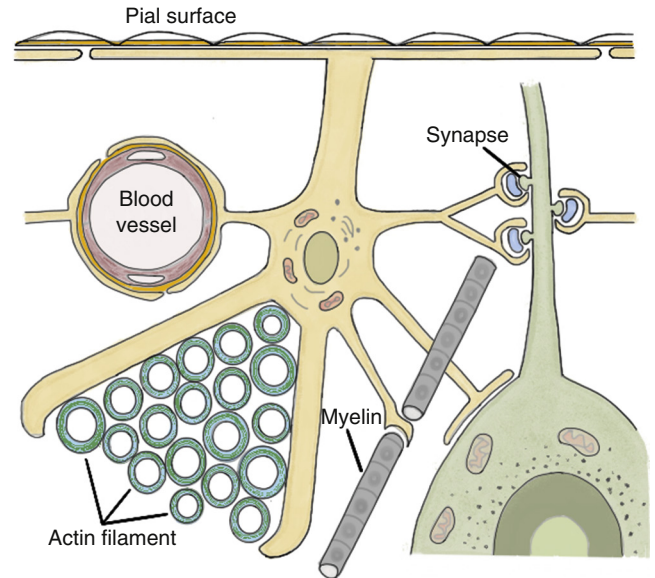


Figure 65.8. Relationships between astrocytes and other central nervous system cells. Astrocyte processes surround blood vessels, synapses, nodes of Ranvier, neuronal cell bodies, and groups of myelinated axons. They form the glia limitans at the pial and ependymal surfaces (not shown). The larger processes contain high concentrations of intermediate filaments.

filaments. In addition to these functions, gray matter astrocytes send processes to neurons, dendrites, and synapses. Because synapses are abundant and often transient structures, gray matter astrocytes are more abundant and their associations with synapses must be dynamic and not restricted by high intermediate filament content. Thus most astrocytes in normal cerebral cortex contain few intermediate filaments and are not prominently stained by glial fibrillary acidic protein antibodies. Major functions of astrocytes are summarized in Fig. 65.8 and are related to astrocyte distribution and morphology in the following paragraphs.

How many types of astrocytes are there? Most textbooks identify three major astrocyte subtypes: radial glial, fibrous astrocytes of white matter, and protoplasmic astrocytes of gray matter. Astrocytes could be classified into dozens of subtypes (most are found in gray matter) based on the differential expression of a variety of molecules, including ion channels, neurotransmitter receptors, neurotrophin, and other cell surface receptors. Astrocytes with unique shapes are found in the retina (Müller cells), the cerebellum (Bergmann glia), and the olfactory bulb (olfactory ensheathing cells). Common to all astrocytes is a unique population of intermediate filaments enriched in glial fibrillary acidic protein (GFAP). Bundles of the 10-nm-thick intermediate filaments are a characteristic ultrastructural feature of astrocytes, as is an abundance of glycogen granules,⁴² reflecting the important role of astrocytes in brain energy metabolism (see Chapter 66). Historically, GFAP staining was considered to be a reliable marker for astrocytes. With the advent of fluorescently labeled tags that bind to all astrocyte surface membranes, we now know that astrocytes virtually cover the entire brain and that cortical astrocytes have a bush-like appearance. Astrocytes are everywhere in the adult brain, and GFAP staining is often a reflection of astrocyte activation rather than generation. The shapes of various astrocytes are shown in Fig. 65.9.

Radial Glia

Transient populations of bipolar-shaped astrocytes are the first glial cells to appear in the developing mammalian brain.⁴³ The

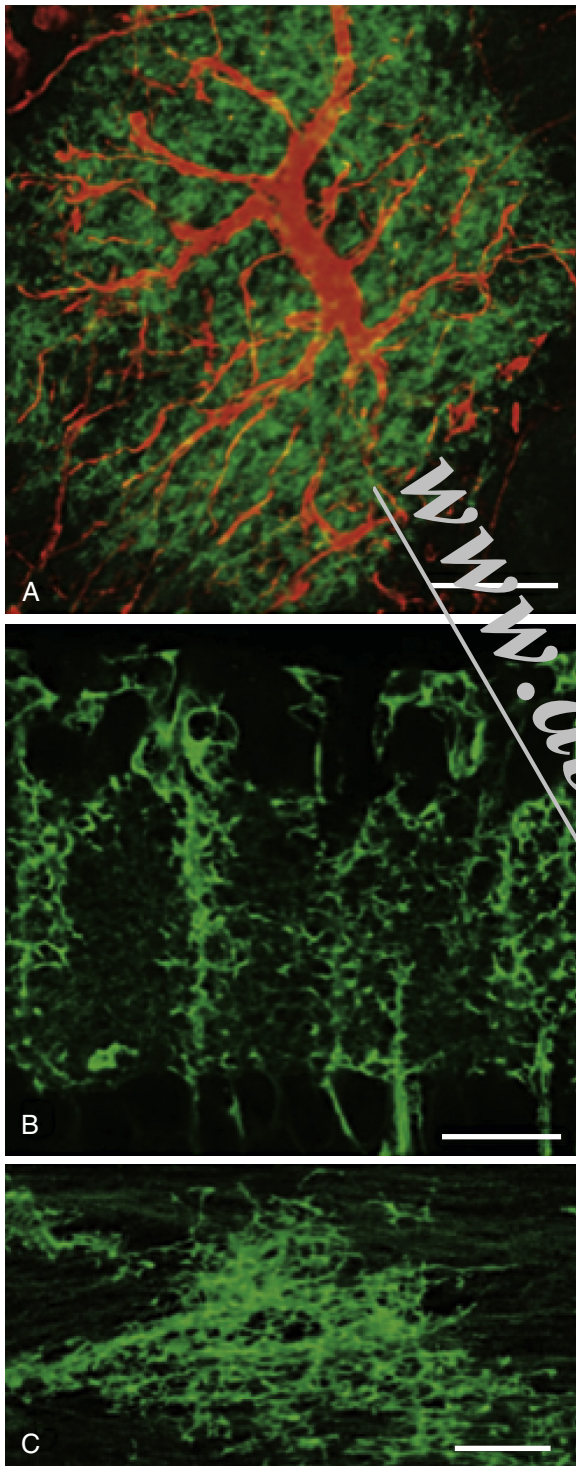


Figure 65.9. Confocal microscopy illustrates the diverse morphologies adopted by astrocytes (green) in the CNS. (A) In cortex large glial fibrillary acidic protein (GFAP)-positive processes (red staining) radiate from the astrocyte cell body and extend a network of fine lacy processes that surround synapses, cell bodies, and blood vessels. (B) In retina, Müller cells extend across the entire retina and intercalate processes among photoreceptors and neurons. (C) White matter astrocytes extend elongated processes along myelinated axons and provide trophic support of axons and other glia. Scale bars, 10 μm . (Courtesy Dr. Maria Smith.)

soma of an astrocyte projects a short process to the ventricular surface and an elongated process to the pial surface. These radial glia transversely compartmentalize the developing neural tube and provide supportive scaffolding for the fragile embryonic neural tissue. Radial glia are the major source of neurons in the developing brain. They generate neuronal progenitor cells by asymmetrical division. Radial glia therefore play an irreplaceable role in constructing the cytoarchitecture of the CNS by generating neuronal precursors and providing the physical substrate for many of the migrating postmitotic neurons that originate in the subventricular zone. Radial glia express a variety of extracellular matrix and adhesion molecules that provide the molecular cues for this neuronal migration. After neurogenesis is complete, most radial glia transform into astrocytes of white or gray matter. Radial glia, however, are not the only source of mature astrocytes; many originate from progenitor cells located in the subventricular zone. Bergmann glia in the cerebellum, Müller cells in the retina, and tanycytes in the brain and spinal cord retain many characteristics of radial glia in the adult brain.⁴⁴

White Matter Astrocytes

Curiously, no astrocyte functions are unique to white matter. Some functions, however, especially those related to structural support, appear to be more prominent in white matter. Further, because of their high content of intermediate filaments, white matter astrocytes are easier to visualize than their gray matter counterparts. Astrocytes provide the cement or structural support to the adult CNS by extending processes to the ventricles and pial surface, where they form a continuous sheet called the *glia limitans*. In contrast to bipolar radial glia, most astrocytes that form the *glia limitans* in the adult brain are multipolar and extend relatively short processes to either the pial or the ventricular surface. Notable exceptions to this are the large astrocytic processes that form a supportive scaffolding for the major white matter tracts and the pia mater of the spinal cord. In all white matter tracts, smaller astrocytic processes serve as guides for axonal migration during development, secrete growth factors that regulate oligodendrogenesis and angiogenesis, and surround and support bundles of axons projecting to similar locations.

As described earlier, neuronal communication occurs via chemical and ionic signals that cross the synapse and other extracellular spaces of the CNS. The extracellular milieu of the CNS therefore must be tightly regulated. The astrocyte is the major homeostatic regulator of the CNS microenvironment. Most importantly, astrocytes help restrict the entry of serum factors into the CNS by extending processes that terminate in specialized “end-feet” that surround almost all blood vessels in the CNS. These astrocytic end-feet provide an extrinsic trophic effect that induces and maintains the tight junctions between neighboring endothelial cells, an essential element for the formation and maintenance of the blood-brain barrier (BBB; see Chapter 68). Astrocytes also buffer extracellular fluxes of ions and neurotransmitters associated with neuronal electrical activity. In white matter, astrocyte processes cover nodal regions of myelinated axons, where they buffer ionic fluxes associated with saltatory conduction. The “structural” astrocytes in white matter may represent a separate population from the astrocytes that send processes to nodes and vessels. This distinction reflects developmental differences in the timing of their initial appearance and progenitor cell origin. The structural astrocytes appear first, and many originate from radial glia. The structural astrocytes have been referred to as type 1 astrocytes, and those associated with nodes and vessels as type 2. Type 2 astrocytes are thought to originate from progenitor cells generated in the subventricular zone. In vitro, this progenitor cell may also give rise to oligodendrocytes.²⁸

Gray Matter Astrocytes

Compared with white matter astrocytes, gray matter astrocytes are more abundant and project more and shorter processes. Gray matter astrocytes send processes to the pial surface, blood vessels, and nodes of Ranvier and therefore share many functions with white matter astrocytes. Gray matter contains less myelin and more vessels than white matter, so gray matter astrocytes perform these functions at different proportions. The major difference between white and gray matter astrocytes is that the latter project processes to and ensheath neuronal cell bodies, dendrites, and synapses. Astrocyte processes surround most synapses and, with the presynaptic terminal and the postsynaptic specialization, comprise a structure known as the *tripartite synapse*. Astrocytic ensheathment of synapses helps inactivate and recycle neurotransmitters, such as the excitatory amino acid glutamate. The glutamate and other neurotransmitter transporters are highly enriched in astrocyte processes that ensheath the synapses.⁴⁵ Gray matter astrocytes are connected to each other by gap junctions and thereby form a syncytium that permits diffusion of ions and small molecules throughout the brain parenchyma.⁴⁶ Potassium ions released from neurons during neurotransmission, for example, are taken up and diffused by astrocytes so they do not interfere with future synaptic activity. Intercellular calcium waves are also generated from astrocyte to astrocyte in response to neuronal stimulation. Gap junctions have been detected between astrocytes and neurons and, along with astrocytic neurotransmitter receptors, may couple astrocytic and neuronal physiology.⁴⁷

The human brain represents 2% of body weight yet consumes 25% of the body's glucose.⁴⁸ Glucose is the obligate energy substrate of the normal human brain and must be obtained from the circulation. The astrocyte is the major regulator of energy metabolism in the brain. One key to understanding this role is the physical connection between astrocytic processes and (1) capillaries, the external source of glucose, and (2) the synapse, a major energy consumer of the brain (see Fig. 65.8). The molecular events that couple synaptic activity, glucose uptake, neurotransmitter pools, and energy substrates can be stoichiometrically directed by synaptic activity. Best understood is the role of glutamate in the excitatory synapse.⁴⁸ For each synaptically released glutamate molecule internalized by the astrocytic glutamate transporter, one glucose molecule enters the same astrocyte from the circulation via endothelial cells. From this glucose molecule, two ATP molecules are produced by glycolysis and two lactate molecules are released and consumed by the synapse to yield 18 ATPs via oxidative phosphorylation. This activation also results in astrocytic release of glutamine, which enters the neuron and regenerates the neuronal glutamate pool. One can see from this description that much of brain energy metabolism related to neuronal function at the synapse occurs in astrocytes. Physiologic increases in brain activity visualized by proton emission tomography of ¹⁸F-2-deoxyglucose in vivo actually reflect increased blood flow and uptake of the tracer into astrocytes, not direct energy consumption by neurons.

Reactive Astrocytes

Another important feature of astrocytes is their reaction to CNS pathology induced by trauma, neurotoxicity, neurodegeneration, infection, and inflammation. Astrocytes react by becoming hypertrophic and, in a few cases, hyperplastic. This astrogliosis includes a rapid and marked increase of GFAP expression and intermediate filament formation. Astrocyte processes therefore help stabilize fragile brain structure caused by brain tissue destruction. As described in Chapter 67, however, reactive astrocytes can secrete a variety of substances, such as proteoglycans and growth factors as well as proinflammatory cytokines, all of which can inhibit or promote axonal regeneration, brain repair, and neuronal function. Reactive astrocytes may represent a double-edged sword,

in that they may stop the progression of tissue damage at the expense of reducing nerve regeneration or brain repair.

Oligodendrocytes

Rapid electrical communication between the $\sim 10^{11}$ neurons in the human brain controls and integrates the sophisticated mental and motor functions that set us apart from other species. Consider, for example, a complex task such as a 7-foot human dunking a basketball. The motor, sensory, and decision-making circuitry of the brain and peripheral nerves must integrate and coordinate jumping, manipulating the torso, handling the ball, avoiding defenders, and putting the ball in the basket. Millions of coordinated nerve impulses govern this action, and many must travel more than a meter in a fraction of a second. Without rapid nerve conduction, the 85 billion neurons in the human brain would not be an advantage for function or survival. Two mechanisms have evolved to permit rapid conduction of nerve impulses. In invertebrates, axonal conduction velocity is related to the diameter of the axon.⁴⁹ Large-diameter axons conduct at a much faster rate than small-diameter axons. Although this situation is sufficient for regulating neural function in smaller, less sophisticated organisms, the CNS of humans cannot accommodate the increase in axonal volume required for rapid nerve conduction. For example, the large-diameter motor axons conduct at a velocity of approximately 40 m/s. If this conduction velocity were regulated solely by axonal diameter, the diameter of this axon would be several millimeters. Multiplying this by the millions of axons in the spinal cord would result in a spinal cord as wide as a telephone pole. Therefore, an additional mechanism evolved to accommodate rapid nerve conduction in the vertebrate brain.

Analogous to the conduction of electrical wire, the mammalian nervous system increases the resistance and decreases the capacitance of axonal membrane potentials by surrounding axons with a multilamellar, tightly compacted membrane insulation called myelin (Fig. 65.10). Myelin is a specialized extension of the plasma membrane of the oligodendrocyte in the CNS⁵⁰ and of the Schwann cell in the PNS.⁵¹ The length of individual myelin segments, or myelin internodes, varies between several hundred micrometers and 2 mm, with larger diameter axons having longer and thicker (more spiral wraps) myelin internodes. Along each axon, individual myelin internodes are separated from their neighbors by a node of Ranvier, a specialized unmyelinated axonal segment (1 to 5 μ m in length) enriched in sodium channels and analogous to the axon hillock or initial axonal segment. Enrichment of voltage-sensitive sodium channels at the node generates ionic impulses only at the node (see Fig. 65.10). The action potential "jumps" from node to node by a process called saltatory conduction. Propagation of the action potential is also an energy-dependent process. Saltatory conduction consumes less energy than nonsaltatory conduction does. Therefore, myelin has three general advantages for the function of the human CNS: fast axonal conduction, energy conservation, and space conservation. Myelin is essential for normal neurological function, and a variety of inherited, metabolic, and immune-mediated myelin diseases occur in humans. Axonal degeneration is a consistent and neurologically important phenotype in the brains of individuals with myelin disease,⁵² indicating that myelin provides extrinsic trophic support for the survival of axons.^{53,54} Myelination therefore is essential for the maturation and survival of axons and should be considered an integral part of nerve regeneration paradigms.

The only known functions of oligodendrocytes are myelination and axonal support. Therefore the distribution of oligodendrocytes correlates with the density of axons requiring myelin. Oligodendrocyte-myelin ratios, however, are not directly proportional, because different oligodendrocytes can myelinate different numbers of axons.⁵⁵ Oligodendrocytes have small, round

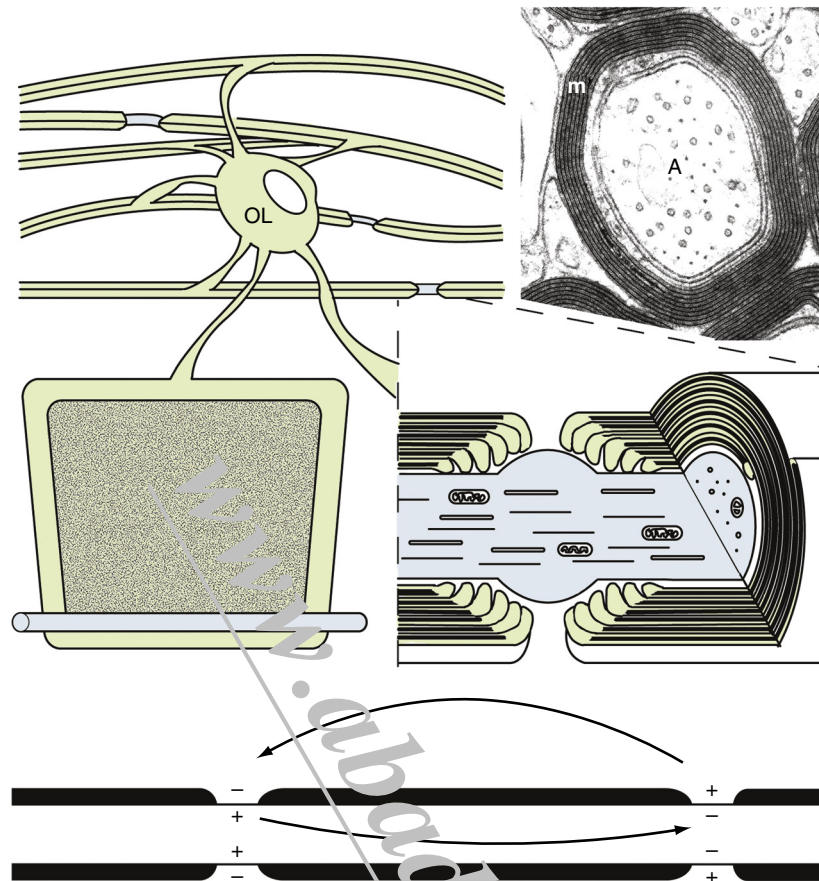


Figure 65.10. Oligodendrocytes (OL) in the central nervous system myelinate multiple axons (A). One myelin internode is “unrolled” to depict continuity between oligodendrocytes and myelin internodes. The compact nature of myelin (m) is shown in the electron micrograph in the *upper right*. Myelin internodes end in paranodal loops at nodes of Ranvier, depicted in the cut-away view. Myelination supports saltatory conduction, in which ion exchange occurs only at the nodes of Ranvier (*lower schematic*). (From Peters A, Palay SL, Webster HF. *The Fine Structure of the Nervous System: Neurons and Their Supporting Cells*. 3rd ed. Oxford University Press; 1991.)

cell bodies; extend single processes to each myelin internode; and can be identified in tissue sections with a variety of myelin-specific antibodies. As expected, oligodendrocyte density is high in white matter tracts, where the cells often occur in rows oriented parallel to axons. Oligodendrocytes are also present at significant densities in gray matter because many axons terminating on and originating from neurons are myelinated. Oligodendrocyte cell bodies can be found close to neuronal cell bodies in gray matter or close to blood vessels in both gray and white matter. It is not known whether these cells perform functions other than myelination.

Schwann Cells

In the PNS, myelin is formed by Schwann cells rather than oligodendrocytes. Peripheral myelin serves functions identical to those of CNS myelin. Schwann cells, however, differ from oligodendrocytes in that they can promote axonal regeneration (see Chapter 67). Schwann cells form single myelin internodes and surround these internodes with a specialized connective tissue or basal lamina (Fig. 65.11). The basal lamina forms a continuous tube around the entire length of each myelinated fiber. When a PNS axon is transected, the distal axonal segment rapidly degenerates, the myelin is removed, and Schwann cells multiply and form a continuum within each basal lamina tube (Fig. 65.12).⁵⁶ The proximal end of the axon, still connected to the neuronal cell body, does not degenerate and can regrow into the Schwann cell tube, which provides a substrate and often direct

continuity for regeneration and reinnervation of appropriate targets. Degenerated peripheral nerve segments, or Schwann cells isolated and expanded *in vitro*, have been experimentally transplanted into the CNS or PNS to promote axonal regeneration.^{57,58} Although this is a common and often successful method of PNS regeneration in humans, Schwann cell transplantation as a therapy for human spinal cord injury is still under experimental development.

Myelination is not the only function of Schwann cells. They also surround the perikarya of PNS neurons, small-diameter axons, and portions of the neuromuscular junction (see Fig. 65.11). These Schwann cells have a molecular phenotype that differs significantly from myelinating Schwann cells.

Microglia

Microglia, the innate immune cells in the central nervous system, have two primary roles in the brain that are common to myelomonocytic innate immune cells in all mammalian organs: they fight off and phagocytize viruses, bacteria and other foreign invaders and they remove cellular debris to facilitate wound repair. Innate immune cells are sparsely distributed in the liver, lungs, and skin. In contrast, microglia occupy all regions of the CNS in a tile-like pattern. Since the entire adult mammalian brain is occupied by microglial cells, it is evident that they have functions that are specific to the brain. Historically, microglial cells were thought to originate from bone marrow-derived monocytes. While microglia share many characteristics with blood-borne

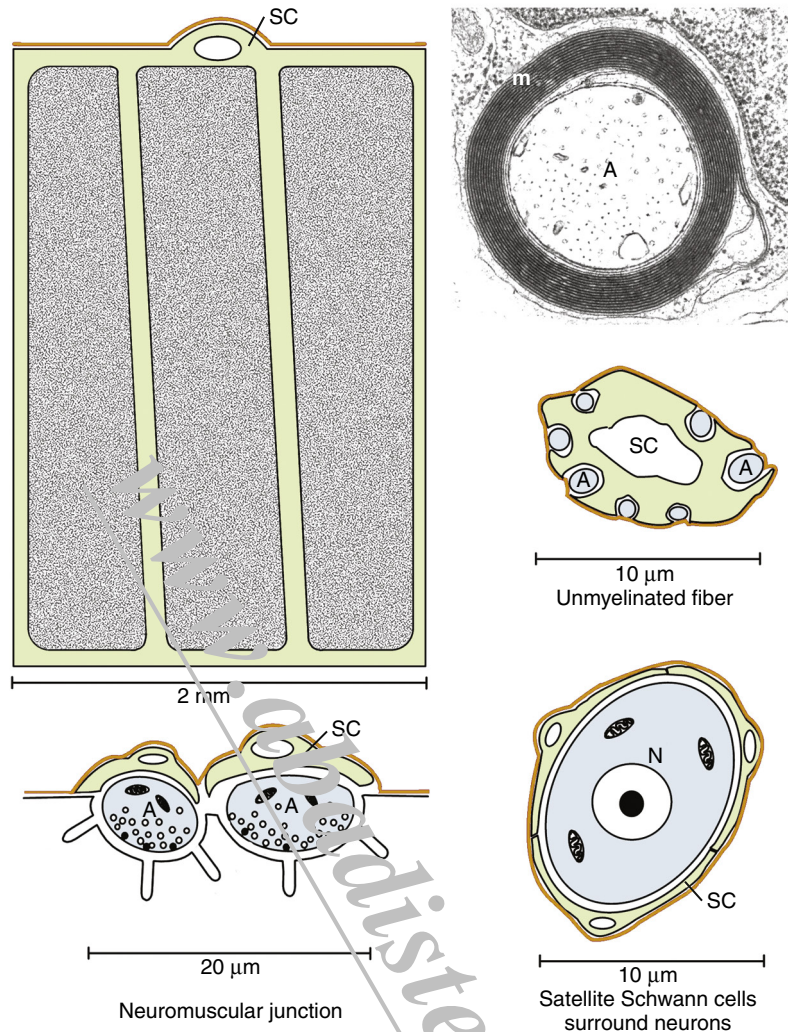


Figure 65.11. Schwann cells (SC) form single myelin internodes in the peripheral nervous system (PNS). Upper left schematic depicts unrolled myelin internode; the *stippled area* represents compact myelin (m) shown in the electron micrograph. The outer surface of PNS myelin internodes is surrounded by basal lamina (orange). Schwann cells also surround multiple unmyelinated axons (A), neuromuscular junctions, and neuronal perikarya (N) in PNS ganglia. Basal lamina also surrounds these Schwann cells.

monocytes, it is now established that microglia originate from a unique stem cell in the yolk sac.⁵⁹ Microglial progenitors colonize the brain during early fetal development and initially have amoeboid shapes. To assure that appropriate neuronal connections are made during brain development, the CNS overproduces neurons and developing neurons compete for connections. Neurons that lose this competition die; microglia do not kill these neurons, but they recognize their dysfunction/degeneration and remove them.⁶⁰

As the prenatal brain develops, individual microglia establish microdomains and symmetrically extend processes. A cell autonomous contact inhibition helps establish and maintain the CNS network of microglial cells (Fig. 65.13A). Ramified microglia constitute 5% to 20% of the glial cells in the adult CNS.⁶¹ They are more abundant in gray than in white matter, and phylogenetically newer regions of the CNS (cerebral cortex, hippocampus) have more microglia than do older regions (cerebellum, brainstem). Regional variations in the number and shape of microglia as well as in their molecular signatures suggest that microglial distribution and morphology are regulated by local environments and that microglia play a role in tissue homeostasis. Although many aspects of this homeostasis remain to be elucidated, microglia respond quickly and dramatically to all forms of brain pathology.

Intravital imaging of microglia reveals that microglial processes are remarkably motile under normal physiological conditions.⁶² The commonly used term *resting microglia* therefore does not appropriately describe microglia in the normal brain. Microglial function in the normal brain is better described as one of surveillance. Constant extension and retraction allow microglial processes to gauge the health of cells and processes within their microdomains.^{63,64} Microglia can identify and remove dysfunctional tissue components. This phagocytic function has been documented in regions of the early postnatal brain where synapses are overproduced. Microglia actively prune superfluous synapses during postnatal synaptogenesis.⁶⁵ This microglial-mediated synaptic pruning depends upon low electrical activity of the synapse, the expression of the complement cascade component C1q by neurons, and the expression of complement receptor 3 by microglia.^{66,67} Microglia can also shape synaptic fields in the adult brain.⁶⁸ Microglia therefore constantly survey the brain and remove damaged or dysfunctional components.

There has been much interest in microglial behavior in the adult mammalian brain.⁶⁹ This is particularly relevant to chronic diseases of the CNS in which microglial activation can be extensive. “Reactive” microglia can be identified by two criteria: change in morphology (see Fig. 65.13) and upregulation of activation markers. Reactive microglia have larger cell bodies

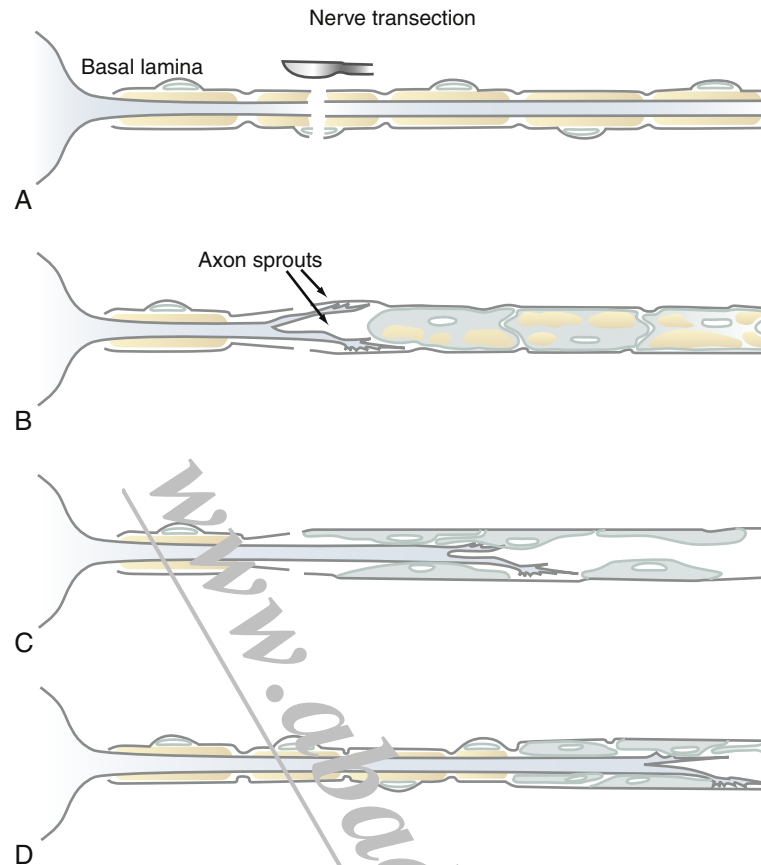


Figure 65.12. Axonal regeneration following nerve transection in the peripheral nervous system (PNS). Following transection of PNS axons (A), the distal axon and myelin degenerate (B). The proximal axon sprouts and crosses the basal lamina (orange) as a substrate for regeneration (C). Regenerated axons are remyelinated (D) by Schwann cells.

and shorter, thicker, and more asymmetrically oriented processes than do surveillance microglia. Reactive microglia are also motile, as they can surround or target structures such as dying cells, neurons, dendrites, blood vessels, and amyloid plaques. Reactive microglia express a variety of cell surface molecules that are not usually detectable in surveillance microglia, including major histocompatibility complex class II molecules and cluster of differentiation CD68 protein.⁷⁰ In response to destructive pathology caused by CNS trauma, resident microglia become “activated” and then phagocytic. Phagocytic macrophages can also originate from circulating monocytes and from neighboring microglia that proliferate and migrate to the site of injury.

Microglial activation in chronic CNS diseases can be extensive. Are activated microglia good or bad? The answer to this question is important for the future development of therapies that target the CNS innate immune system. Let us consider the good. The innate immune system was designed to protect the brain. It is therefore safe to assume that many activated microglial functions are protective. This is particularly the case in chronic brain diseases, in which the majority of microglia are activated. If these activated microglia were destructive, these conditions would not be chronic. More convincing are conditions in which microglial activation occurs in the absence of frank pathology. Following transection of the PNS portion of the rodent facial nerve, resident microglia in the facial nerve nucleus become activated and displace afferent synaptic terminals from facial motoneurons. This synaptic stripping is associated with facial nerve regeneration and considered neuroprotective.⁷¹ In a preconditioning paradigm in rodent brain, microglial cells migrate to neuronal cell bodies (Fig. 65.13B) and displace inhibitory synapses. This stripping of

inhibitory synapses helps protect the brain from traumatic injury by activating signaling pathways that increase neuronal expression of antiapoptotic and neurotrophic molecules.⁶⁸ An example of the close association between microglia and neurons in human brain is the rod-shaped microglia (Fig. 65.13C) that surround neuronal cell bodies and dendrites in a variety of CNS diseases including neurosyphilis, amyotrophic lateral sclerosis, Alzheimer disease, and multiple sclerosis (MS). The majority of neurons covered by rod cells appear relatively healthy, suggesting that the microglia are protective or possibly providing trophic support. It remains to be established whether rod cells in human brain strip synapses from neurons and their dendrites.

Significant attention has been paid to the possible role of microglia in exacerbating CNS diseases.⁷² Conclusive evidence for a toxic or CNS cell-killing microglial phenotype remains to be established and distinguished from a phagocytic phenotype of removing dead or damaged cells. While the innate immune system functions to protect the brain, it is possible that microglia lose their protective functions and contribute to disease progression. One obvious factor in neurodegenerative diseases is the age of the patients. Microglia can senesce and lose their phagocytic and protective properties. Microglia can release cytotoxic substances, including nitric oxide, tumor necrosis factor, proteases, cytokines, and glutamate.⁷³ One of the more intriguing responses of microglia occurs in the brains of individuals with Alzheimer disease. Alzheimer disease is often referred to as an inflammatory disease of the CNS, but the inflammation in the brain does not consist of the classic perivascular accumulation and diffuse parenchymal distribution of blood-borne monocytes and lymphocytes in the cerebral cortex; rather, it consists of a primary

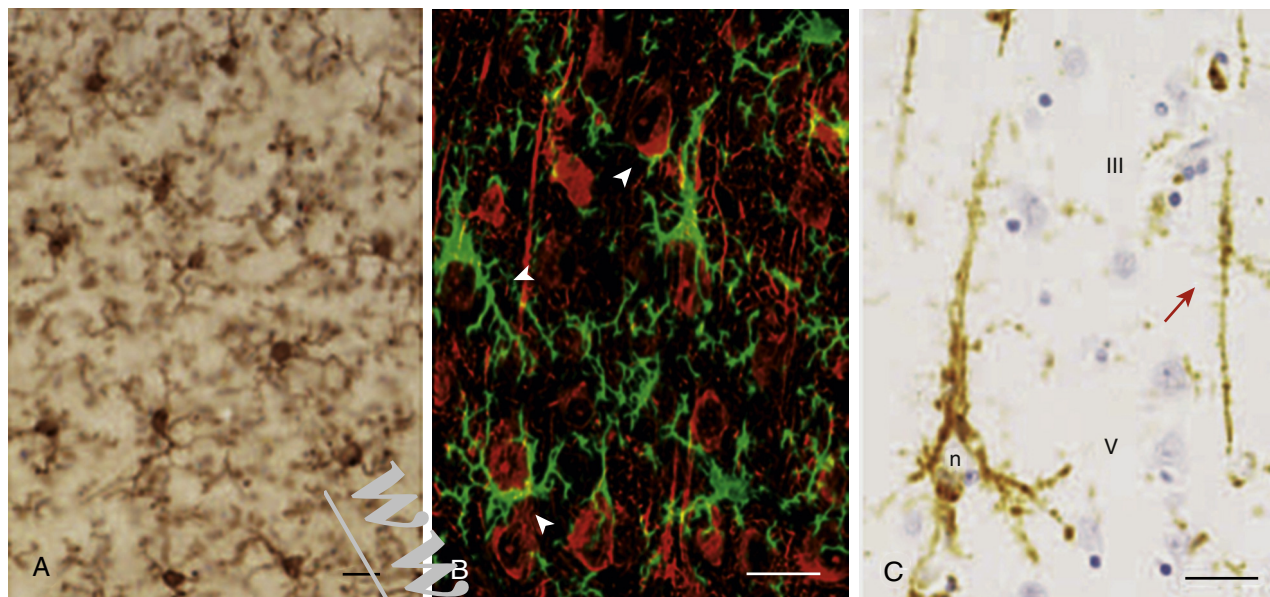


Figure 65.13. Microglia in the mammalian brain. (A) Microglia in normal mouse brain extend thin and symmetrically distributed processes. (B) Activated microglia (green) in the rodent brain (arrowheads) surround neurons (red) in the cerebral cortex in a case of subacute sclerosing panencephalitis (SSPE) as part of a neuroprotective response. (C) Activated microglia (brown) can assume a “rod-like” appearance in the human brain and surround neuronal cell bodies (n) and proximal dendrites. The arrow points to a single rod cell. III and V indicate cortical layers. Scale bars: (A) 10 μm ; (B) 20 μm ; (C) 60 μm . (B, From Chen Z, Jalabi W, Li W, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain. *Nat Commun.* 2014;5:4486. C, From Graeber MS. Changing face of microglia. *Science.* 2010;330:783.)

microglial activation. Most prominent among these responses is the migration to and infiltration of amyloid plaques by microglia (Fig. 65.14).^{28,29} It is likely that these microglia try, but fail, to phagocytize core amyloid. As part of this activated microglial response to amyloid, neurites may become injured or dystrophic as a bystander effect of microglial cytotoxic substances. Axons may be transected by a similar mechanism in the lesions of MS.⁵⁵

Although microglial activation and reactivity were designed to be protective, it is possible (as proposed in Alzheimer disease) that attempts to remove amyloid may destroy axons and dendrites and release cytokines that drive susceptible neurons toward cell death. This and other examples have led to the concepts of good inflammation and bad inflammation. One should not, however, underestimate the benefit of microglial-mediated removal of cellular debris in brains of individuals with neurodegenerative diseases. In many conditions, brain volume can be reduced by 30%, without any evidence of debris accumulation. Microglia do a remarkable job of removing debris and dysfunctional neurons that could have a dramatic negative effect on brain function. It is therefore important to distinguish protective, phagocytic, and destructive phenotypes in the human brain as inhibition of microglial protection and phagocytosis may exacerbate disease progression. This is an important question for the development of therapies for chronic neurodegenerative diseases of the CNS. Therefore a goal should be to develop therapies that reduce destructive behaviors or increase protective behaviors of activated microglia.

Turnover of Microglia

Once microglia colonize the brain, the BBB forms and isolates microglia from the periphery. Brain infiltration of blood-derived monocytes rarely occurs in the normal brain. Once the BBB is formed, microglia become an autonomous cell population and retain the ability to divide and self-renew. Under pathologic conditions, both proliferation of microglia and infiltration of blood-borne monocytes can occur. It is debated whether peripheral

monocytes can transform into resident microglia. Molecular markers that distinguish yolk sac–derived microglia and peripheral monocytes are not available. Microglia, however, are dependent on colony-stimulating factor 1 receptor (CSF-1R) for survival. When inhibitors of CSF-1R are administered to adult rodents, 99% of all microglia are eliminated.⁷⁴ Once the inhibitor is removed, the CNS is fully repopulated with microglia within days. These microglia originate from a CNS stem cell and/or microglia that survive the CSF-1R inhibition. Peripheral monocytes do not appear to contribute to this microglial cell repopulation of the adult CNS. Recent data therefore support the concept that microglia represent a yolk sac–derived autonomous cell population within the CNS.

Oligodendrocyte Progenitor Cells

Although little is known about OPC function in the adult brain, a significant literature describes *in vitro* properties of OPCs isolated from neonatal rodent CNS. Because these cells give rise to oligodendrocytes in serum-free media and to type 2 astrocytes in serum-containing media, they were initially referred to as O2A cells.⁷⁵ They can be identified *in vitro* by the expression of A2B5 gangliosides. Characterization of O2A cells *in vivo* was initially hampered by the ubiquitous expression of A2B5. This changed when O2A cells were demonstrated to express two polypeptide antigens: platelet-derived growth factor receptor α (PDGFR- α) and the sulfated proteoglycan neural/glial antigen 2 (NG2). With the use of these markers, substantial evidence now exists that OPCs can give rise to oligodendrocytes in developing and adult brain.⁴¹ The potential for OPCs to give rise to astrocytes *in vivo*, however, appears to be limited.

Oligodendrocyte Progenitor Cells in Development

Because few studies have characterized OPCs during human brain development, the following description is based primarily on studies of rodent brain development. All available evidence

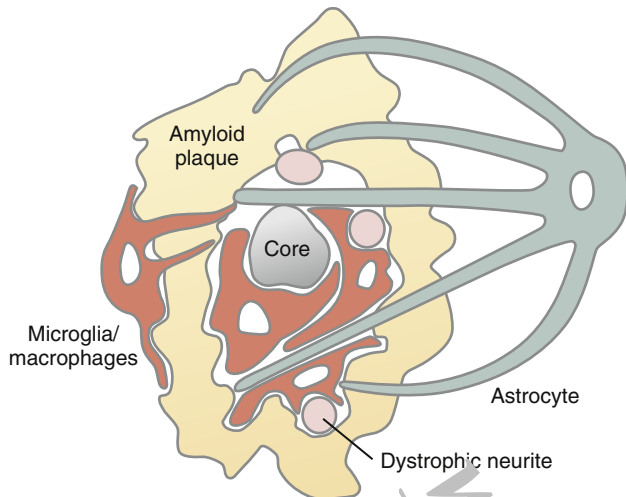


Figure 65.14. Glial reaction to amyloid plaque. Microglial cells (orange) become activated and enter the amyloid plaque (yellow). Astrocytes (green) also send processes into the amyloid plaque. Dystrophic or damaged axons, dendrites, or both (pink) are commonly found around the core of amyloid plaques.

suggests that gliogenesis is remarkably similar in human and rodent brains. OPCs originate from discrete regions of the subventricular zone during early brain development. In the spinal cord, OPCs originate from the ventral subventricular zone, dorsal to the floor plate, and their development depends on sonic hedgehog⁷⁶ and neuregulin⁷⁷ expression. In the cerebrum, OPCs originate from the subventricular zone as PDGFR- α -positive cells.⁴¹ These cells migrate throughout the brain and, shortly after leaving the subventricular zone, express detectable levels of NG2. These bipolar cells multiply as they migrate and eventually establish a network of stellate cells throughout the entire brain. The timing of oligodendrocyte production varies in different brain regions. Signals that regulate oligodendrocyte production are poorly understood, but PDGF-driven proliferation of OPCs appears to be one requirement.⁷⁸ The stellate OPCs are highly mitotic (~30% can be labeled by short bromodeoxyuridine labeling) during early brain development.⁷⁹ OPCs differentiate into oligodendrocytes (Fig. 65.15). Following this differentiation, a neighboring NG2 cell divides and one daughter cell will replace the NG2 cell that differentiated into the oligodendrocyte. OPC division therefore follows oligodendrocyte production. The oligodendrocyte initially displays a premyelinating phenotype by extending multiple myelin protein–positive processes that do not immediately ensheath and myelinate axons⁸⁰ (see Fig. 65.15). These cells have a limited life span and either go on to myelinate axons or die by programmed cell death.

Oligodendrocyte Progenitor Cells in Adult Brain

OPCs do not disappear as the brain matures, and they continue to express PDGFR- α and NG2, but not markers specific for astrocytes, microglia, and oligodendrocytes.⁴¹ OPCs are abundant (see Fig. 65.15) and account for 10% to 15% of adult brain glial cells.^{81,82} OPCs are difficult to visualize in routinely processed autopsy tissues and so are underrecognized by neuropathologists. When isolated from adult brain, they can give rise to oligodendrocytes.⁸³ The stellate morphology and abundance of OPCs and the low turnover of oligodendrocytes in normal brain raise the possibility that they have functions in addition to oligodendrocyte production. In adult rodent brain, OPC processes appose nodes of Ranvier,⁸⁴ associate with synapses,⁸⁵ and terminate on blood vessels. While OPCs can also receive synaptic input from

neurons⁸⁶⁻⁹⁰ and depolarize, OPCs do not appear to be electrically connected to each other. Collectively, these observations support the possibility that OPCs help astrocytes maintain CNS homeostasis, including regulation of neuronal electrical activity. Similar to astrocytes and microglia, OPCs respond to CNS injury by becoming activated: a more elongated shape, fewer processes, and upregulation of NG2.⁴¹ If the lesion includes demyelination and loss of oligodendrocytes, NG2-positive cells can generate new oligodendrocytes.⁹¹

The coexistence of mature oligodendrocytes and OPCs in the adult brain suggest that the oligodendrocyte lineage is unlikely a static constituent of the CNS. Emerging evidence suggests that myelin formation is an activity-dependent process in the fully developed brain.⁹² The transcription of myelin genes, the synthesis of myelin proteins, and the thickening of the myelin sheath made by preexisting oligodendrocytes on the axons are controlled by neuronal activity.⁹³ In conditions in which brain activity is restricted, such as social isolation, the formation of new myelin is reportedly impaired.⁹⁴ This neural activity-driven myelination is reminiscent of activity-dependent synaptic plasticity. Largely based on rodent models, neuronal activity was shown not only to drive myelin synthesis by existing oligodendrocytes, but also to drive oligodendrogenesis through the differentiation of OPCs in the adult cerebral cortex.^{95,96} Such formation of new myelination is required for motor learning^{96,97} and the formation of fear and spatial memory.⁹⁷⁻⁹⁹ Myelin-regulatory factor appears to be the switch that turns on activity-driven myelin transcription. Although the precise cellular and molecular mechanisms governing this adaptive plasticity remain an open question, activity-dependent myelination is likely to be instrumental in learning and memory.

Oligodendrocyte Progenitor Cells and Glial Neoplasms

After many historical efforts to classify gliomas, the World Health Organization (WHO) formalized the first classification system for tumors of the CNS in 1979. Most gliomas diffusely infiltrate surrounding brain tissue and together represent a large diagnostic group, which is divided into three main categories according to WHO criteria: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Morphologic features including mitosis, nuclear atypia, microvascular proliferation, and necrosis are used to group these tumors into four grades, where grades I and II are low-grade gliomas and grades III and IV are high-grade or malignant gliomas. In this system, grade I (pilocytic astrocytoma) includes tumors with lesions that have a low proliferative potential and therefore are usually cured by surgical resection. Grade II tumors (diffuse astrocytoma, oligoastrocytoma, and oligodendroglioma) are infiltrative and tend to recur, with a survival period from 5 to 15 years. They have a low level of proliferative activity and usually progress to higher grades of malignancy. Grade III applies to tumors with lesions that have histologic evidence of malignancy. These tumors exhibit nuclear atypia and brisk mitotic activity and may be classified as anaplastic astrocytoma, mixed anaplastic oligoastrocytoma, or anaplastic oligodendroglioma. Grade IV gliomas, also known as *glioblastoma multiforme*, are the most aggressive subtype and are characterized by the presence of microvascular proliferation and pseudopalisading necrosis.¹⁰⁰

Many scientific investigations have used a wide variety of approaches in an attempt to identify the cell of origin for gliomas. Two main theories to explain glioma formation have arisen from this body of work: the dedifferentiation and neural stem cell theories. The *dedifferentiation theory* postulates that glioma occurs as consequence of genetic and epigenetic alterations in a differentiated cell in the CNS. These alterations provide a proliferative advantage and over time lead to the uncontrolled growth and spread of malignant tumor cells. According to this theory, mature astrocytes or oligodendrocytes can dedifferentiate

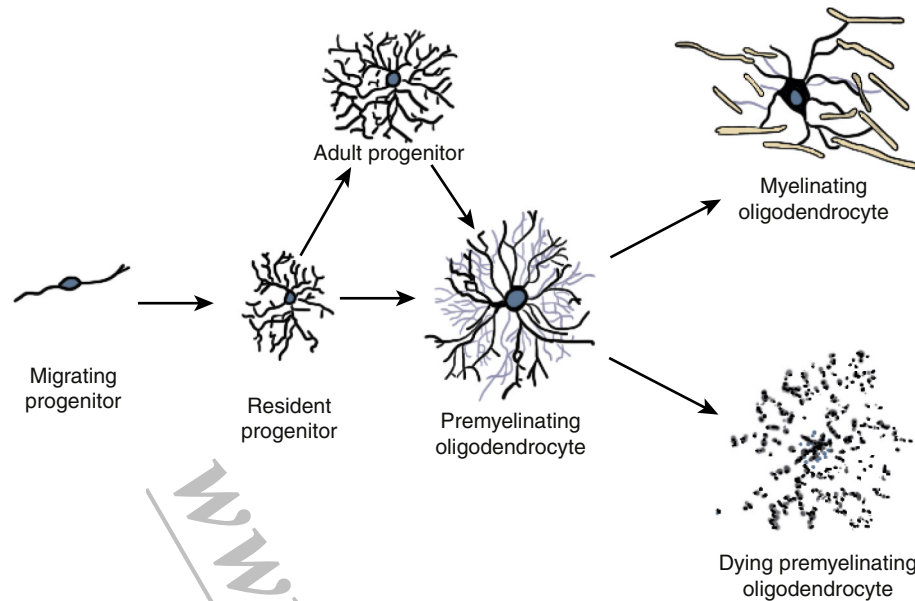


Figure 65.15. Oligodendrocyte progenitor cells originate from the subventricular zone, then migrate into and colonize the brain during early development. The early progenitor transforms into a stellate resident progenitor that produces premyelinating oligodendrocytes or remains as an adult progenitor. Premyelinating oligodendrocytes have a limited life span and either go on to myelinate axons or die by programmed cell death. Adult progenitors may have the potential to produce oligodendrocytes needed for remyelination.

as a result of genetic mutations into a less differentiated phenotype and become fully malignant. Several lines of evidence support the concept of the dedifferentiation of mature glia.¹⁰¹⁻¹⁰⁴

A competing theory proposes that neural stem cells (NSCs) or OPCs are the source of gliomas. Many initial studies identified NSCs as a cell of origin for gliomas.¹⁰⁵ However, these studies are controversial, as several other groups have used different genetically engineered mouse models and elegant lineage tracing to identify OPCs as the cell of origin for gliomas.¹⁰⁶ To address the debate surrounding NSCs versus OPCs as a cell of origin for gliomas, Liu and colleagues¹⁰⁷ used a genetic approach called mosaic analysis with double markers to demonstrate that even if mutations (e.g., *NF1* and *p53*) are originally induced in NSCs, they lie dormant and trigger malignant transformation only upon differentiation into OPCs. These results highlight the important distinction between where a mutation originally occurs (cell of mutation) and where the final transformation occurs (cell of origin). While the NSC could only be the cell of mutation, the OPC can be both the cell of mutation and the cell of origin.¹⁰⁷

Distribution of Microglia and Oligodendrocyte Progenitor Cells

Although the function of microglia and OPCs is not known to be intimately related, their distribution and morphology are compared here because of their striking similarity. Both cell types are ubiquitous in the normal adult CNS, they project multiple processes from relatively small cell bodies, and each cell occupies distinct domains with little overlap between processes of neighboring cells. The processes of neighboring microglial cells do not touch; the ends of OPC processes are often closely apposed, and some project to blood vessels. Microglia and OPCs can be distinguished molecularly by immunocytochemistry and, to the experienced observer, by morphology. Regional variation in the density and shape of each cell type (e.g., white versus gray matter) occurs, however, indicating that their distribution and shape

are regulated by local environments. Based on these morphologic characteristics, both cell types form a lattice-like network that covers most of the brain parenchyma. Therefore they are appropriately positioned to function as homeostatic regulators of normal brain function and as guards ready to respond to brain pathology or neural dysfunction. These functions are clearly established for microglia. With the exception of oligodendrocyte production, little is actually known about OPC functions in the adult brain.

Ependymal Cells

Ependymal cells line the ventricular spaces of the adult brain. They have a simple ciliated cuboidal morphology.⁴⁴ The cilia project into the ventricular space and spinal canal, oscillate approximately 200 times per minute, and are thought to assist the rostrocaudal flow of cerebrospinal fluid. Ependymal cells are connected by apicolateral gap and zona occludens junctions. The lack of tight junctions between ependymal cells permits free exchange between the extracellular space of the brain and cerebrospinal fluid. During embryonic and early postnatal stages of brain development, ependymal cells arise from the radial glia in the ventricles to form the simple ciliated epithelium.¹⁰⁸ Once mature, these ciliated ependymal cells in the adult brain are generally considered as terminally differentiated and postmitotic,¹⁰⁹ yet these postmitotic ependymal cells are susceptible to genetic changes associated with tumorigenesis.

TRANSPLANTATION THERAPIES

As described throughout this chapter, the nervous system consists of diverse cell populations that are essential for normal neurological function. The cells are also the target of inherited and acquired diseases of the nervous system, and therapies designed to replace diseased or destroyed cells are a major focus of translational neurosciences research. Two general cell replacement approaches—enhancement of endogenous repair and

transplantation of exogenous cells—are being pursued. We focus here on transplantation therapies as they will be neurosurgery-based therapies. Proof of principle for effective transplantation of three neural cell populations—Schwann cells, neurons, and oligodendrocytes—has been established in animal models of CNS disease. Transplantation of Schwann cells or peripheral nerve segments is routinely used to enhance human peripheral nerve regeneration and will not be discussed further (see Chapter 67).

Transplantation of neurons and oligodendrocytes presents formidable challenges, including the source and type of the donor cell and appropriate recipient. Also, of great importance is the target disease or cell. The general inability of neurons to extend axons long distances and connect to appropriate targets presents a serious obstacle for replacement of projection neurons in the adult brain. An alternative approach is to provide transplanted cells (mesenchymal stem cells), which provide trophic support that increases the function and survival of endogenous neurons or glia. Transplantation of cells designed to enhance neuronal or axonal survival in animal models of amyotrophic lateral sclerosis, stroke and spinal cord injury have been encouraging.

A more realistic strategy is the replacement of dopaminergic neurons in individuals with Parkinson disease. Parkinson disease is characterized by progressive loss of dopaminergic neurons in the substantia nigra and reduced dopamine in the striatum. In animal models of Parkinson disease, fetal dopaminergic neurons survive when grafted into the striatum and improve motor function. Since these neurons are placed at the site of innervation, they do not need to extend long processes. Open-label transplantation trials of fetal dopaminergic neurons into the striata of a small number of Parkinson disease patients showed efficacy.¹¹⁰⁻¹¹² However, two double-blind, placebo-controlled trials were disappointing as a whole, but appear to benefit a subpopulation of patients less than 60 years of age.^{113,114} There has been much discussion regarding the possible reasons for the discrepancies between the open-label and double-blind studies (for review, see Winkler and coworkers,¹¹⁵ Barker and associates,¹¹⁶ and Petit and colleagues¹¹⁷). Parkinson disease is an attractive disease candidate for neuronal cell grafting and transplantation because the nigrostriatal pathway is anatomically defined and relatively small and accessible. Emerging sources of dopaminergic neurons from pluripotent stem cells or reprogrammed somatic cells may reduce major logistical and ethical issues associated with the use of human embryo-derived cells.

The best example of endogenous cell replacement in the adult human brain is the generation of new oligodendrocytes in some but not all demyelinated lesions in individuals with MS.^{118,119} Since remyelination can occur in the adult human brain, transplantation therapies may be effective for the MS lesions that fail to repair. Much is known about the cellular aspects of oligodendrocyte production during myelination and remyelination. Transplanted OPCs can produce myelinating oligodendrocytes in the adult mammalian brain.¹²⁰ While MS would appear a logical target for cell replacement therapies, multiple obstacles need to be overcome prior to transplantation trials for MS patients. These include risk-benefit odds, source of donor cells, delivery of cells to multiple sites, age of recipient, lack of reliable surrogate markers for detecting effective treatment, and little proof of principle in relevant animal models. At present, individuals with inherited diseases of myelin appear more appropriate for human transplantation therapies. Their poor prognosis provides a positive risk-benefit assessment, and proof of principle in animal models has been clearly established, as transplantation of human OPCs into neonatal brains can rescue neurological phenotypes and extend the life spans of mice with inherited diseases of myelin.¹²¹ These OPCs colonized the developing brain and produced oligodendrocytes that successfully myelinated major white matter tracts. The neonatal brain appears to be a more receptive host for transplanted cells than adult brains. Initial OPC transplantation studies in patients with leukodystrophy

have been very encouraging.¹²² Cell replacement therapies will be a significant aspect of future research, and human clinical trials will follow. Some caution must be taken, however, as one adverse event could substantially delay this promising therapeutic approach for treating diseases of the human brain.

TOWARD THE MOLECULAR IDENTITY AT A SINGLE CELL LEVEL

The complexity of tissue architecture in the brain not surprisingly turns out to be a reflection of an enormous diversity of cellular morphology and specific antigen expression. While histologic and morphologic criteria have been the basis of cellular neuroscience, a more robust technology is now available that is capable of delineating the dynamic nature of neurons and neuroglia at the molecular level. The widespread use of next-generation sequencing during the past decade has provided a new, nearly unparalleled power to map the entire genome (DNA sequencing) and transcriptome at the level of a single cell (RNA sequencing). The latest developments of single-cell RNA sequencing (scRNA-seq) technology have only begun to make themselves felt in the area of brain cell biology,^{123,124} so it is not hard to predict that a sea change in the characterization of brain cell types will soon be upon us. There are several different scRNA-seq platforms. Each employs a different strategy—nanodroplet, picowell, or in situ hybridization—to link a unique bar code to individual cells. Such bar-coding procedures enable the segregation of RNA sequencing data to each cell.¹²⁵ By mapping hundreds to tens of thousands of individual cells one at a time, the big transcriptomic picture of the brain in health and disease, such as neocortical development or glioblastoma, can be redefined at the resolution of single cells.^{125,126}

An example of scRNA-seq data can be found in Fig. 65.16. Algorithms have been developed that allow an investigator to define “clusters” of cells in multidimensional space based on the similarities of their gene expression (Fig. 65.16A). Each cluster can be assigned to a specific cerebral cortical cell type based on the expression of cell type-specific markers. For example, based on the expression of the transcription factor gene *CUX2*, excitatory neurons can be seen to populate several clusters (Fig. 65.16A, lime-green dots; Fig. 65.16B, red dots). Mature oligodendrocytes can be identified as populating a single cluster based on their expression of the mature myelin protein gene *MOG* (Fig. 65.16A, dark green dots; Fig. 65.16C, red dots). The OPCs, defined by their expression of *NG2* (the *CSPG4* gene), are interspersed with other cells in a nearby, but distinct cluster (Fig. 65.16A, black dots; Fig. 65.16D, red dots). Note, however, that a small fraction of all marker genes are found scattered in the overall pattern. The meaning of this scatter is at present unknown.

While this view of the brain is divorced from anatomy, it provides an unprecedented view of molecular “space” as it segregates cells based on the expression level of different genes of interest in different cell lineages of the brain. As such cluster behavior is sensitive to experimental conditions, the pattern of cells in an MS brain will be different from that in a healthy brain, and where and how those differences reveal themselves can tell us a great deal about disease mechanisms. Needless to say, the initial computational analysis of these vast data sets requires advanced bioinformatics and data science expertise. Once the data are collected, however, they are systematically deposited in publicly accessible online platforms, such as the Allen Brain Map from which the images in Fig. 65.16 were acquired. These provide valuable insights to empower the work of scientists, neurosurgeons, and neuropathologists alike. It requires some adjustment to think in molecular, not anatomic, space and to do so at the single-cell level. Fortunately there are teaching resources that offer guidance and introduction as to how to explore this new wealth of data.¹²⁷

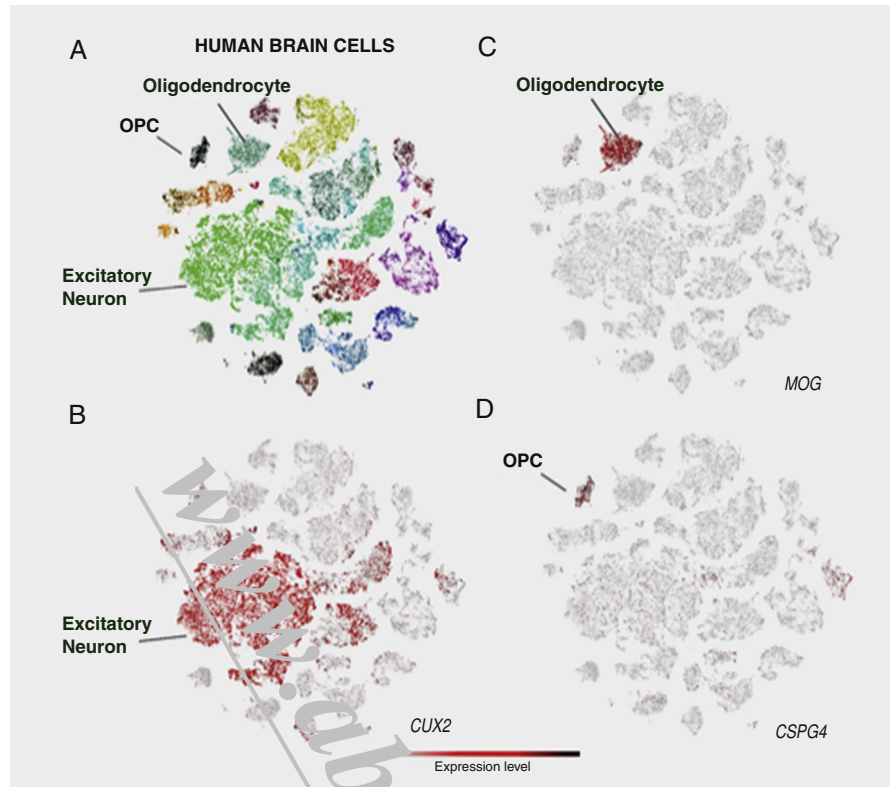


Figure 65.16. Single-cell RNA sequencing (scRNA-seq) expression on an Allen Brain Map atlas (<https://brain-map-portal-stage.us.aldryn.io/>). (A) Classic t-distributed stochastic neighbor embedding (t-SNE) map describing the distribution of different cell clusters of the human cerebral cortex scRNA-seq data set, where oligodendrocyte lineage, excitatory neurons, and other cell type are highlighted in different colors. (B–D) A query of a cortical neuron-specific gene, *CUX2* (B), a mature oligodendrocyte-specific gene, *MOG* (C), and an NG2-positive OPC-specific gene, *CSPG4* (D) suggests that these cell types are well segregated in defined clusters of the scRNA-seq. (Note: Expression level not to scale.)

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