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Glia-neuron Interactions in the Mammalian Retina

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Glia-neuron interactions in the mammalian retina

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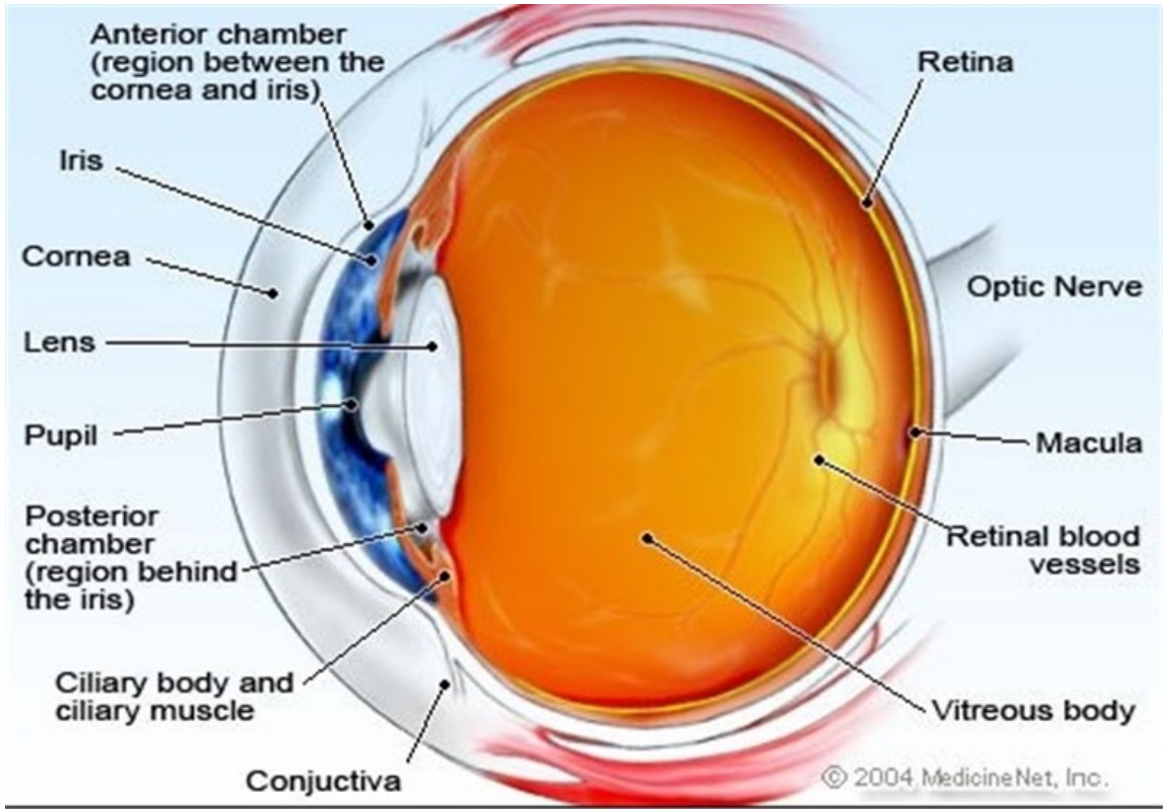
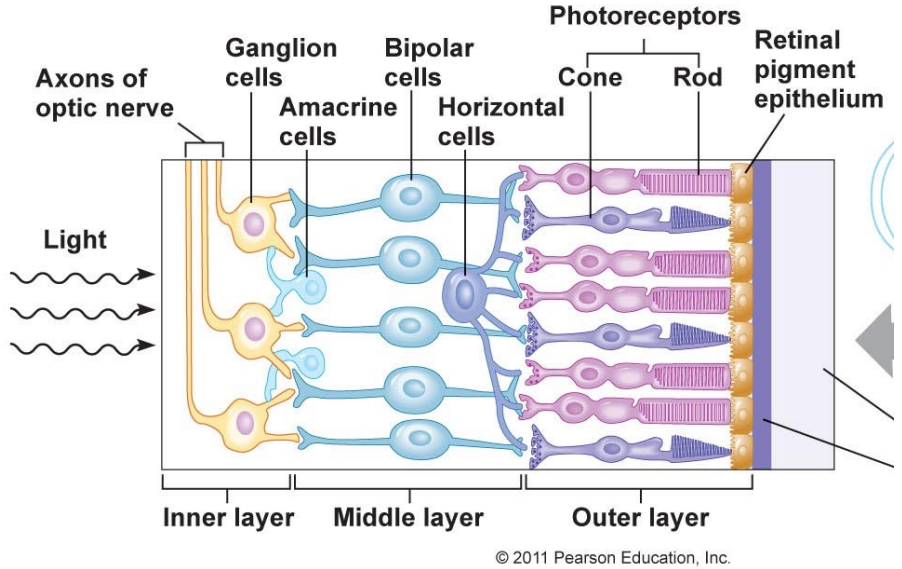
Mammalian retina

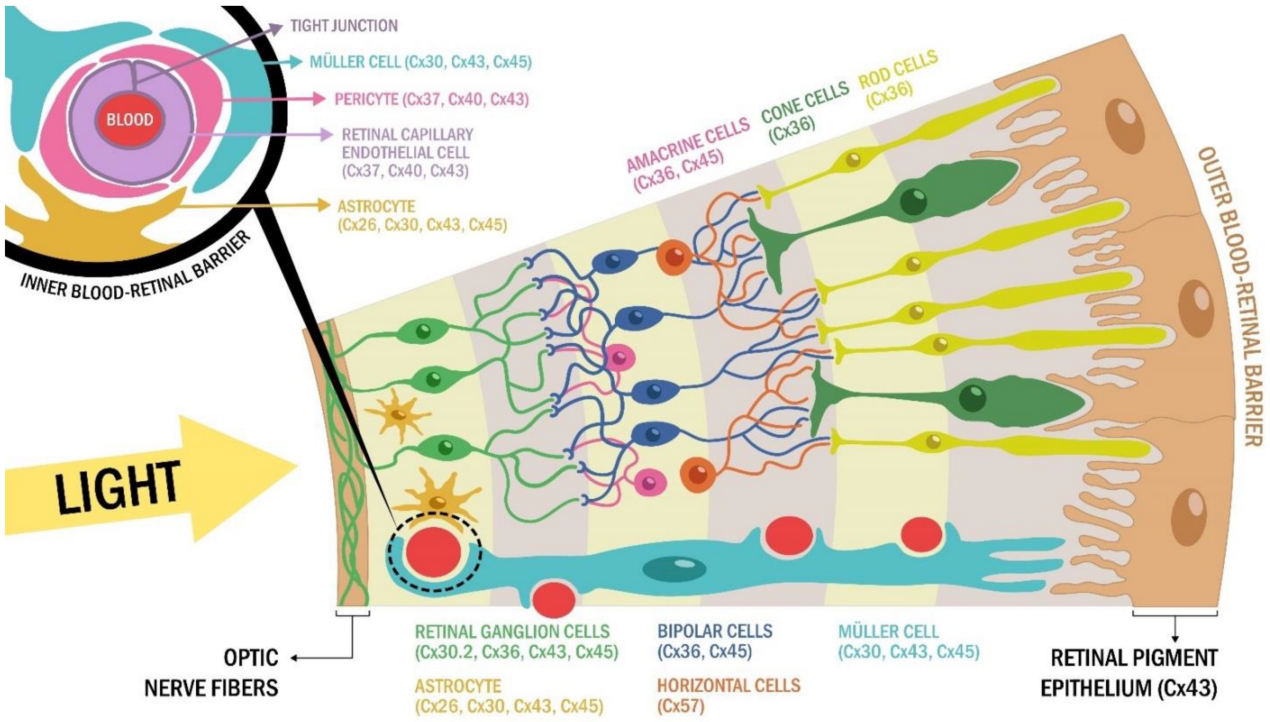


- The retina is where visual signals are processed and sent to the brain for further processing
- Neurons primarily contribute to the processing of visual information, but the glial cells also play important roles in the retina



➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Mammalian retina

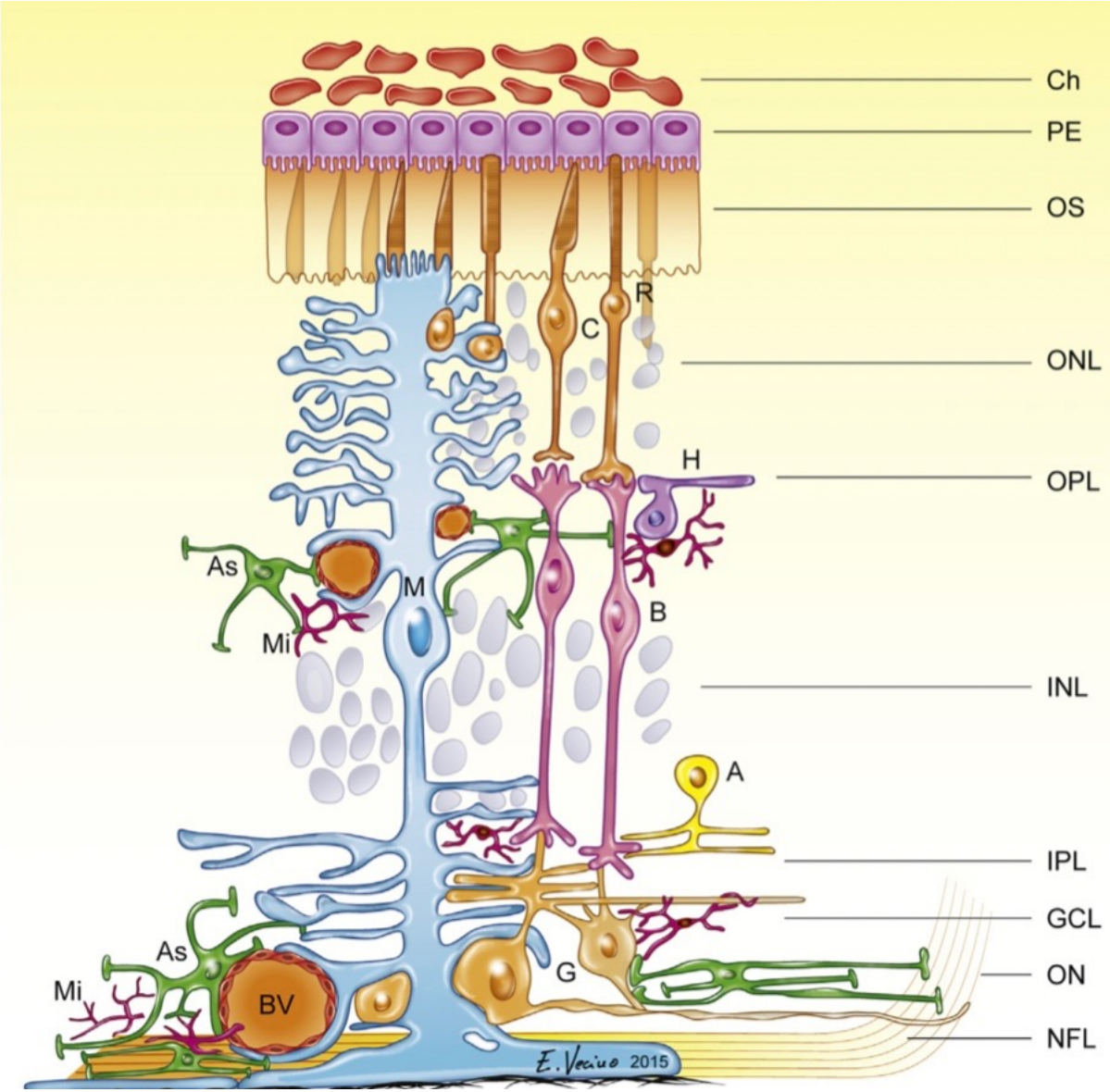


- There are three main types of glial cells in the retina:
  - Muller cells
  - Astrocytes
  - Microglia
- Each of these glial cells have specific functions but their roles can overlap
- There is recent evidence to show that retinal glial cells can also play a part in visual processing

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Muller cells

- Make up 90% of retinal glia
- Co-operativity theory: early theory (1987) that state the functional units of the eye (containing neurons and their corresponding glial cells) work together to process light
- However, more recently (1993), there came evidence that each functional units of the eye originate from a common stem cell and thus functional units act independently
- This explains their vertical shape



➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

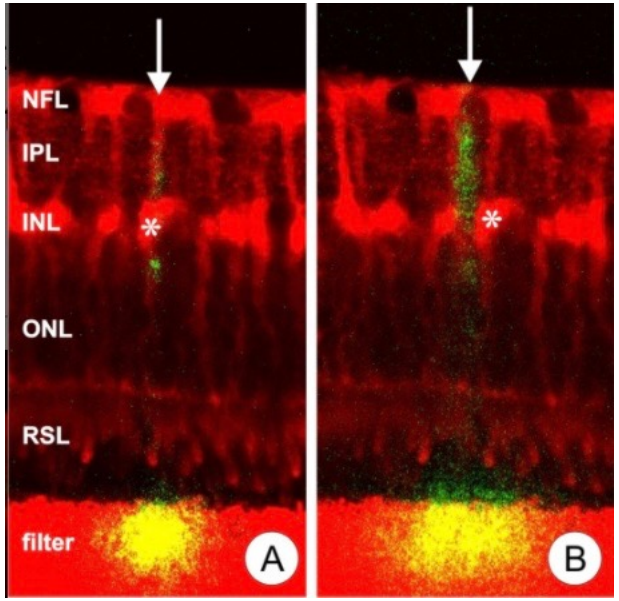
Muller cells

- Have large endfeet which ensheath photoceptors
- Muller cells ensheath nearby retinal neurons, especially after retinal damage
- Thus, Muller cells are thought to provide energy substrates to synthesize synapses as well as form precursors for neurotransmitters
- Muller cells may also have a role in the blood-retina barrier
  - Muller cells also ensheath blood capillaries, allowing for communication between the retina and the blood
- Lastly, Muller cells support neural development, survival, and information processing

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Muller cells

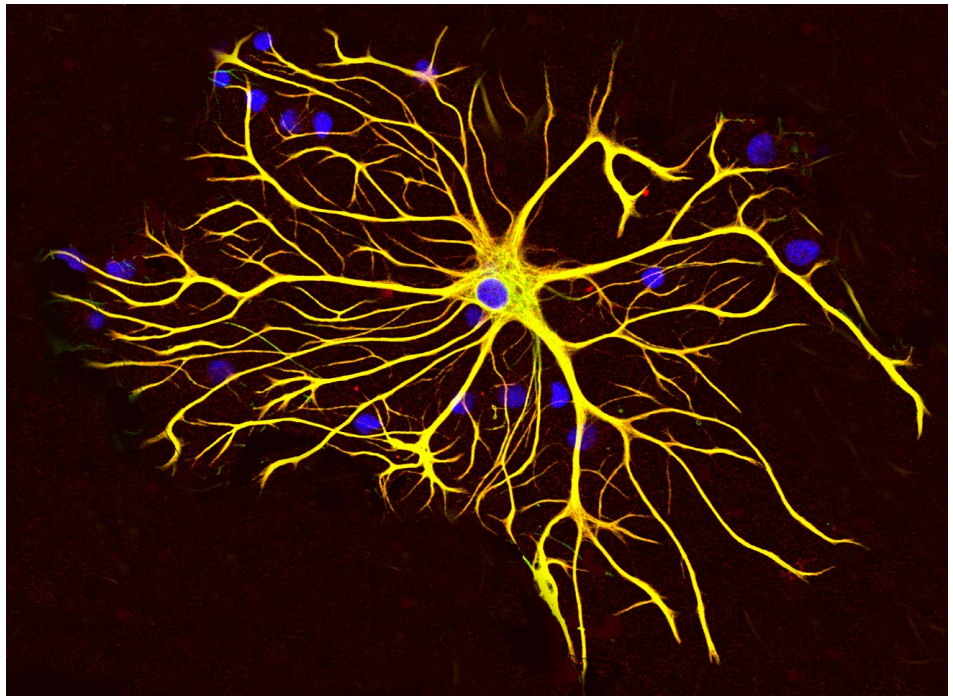
- Muller cells in information processing
  - They are thought to guide the light from the surroundings to the photoreceptors (rod and cones) within their functional unit
  - This would explain why they span the entire surface of the vitreal-retina surface and have large endfeet ensheathing the photoreceptors
- Support
  - A – (light directed at Muller cell) light scatter absent, focused light
  - B – (slide moved a couple of micrometers) considerable light scatter, beam diverges to activate many photoceptors



➤ Reichenbach, Bringmann 2013

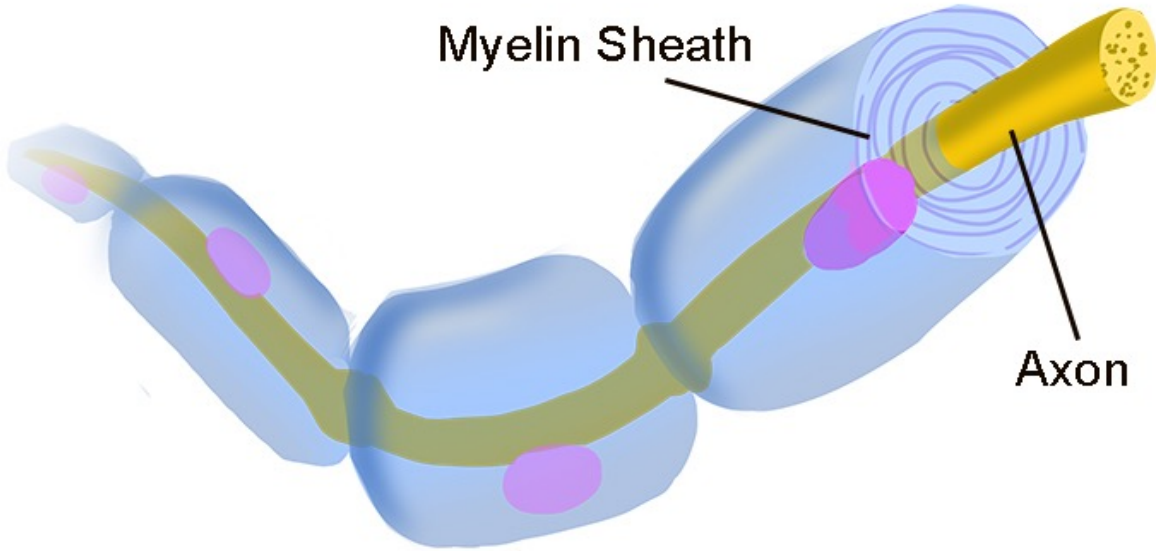
Astrocytes

- Named for their stellate shape
- Sparse in comparison to Muller cells
- Origin
  - Do not originate from the retinal embryonic epithelium and are believed to migrate from the optic nerve
  - Not found in unvascularized retinas, are distributed diffusely in diffusely vascularized regions, and are restricted to the vascularized regions in other retinas
  - Thus, there believed to migrate into the retina with its vasculature



➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Astrocytes



- Interface with blood vessels and neurons
  - Distributed particularly in vascularized regions
  - More abundant around neurons with larger nerve fibers
- Astrocytes are thought to mop up excess K+ ions from the extracellular space, transporting them to other regions
  - Vitreal and retinal capillaries can serve as a sort of “sink” for excess K+ ions
  - Astrocytes can associate with one another and with oligodendrocytes through gap junctions, forming a panglial syncytium, through which excess K+ ions are transported to K+ deficient areas

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Astrocytes

- Astrocytes are permeable to water
  - This allows for the transport of water from the blood vessels to the CSF
  - However, this means that astrocytes can swell
- IFs (intermediate filaments)
  - Intermediate filaments in astrocytes are thought to maintain the mechanical integrity of these cells and neurons
  - However, astrocytes are also thought to hinder nerve regeneration
- However, astrocytes support neurons by providing growth factors, releasing cytokines, and distributing metabolites, allowing for neuron regeneration and repair in pathological disease states

➤ Lafrenaye, Simard 2018 & Sidoryk-Wegrzynowicz , Wegrzynowicz, Lee, Bowman, Aschner 2011

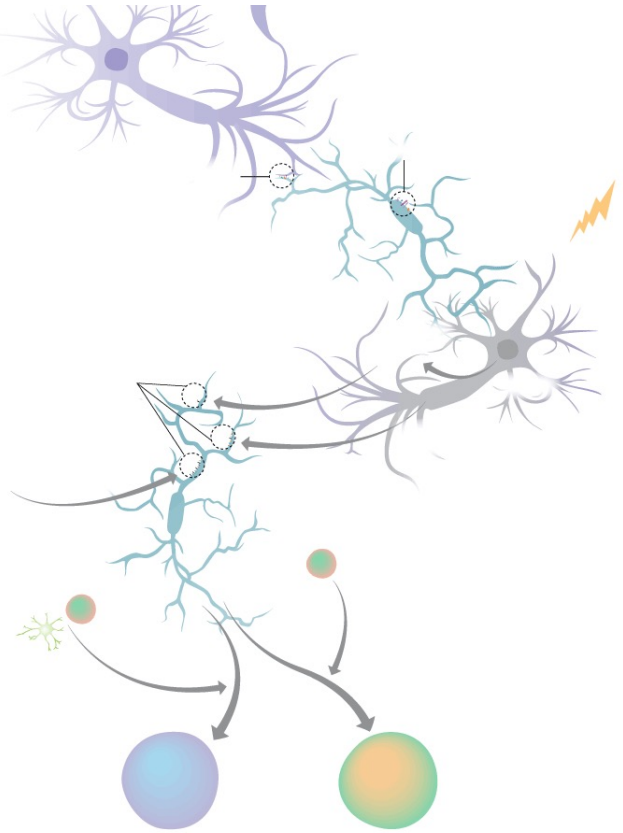
Microglia

- The blood-brain barrier is mediated by a host of cells, including astrocytes and microglia
- The blood-brain barrier allows the brain to have a sort of ”immune privilege” from the rest of the body
  - However, immune cells are enhanced by distant immune cells
  - Additionally, these immune cells in the brain communicate with peripheral immune cells through direct and paracrine interactions
- As compared with other immune cells, microglia are believed to originate from cells in the egg sac, not from the bone marrow
  - In addition, population of local progenitor cells maintain the population of microglia within the brain

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Microglia

- Play a key role in immune surveillance
- Have long processes, allowing them to survey surrounding cells
- Once activated, microglia resemble macrophages
  - Processes shorten thicken
  - Cell body enlarges
  - Enable them to perform phagocytosis
- Release cytokines which trigger a further immune response
- Eliminate cellular debris and dysfunctional synapses



➤ Benusa, Lafrenaye 2020

Microglia

- Spider effect – when exposed to injury, microglia extend their processes into the injured site and thereafter retract
- Microglia are known to release a number of neurotrophic factors in response to stress:
  - BDNF (brain-derived neurotrophic factor)
  - GDNF (glial cell-line derived neurotrophic factor)
  - IGF (insulin-like growth factor)
  - FGF-2 (fibroblast growth factor 2)
- However, microglia have also been linked to autoimmunity

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

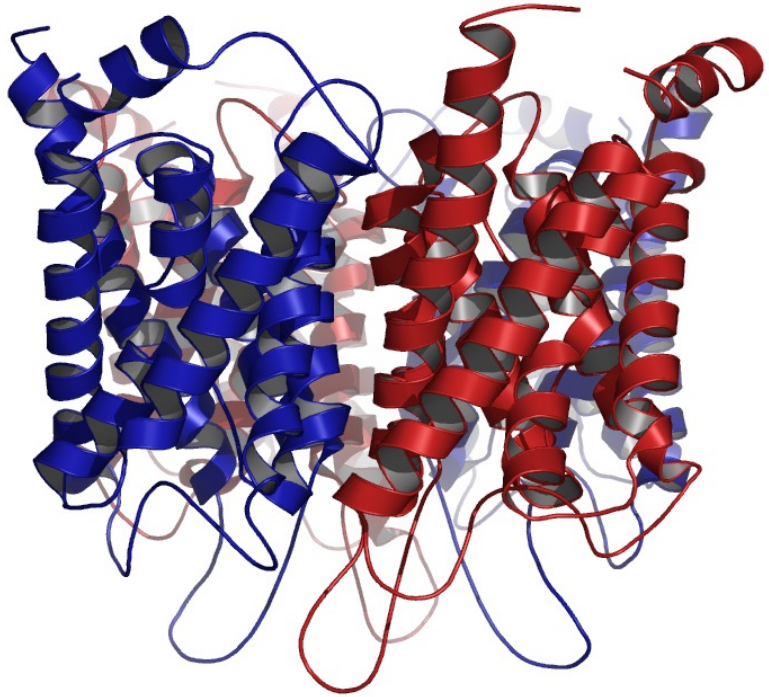
Viscoelastic properties

- As the retina develops, cells must stretch in order to accommodate the increased size
- The glial cells are significantly more elastic than the neurons
- Muller cells and astrocytes can alter the levels of IFs (intermediate filaments) within them, allowing them to harden or become more more elastic
- Glial cells may also have mechanosensory
  - Astrocytes near the optic disc may sense changes in intraocular pressure following eye movements and release ATP
  - ATP release could potentially stimulate microglia to migrate to the optic disc, thus activating astrocytes to influence neurons or blood flow

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Volume regulation

- Neurons are more excitable when they are small
- Although excitability may be good in small amounts (long-term potentiation), over-excitement results in excitotoxicity, resulting in neuronal death
- A key regulator of volume is water
  - AQP4 on astrocytes help regulate the amount of water in the extracellular space, as well as waste clearance, potassium buffering, cell migration, and calcium signaling



➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Regulation of neuronal activity

- There is evidence of two-way neuron-glia interactions at the synapse
- Neurotransmitters released from presynaptic neurons causes increases in Ca^{2+} in nearby glial cells
- Activated glia can then release glutamate and ATP, which can further result in neurotransmitter release
- Muller cells envelop synapses, influencing their shape
- Astrocytes and microglia work together to perform synapse pruning

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Synaptic pruning

- Synaptic pruning is the process of reducing and refining synapses to form neural circuits
- In mouse, for example, microglia engulf synapses as they mature if those microglia contain PSD95 and SNAP25
- Astrocytes upregulate functional synapses through glypican 4 and 6 (Gpc4, 6)
- Astrocytes also downregulate synapses through Megf10 and Mertk
- Muller cells can ensheathe gangion cell somas as well as astrocytic processes
  - This process is believed to promote synapse formation

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Immune responses

- Retinal ganglion cells are believed to recognize and clear pathogens during infection, meaning they serve as the first line of defense
- Microglia are the main innate immune cells of the CNS
  - However, their activity is tightly regulated by a number of inhibitory pathways as as to prevent autoimmunity
- Muller cells bear weight on the adaptive arm of retinal immunity
  - They inhibit the proliferation of T cells
  - Inflammatory cytokines are release

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Gliosis

- Reactive gliosis refers to the process whereby the retina enlarges (retinal cells proliferate)
  - As in the case with trauma, ischemic damage, infection, neuroinflammation, and neurodegeneration
- Astrocytes and Muller cells both participate in reactive gliosis (in response to injury)
- Proliferative gliosis occurs when glial cells proliferate at random
  - Blood-brain barrier is comprised, allowing serum components to leak into the retina
  - Muller cells proliferate as a result

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Neuroprotection

- Glial cells release neurotrophic factors which aid in neuron regeneration and development
- CNTF
  - Prevents apoptosis, trigger Muller cells to release photoreceptor survival factors
- bFGF
  - Released by Muller cells in response to ischemic and diabetic conditions
- PEDF
  - Released by Muller cells following hypoxia or injury; antioxidant and anti-inflammatory effects
- IGF-1
  - Triggers mitosis and metabolic activity; promotes survival under serum deprivation

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Phagocytosis

- Muller cells can perform phagocytose (as shown with *S. aureus*)
- Astrocytes engulf mitochondria discarded by optic nerve fibers
- Astrocytes express Mac-2, suggesting that they may play a role in axonal degeneration
- Microglia and astrocytes are both involved in the injury of the optic nerve
- Pathways involving TNF-α (tumor necrosis factor – α) can influence neurodegeneration and serve as neuroprotectors

➤ Vecino, Rodriguez, Ruzafa, Pereiro, Sharma 2015

Discussion Questions

- Many glial cell types in the retina share many of the same functions. What could be some advantages of having them perform similar functions instead of specializing?
- Glial cells are very important as they promote retinal neuron growth, support the retina structurally, and help form neural networks. Many therapies target neurons, but few drugs target glial cells. Should glial cells come under greater focus?
- The CNS has a broad network of support cells (glial cells) while other body systems do not have such support. Why do you think this is?

Citations

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