NBL 355-655 Module 2 Review Q&A

1. *What are the functions and localization each of the glial cells? In the CNS: microglia, radial glia, astrocytes, oligodendrocytes, ependymal cells, and in the PNS: Schwann cells and satellite cells. PNS: Schwann cells and satellite cells*

A. Microglia: Microglia are the resident immune cells in the CNS. Because of the blood-brain-barrier, most of the body’s immune cells are unable to enter into the CNS to fight infection or clean up damage. This leaves microglia with the responsibility of finding pathogens including bacteria, viruses, parasites, and fungi and eliminating them. Microglia can also help remove dying neurons. Microglia are derived from the yolk sak (while most other immune cells are derived from mesoderm) and act as phagocytic cells (that engulf and break down pathogenic cells and dying neurons). They also function as antigen presenting cells that help to activate infiltrating T cells. Microglia can also help remove damaged neurons and other damaged glial cells. They have also been implicated in synaptic pruning and neuronal plasticity. (They are proposed to engulf and remove the parts of the synapses that are not needed and destined for removal.)

B. Radial glial cells (RGCs): RGCs are present during development and function as an important type of neural progenitor cell. RGCs initially extend a long process from the ventricular zone out to the outer pial surface, and express astrocyte markers. Other developing neurons use the RGC process as a guide as they are migrating to their final destination in a specific layer of the cerebral cortex. Later in development of the cerebral cortex, RGCs differentiate into neurons or glia.

C. Astrocytes: There are two types of astrocytes: protoplasmic (type I found in gray matter) and fibrous (type 2 found in white matter). Astrocytes have a variety of functions. Capillaries are found in both gray and white matter. Both type 1 and 2 astrocytes extend end feet (called astrocytic end feet) that surround the capillaries and transport nutrients into the astrocytes and release them into the extracellular fluid (ECF). In this role, astrocytes transport ions, amino acids, sugars, water-soluble vitamins, and other nutrients into neural tissue (brain parenchyma), and thus provide neurons, other astrocytes, axons, oligodendrocytes, and microglia with energy substrates and nutrients. The astrocytic end feet also release factors, which are sensed by and affect the pericytes so they regulate the dilation of the capillary and blood flow. Astrocytes also surround synapses, forming the tripartite synapse. Around the synapse, astrocytes can regulate extracellular glutamate and K+ levels and release gliotransmitters such as ATP. They can also promote neuronal survival through release of neurotrophic factors. In response to damage, astrocytes form reactive astrocytes (AKA reactive glia) and glial scars that stimulate immune-like responses and impede/prevent axonal regeneration in the CNS.

D. Ependymal cells: Ependymal cells form part of the choroid plexus, a structure located within the brain ventricles, and they also line the brain ventricles and spinal cord central canal. Both types contribute to the production of cerebrospinal fluid (CSF). A specialized type of ependymal cell forms the choroid ependymal cells in the choroid plexus (together with choroid capillaries), which are found in all the ventricles and they synthesize the majority of CSF. Choroid ependymal cells are also called choroid epithelial cells since they form a sheet of cells around the choroid capillaries. The choroid plexus and lining ependymal cells also act as filtration systems to remove metabolic waste, foreign substances, and excess neurotransmitters from the CSF back into the capillary blood. The choroid ependymal cells form an epithelial sheet of cells with tight junctions between the cells, and form the blood-CSF barrier (see below).

E. Pericytes: (We will also cover these again in a later module on the blood-brain barrier) Pericytes are a type of glial cell that line the outside of CNS capillaries. CNS capillaries are formed by vascular endothelial cells (which are not a type of glial cell) that form tight junctions and prevent the entry of hydrophilic molecules and cells into the brain parenchyma. The brain parenchyma refers to the functional brain tissue that includes neurons and their dendrites, axons, and synapses, and glial cells: oligodendrocytes, astrocytes and microglia. Pericytes help control the tight junctions between the vascular endothelial cells (by secreting factors) and therefore help keep the blood-brain-barrier intact. Astrocytic end feet are also located next to the vascular endothelial cells and adjacent to the pericytes. Pericytes are also contractile cells (similar to vascular smooth muscle cells that surround the arteries and veins) and they participate in the control the diameter of the blood capillaries causing vasodilation, and therefore control the rate of blood flow.

F. Oligodendrocytes: A main function of oligodendrocytes is to provide the myelin membranes that wrap around and insulate CNS axons. A single oligodendrocyte can myelinate multiple axon segments in the CNS (up to about 50 axons). Having a myelin sheath around the axon enables action potentials to travel faster and more efficiently along axons, which is especially important for longer axons. The myelin membrane also protects axons from shearing. Oligodendrocytes may also help nourish axons in the CNS. Following damage oligodendrocytes also produce molecules that inhibit axonal regeneration in the CNS. (Together, astrocytes and oligodendrocytes block axonal regeneration in the CNS.)

G. Schwann cells: Schwann cells are well known for their function as the myelinating cells in the PNS. They are located within the nerve near the axons they myelinate. Schwann cells can also support the few non-myelinated axons located in the nerve. Myelinating Schwann cells wrap their myelin membranes around axons of motor and sensory neurons; each Schwann cell is responsible for myelinating one segment of one axon. Non-myelinating Schwann cells help maintain unmyelinated axons in the nerve. Schwann cells promote regeneration of damaged axons, which allows axons to regrow in nerves so they can functionally reinnervate their targets (including muscles, skin, joints, tendons and glands.)

H. Satellite Cells: Satellite cells are found in the PNS and they surround neuronal cell bodies (of sensory and autonomic neurons), which are located in the ganglia. They supply nutrients and structural support to these neurons. (Satellite cells have some analogous functions to astrocytes in the CNS.)

1. *Which stages of nervous system development occur predominantly prenatally, which occur predominantly postnatally, and which occur both prenatally and postnatally? What general mechanisms control prenatal and postnatal development?*

Prenatal development: formation of the gross structures of the nervous system by the processes of gastrulation, neurulation, segmentation/regionalization, and gyrification. Generation of the great majority of neuronal populations through neurogenesis. Prenatal development is governed by intrinsic hard-wired genetic programs and genetic factors.

Both prenatal and postnatal development: generation of glial cells by gliogenesis, axonal and dendritic outgrowth, dendritic arborization, synaptogenesis, naturally occurring neuronal death.

Postnatal development: the great majority of synaptic refinement and myelination. Postnatal development is controlled by neuronal activity that depends on interaction with the environment and experience.

1. *What is the epiblast and what does it give rise to? Briefly describe the process of gastrulation and what it produces? Which germ layer gives rise to the nervous system?*

The epiblast is a layer of cells that develops from the inner cell mass. The epiblast gives rise to the great majority of tissues in the embryo and adult animal. (Note that microglia are the only type of neural cell that develop from non-epiblast tissue; they develop from the yolk sac.) During gastrulation, the epiblast cells proliferate and migrate along the surface toward the midline, and then down through the primitive groove. Epiblast cells that migrate first become the endoderm; cells that migrate next will lie above the endoderm and form the mesoderm; cells that don’t migrate will stay on top (on the dorsal side of the embryo) and form the ectoderm. The outermost layer, the ectoderm, gives rise to all the cells of the nervous system (both CNS and PNS). Hence gastrulation establishes the three primary germ layers from the epiblast.

1. *What is neural induction, and what structure provides the induction morphogens? Morphogens are proposed to work in a \_\_\_ to induce cells toward a specific phenotype.*

Neural induction involves the instruction of the central region of the ectoderm to form what is called neuroectoderm, and eventually the neural plate, margins and placodes. The notochord and paraxial mesoderm provide diffusible factors called morphogens that diffuse away and bind to cell receptors on the overlying ectoderm and induce those ectoderm cells to become neuroectoderm. The neuroectoderm forms the neural plate, the adjacent margins of the neural plate, and placodes, that will eventually form all the cells of the nervous system. Morphogens are proposed to work in a gradient to induce cells toward a specific phenotype.

1. *Describe the process of neurulation. What main structures does neurulation initially produce? What types of cells does each of these structures give rise to?*

Neurulation involves the bending and adherence of cells in the neural plate, that fold to form the neural tube, and formation of the cells that overlie the neural tube called the neural crest cells that develop from the margins of the neural plate. The great majority of CNS cells (neurons and glia) are derived from the neural tube. The great majority of PNS cells (neurons and glia) are derived from neural crest cells. The placodes are small regions next to the margins of the neural plate that contribute a few populations of sensory neurons and glia and some other structures in the embryo.

1. *What are the five macroscopic vesicles produced during segmentation/ regionalization. What brain structures does each vesicle give rise to in the brain?*

Telencephalon: cerebral cortex, basal nuclei/ganglia and amygdala; Diencephalon: thalamus, hypothalamus and optic cup (retina and optic nerve); Mesencephalon: midbrain; Metencephalon: pons and cerebellum; and Myelencephalon: medulla

1. *What do neurogenesis and gliogenesis produce? What three processes/activities do neurogenesis and gliogenesis involve? What are neural stem cells and neural progenitor cells? What does neural migration accomplish? What cells guide radially migrating neural cells, and what type of cells do they differentiate into? In the cerebral cortex, which types of neurons are involved in radial migration and which are involved in tangential migration?*

Neurogenesis and gliogenesis are the processes whereby the neural tube cells proliferate, differentiate and migrate to form the neurons and glia, respectively, of the nervous system. In the neural tube, neural stem cells (NSCs) divide and some differentiate into neural progenitor cells (NPCs) in the ventricular zone and subventricular zone. NPC divide and differentiate into neurons and glia of CNS. After cells divide, they migrate away from the ventricular zone and form the various populations and layers of the CNS. Radial glial cells (RGCs) are long cells that guide the migrating NPCs and differentiating neurons to their correct layer of the cerebral cortex during their migration. RGCs express glial cell markers early on (which is how they got their name) but most differentiate into neurons. In the cerebral cortex, the majority of glutamatergic neurons use radial migrations while most GABAergic neurons use tangential migration.

1. *What types of factors/cues guide axons and dendrites during development?*

Axons and dendrites grow toward their targets by guidance from positive and negative guidance cues/molecules in the environment. Guidance cues for axon and dendrite outgrowth include both attractive and repellent cues, and both long range secreted-diffusible and short range attached (to the cell or matrix) cues.

1. *Some neurons undergo naturally occurring cell death during development. What is the proposed mechanism and purpose of neuronal apoptosis during development.*

More neurons are generated during development than are present (and needed) in the mature nervous system. One hypothesis is that neurons need to form the proper connections with their target cells, or circuits, in order to survive. The target cells may provide neurotrophic factors (such as NGF or BDNF) that support the survival of neurons. Neurons that don’t form connections with their targets undergo apoptosis. By initially overproducing neurons, this ensures the correct connectivity and formation of functional circuits in the nervous system.

1. *What are synaptogenesis and synaptic refinement, and when do they occur? What does synaptic refinement depend on?*

Synaptogenesis is the formation of synapses, which are formed by a presynaptic axon and its postsynaptic target. Synaptogenesis begins in mid-late prenatal development, and continues through between two to six years of postnatal development (depending on the brain region). The presynaptic region always forms from the axon of a neuron, but the target can be another neuron, a muscle cell or a gland. Between neurons, a synapse can occur between a presynaptic axon and a postsynaptic dendrite, cell body or axon.

Synaptic refinement (SR) (also called synaptic pruning or synaptic elimination) is a process that starts after birth, during which some synapses, which were formed previously by synaptogenesis, are removed. Microglia have been implicated in the removal of synapses. SR depends on experience and neuronal activity. The idea is that synapses that form but don’t receive incoming activity are then removed, whereas those that are active will be kept/retained and possibly even strengthened. SR occurs at different times in different circuits during postnatal development.

1. *Speculate on why myelination occurs postnatally.*

Oligodendrocytes are the myelinating cells in the CNS, and Schwann cells are the myelinating cells in the PNS. Most myelination occurs in early postnatal development. Most axons don’t develop fully until after birth. It is most probable that axons must be present, having contacted their targets before they can be myelinated.

1. *What does gyrification produce? Speculate on the purpose of gyrification.*

Gyrification produces the gyri and sulci in the brain. During evolution, there was an expansion of the number of cortical neurons and hence the area of the cerebral cortex. This allowed for an increase in cerebral cortical areas, adding new functional areas to the brain, within the same cranial volume determined by the skull.

1. *What are the majority of PNS neurons and glia derived from? What types of neurons are found in the PNS? What are placodes and what do they give rise to?*

The vast majority of PNS neurons and glia are derived from neural crest cells during development. Placodes are small regions found just outside the margins of the neural plate, which don’t become neural tube or neural crest, but form some sensory neurons (such as the olfactory neurons and otic-auditory sensory cells.) (Several other non-neural tissues also develop from placodes.) The neurons in the PNS (which develop from the neural crest) include somatic sensory neurons, visceral sensory neurons, and post-ganglionic neurons of the autonomic nervous system. (Note that somatic lower motor neurons, and preganglionic autonomic neurons develop from the neural tube, and their cell bodies lie in the CNS, but their axons extend out of the CNS and become the axonal components of spinal and cranial nerves, so their axons are part of the PNS.)

1. *What are the two types of neural tube defects and what is the underlying developmental process that is disrupted. What are microcephaly and heterotopias and what developmental process is disrupted in each. In what disorders have errors in synaptogenesis and synaptic refinement been implicated in?*

From Wikipedia: neural tube defects (NTDs) are a group of birth defects in which an opening in the spinal cord or brain remains from early in human development. Between 3-5 weeks after fertilization, ectoderm cells on the dorsal side of the embryo (neural plate) begin to change shape and form the neural tube. When the neural tube does not close completely, an NTD develops. Specific types include: spina bifida, which affects the spine, and anencephaly, which results in little to no brain. NTDs are one of the most common birth defects. Spina bifida affects approximately 1,500 births annually in the USA. Incidence of NTDs have decreased with prenatal folate (folic acid) supplements. Microcephaly is a medical condition in which the brain does not develop properly resulting in a smaller than normal brain and head. Often people with the disorder have an intellectual disability, poor motor function, poor speech, abnormal facial features, seizures, and dwarfism. Microcephaly is proposed to involve errors in neurogenesis and gliogenesis. Gray matter heterotopias are neurological disorders caused by clumps of gray matter (ectopic nodules of neurons) located in the wrong part of the brain. It is characterized as a type of focal cortical dysplasia. The neurons in heterotopia appear to be normal, except for their mislocation. The condition causes a variety of symptoms, but usually includes some degree of epilepsy (recurring seizures), and often affects the brain's ability to function on higher levels. Heterotopias are thought to be caused by errors in neuronal migration.

Errors in synaptogenesis have been implicated in intellectual disability (mental retardation), and trisomy 21 (Down Syndrome). Errors in synaptic refinement have been implicated in autism and schizophrenia.

1. *What does postmitotic mean? What are adult neurogenesis and adult gliogenesis?*

From Wikipedia: G0 is a resting phase where the cell has left the cycle and has stopped dividing. The cell cycle starts with this phase. The word "post-mitotic" is sometimes used to refer to both quiescent and senescent cells. Non-proliferative (non-dividing) cells in multicellular eukaryotes generally enter the quiescent G0 state from G1 and may remain quiescent for long periods of time, possibly indefinitely (as is often the case for neurons). This is very common for cells that are fully differentiated. Some cells enter the G0 phase semi-permanently and are considered post-mitotic, e.g., some liver, kidney, and stomach cells (though they retain the ability to enter the cell cycle under specific conditions). Many cells do not enter G0 and continue to divide throughout an organism's life, e.g., epithelial cells. Cellular senescence occurs in response to DNA damage and external stress and usually constitutes an arrest in G1. Cellular senescence is a state that would make a cell's progeny nonviable; it is often a biochemical alternative to the self-destruction of such a damaged cell by apoptosis.

Adult neurogenesis (AN) involves the formation of new neurons in the adult brain from neural stem or neural progenitor cells, and has been well characterized in a few brain regions, including the dentate gyrus of the hippocampus and the olfactory bulb. There is some evidence that AN occurs in some other regions of the neocortex and the basal ganglia/nuclei region called the striatum. AN has been implicated in memory. Adult gliogenesis involves the formation of new glial cells, in particular astrocytes and oligodendrocytes in the adult brain. Adult astrocytes may be formed by the proliferation of existing astrocytes, or from neural stem/progenitor cells that reside in the ventricular/sub-ventricular zone. The presence of oligodendrocyte precursor cells has been shown in the adult brain.