Neurons and glia – an essential partnership.

By Tad Wanveer

What are glial cells and what do they do? The central nervous system (CNS) is comprised of two types of cells, neurons and glial cells. Eighty-five to ninety percent of CNS cells are glia. Neurons are unable to function without the support of glial cells, and likewise the glia require neurons to complete their tasks. Not surprisingly, neurons and glia work together to fulfill almost all CNS processes.

Four primary types of glia exist within the CNS: astrocytes, ependymal cells, oligodendrocytes, and microglia. Each of these glial cell types, along with their main functions, is described below.

Astrocytes create integrative domains.

Astrocytes have a central cell body with thousands of processes extending outward from that cell body. The tips of each process expand slightly, and these tip expansions are called *end-feet*. End-feet surround all of the CNS vasculature, synapses, neurons, and axons, and interconnect astrocytes by way of transmembrane channels, called *gap junctions*, which form an astrocyte matrix throughout the entire CNS referred to as the *glial syncytium*.

Astrocytes form individual non-overlapping domains throughout the entire CNS. Each astrocyte creates a structural/functional hub of integration with the structures it encases and interconnects. For instance, an astrocyte encases thousands of synapses within its domain. One primary astrocyte response to synaptic activity is to generate intracellular calcium fluctuations. These fluctuations, known as *calcium waves*, stimulate the release of substances that modify synaptic activity, called *gliotransmitters*. These gliotransmitters help integrate synaptic activity within the domain as a whole and within adjacent domains.

Astrocytes are part of the blood-brain barrier.

Astrocyte end-feet encase the vasculature throughout the entire CNS, and are referred to as the *perivascular glial limiting membrane (PVGLM)*. PVGLM end-feet form part of the blood-brain barrier. The PVGLM is a membrane barrier between the vasculature and the interstitium. Substances passing through capillary walls must pass through the PVGLM before gaining entry into the CNS interstitium. The PVGLM is a barrier that both protects the interstitium from harmful substances and helps to regulate the inflow of essential elements. A disruption of the PVGLM can allow toxins or pathogens entry into the interstitium, or may block the inflow of vital substances.

CNS blood flow is regulated by the neurovascular unit.

Blood substances passing into the interstitium are regulated to meet cellular demand, which is primarily neural activity. This regulation occurs moment-to-moment on a micro-level throughout the entire CNS. As blood flow is regulated through the interconnection of the blood-brain barrier with synaptic activity, astrocytes link together synapses with the blood-brain barrier by encasing both synapses and blood vessels (the blood-brain barrier) with end-feet. As a result, the interconnection of synapses with the blood-brain barrier by way of an astrocyte is referred to as the *neurovascular unit*.

End-feet encasing synapses constantly monitor synaptic activity. Synaptic activity is transmitted through the neurovascular unit to the blood-brain barrier. The blood-barrier responds by increasing or decreasing the flow of blood substances into the interstitium to match the level of synaptic work. Disturbances of the neurovascular unit can cause less than optimal blood flow, which may trigger neural distress and dysfunction.

Astrocytes help neurons meet their energy needs.

Glucose, which is used by both neurons and glia for energy production, is an essential substance that passes from the blood into the interstitium. Glucose intake

by a neuron and its surrounding glia are equal when the neuron is not signaling: however, when a neuron signals, it no longer takes in glucose even though its energy consumption is very high. With the aid of astrocytes, neurons are able to meet their energy needs.

Astrocytes convert glucose into lactate that is either used by the astrocyte or stored within the astrocyte. When a neuron sends an action potential, astrocytes secrete some of their stored lactate, which is then taken up by the working neuron. The neuron rapidly converts lactate into adenosine triphosphate (ATP). Without astrocyte lactate, neurons would quickly run out of energy, causing injurious interruptions in signaling.

Astrocytes support synaptic function.

Astrocyte end-feet encasing synapses help to maintain an optimal synaptic environment. One essential way this is done is by clearing damaging or inhibiting neurotransmitters from the synaptic cleft. Two examples are: Glutamate, a primary excitatory neurotransmitter that can become neurotoxic if it accumulates within synapses, and gamma-aminobutyric acid (GABA), a primary inhibitory neurotransmitter that can shut down neurological processing if it accumulates within synapses. End-feet remove the excess glutamate and GABA, which are then taken up into an astrocyte. The astrocyte converts the glutamate or GABA into glutamine. Glutamine is released by astrocytes to be taken up into neurons that then use glutamine as a substrate to synthesize glutamate or GABA. This process is known as the *glutamate-glutamine shuttle*.

Astrocytes are involved in neural plasticity.

Astrocytes actively participate in the ongoing process of neural plasticity by modifying synapses. Astrocytes secrete substances that help to stimulate and support the creation of new synapses; they also secrete substances that help to dissolve (prune) established synapses.

Astrocytes also use their end-feet to structurally modify synapses by extending an end-foot into a synaptic cleft, which seals the synaptic cleft and shuts down transmission; or removes an end-foot from the synaptic cleft, which reestablishes the synapse and allows transmission to occur.

An astrocyte transports substances within its body, a network, or a system.
Selective substances pass into or out of an astrocyte's cytoplasm through channels and transporters within the cell membrane. These substances can be transported within the astrocyte's local domain to areas of low concentration, or flow among interconnected astrocytes (the glial syncytium) to areas of low concentration, or flow into perivascular channels to exit the CNS. This kind of transport of substances within astrocytes is called *spatial buffering.*

Potassium regulation by astrocytes is an example of spatial buffering. Potassium is precisely regulated, since a buildup of excess potassium can severely disrupt neurological signaling. One way this is accomplished is through astrocyte uptake. End-feet encase nodes of Ranvier (small gaps between myelin segments), and the excess potassium enters the end-feet. Once potassium enters the astrocyte it may flow to a region of the local domain that has a low concentration of potassium, flow within the glial syncytium to a distant region of low potassium concentration, or flow into the perivascular space to be reabsorbed into either the venous system or lymphatic system.

Spatial buffering is one of the primary means of maintaining optimal biochemical balance throughout the CNS.

Astrocytes signal to one another.
Neurons talking to neurons, referred to as *wired transmission*, is not the only way information is transmitted or stored in the CNS. Astrocytes have many membrane channels and receptors that enable them to respond to both neural activity and glial activity. Through the production of calcium flows, astrocytes are able to modify

their internal processes or communicate with other cells in their domain. Astrocyte calcium flows are referred to as *intracellular volume transmission*. When these flows occur among interconnected astrocytes it is called *long-range interglial calcium waves*, and these waves can influence broad areas of the CNS.

Astrocytes also secrete communicating substances into the extracellular space; this activity is called *extracellular volume transmission*. These communicating substances are called *gliotransmitters*, and they can modify both neural transmission and glial processes. Sometimes gliotransmitters travel great distances to produce effects, and may produce effects lasting much longer than neurotransmitters—sometimes lasting hours or days.

Astrocytes regulate cerebrospinal fluid flow.

Astrocyte end-feet regulate the flow of cerebrospinal fluid into and out of the CNS interstitium. Cerebrospinal fluid (CSF) not only supplies the CNS with essential water, nutrients, and trophic substances, but it also helps to cleanse the CNS of waste and toxins. The CSF enters and exits the interstitium through channels.

Astrocyte end-feet forming the PVGLM have channels within their cell membrane, called *aquaporins*, through which CSF passes into the interstitium (PVGLM channels and end-feet aquaporins regulating CSF flow are referred as the *glymphatic system*). Once CSF enters the interstitium, it becomes part of the interstitial fluid. The interstitial fluid carries CSF substances, as well as other vital elements, throughout the parenchyma. The constant movement and optimal composition of interstitial fluid is essential for the health and function of the CNS. Also essential to the wellbeing of the CNS, is the ongoing cleansing of the interstitium. Interstitial fluid carries waste and toxins out of the CNS by exiting the CNS through aquaporins. After passing thorough aquaporins, the interstitial fluid enters the perivascular space to be is reabsorbed by either the venous system or lymphatic system.

If the quality or quantity of CSF entering into the interstitium is inadequate, neurological distress may occur due to a lack of water, nutrients, vitalizing elements, or poor movement of substances. The inefficient clearance of waste, pathogens, or toxins can cause pathology because harmful cell stress can damage both neurons and glia; waste can accumulate, which congests the CNS so that substances cannot flow efficiently; or a buildup of waste can cause excessive and damaging pressure upon cells.

Ependymal cells produce CSF.

CSF is produced in the ventricular system. Ependymal cells line the ventricular cavities and form part of the choroid plexuses. The choroid plexuses are the primary sites of CSF production, and are referred to as the *blood-CSF barrier*. A choroid plexus is found within each ventricle. Each choroid plexus consists of ependymal cells surrounding fenestrated capillaries. Blood elements flow through the capillary walls and enter surrounding ependymal cells, which then filter specific elements from the blood entering the ventricular cavity. Optimal CSF composition is dependent upon ependymal cell structure and function.

CSF produced within the ventricles flows in a caudal direction to enter the subarachnoid space. Ependymal cells have cilia extending from their cell bodies that face into the ventricular cavities. Ependymal cilia create wavelike pulsations that help to move CSF within the ventricles. The pulsations also help cleanse the inner surface of the ventricular cavities. Lack of ventricular cleansing can create CSF toxicity; and lack of flow can cause a sluggish movement of CSF, which may alter the typical rate of CSF production.

Oligodendrocytes are CNS myelinating cells.

Fast and organized neurological signals are dependent upon the amount and organization of the lipid insulation encasing axons (myelin). Myelinating cells of the CNS are oligodendrocytes. Each oligodendrocyte extends processes to myelinate

individual sections of approximately fifty axons. Disruption of myelin can radically alter neural signals, and can eventually lead to severe disabilities.

Microglia are specialized CNS immune cells.

The CNS has specialized immune/phagocytic cells within its interstitium, called microglia. Microglia establish individual domains throughout the CNS, and each microglial cell constantly scans its domain for harmful substances such as toxins, pathogens, and waste material. If harmful substances are found, microglia engulf and degrade the substances.

Microglia respond to meet the level of challenge created by a harmful substance. There are times when it is necessary for microglia to replicate and swarm into an area to neutralize and cleanse the area of a harmful substances or debris. Once the area is cleared, the excess microglia degrade. Microglia also secrete healing substances that are absorbed by both neurons and glia.

Neurons and glia are a functional partnership.

CNS neurons cannot function without the support of glial cells, which perform essential functions, such as maintaining an optimal metabolic environment; protecting and cleansing the parenchyma of pathogens, toxins, and debris; secreting healing substances for both neurons and glia; participating in neural plasticity; forming protective and regulatory barriers; producing CSF and helping to regulate CNS flow; contributing to blood flow regulation; and participating in the transmission and storage of information. Neurons and glia work together to fulfill almost all CNS processes, and as such, it is not surprising that glia appear to be involved in all CNS pathology. Neurons rely on glia for their ability to survive and function. Therapeutic applications of this relationship are just being realized as science unveils more and more about the reciprocal, dynamic, and essential neural–glial partnership.