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Module 7 – Neurorepair

What Inhibits Axonal Regeneration

In module 4, we discuss the formation of the glial scar, a physical barrier around the injury that contains molecules that prevent nerve regeneration and block axon growth.
Before we begin talking about inhibitors of axon regeneration, we need to look at a top-down view of why the spinal cord has so many ways to stop axon growth. In an uninjured spinal cord, if you send a movement command from the brain, that movement should be executed exactly as you sent it.

If something touches your leg, that signal should relay to the brain and register as a touch on the leg. The circuitry is interconnected in such a precise manner in order to let us function the way we do.

The spinal cord is rich with inhibitory molecules both within neurons, and in the extracellular environment, that function to stop abnormal growth of axons which may lead to inappropriate connections being made. Imagine trying to move your finger and instead you feel a bump in your shoulder!

The inhibitors within the spinal cord function to help maintain spinal neuron connectivity in a meaningful way.

Unfortunately, that also means that many of these inhibitory molecules will interfere with regeneration of damaged axons after a spinal cord injury.

Worse yet, even more inhibitory molecules are produced in response to injury, both around and within the lesion. To the best of our knowledge, these inhibitory molecules are produced in response to acute inflammation in an attempt to stop that inflammation from spreading within the spinal cord.

To understand what inhibits axon growth and regeneration we can separate our focus into three main areas.

1) The glial Scar
2) Myelin Inhibitors
3) Intracellular inhibitors

The glial scar is a physical barrier around the damaged area that separates healthy cells from injured ones. The glial scar is believed to inhibit regeneration by acting as a physical and chemical barrier to growth. Cells in the glial scar produce several molecules (such as CSPGs) that stop axons from growing.

Let's talk about the glial scar a bit more in depth. The process of producing a growth-inhibitory barrier around an SCI lesion has been termed the glial scar.

Under normal circumstances, astrocytes are highly organized and dispersed diffusely throughout the nervous system and play a role to support neuron health and stabilize the connections between neurons.

After a spinal cord injury, however, astrocytes divide rampantly around the injury location and spread processes far and wide. Astrocyte growth and proliferation becomes very dense which is thought to potentially form a physical barrier that prevents growth and migration of other cells.

Macrophages are a source of immune cell from outside of the spinal cord that infiltrate into the spinal cord after an injury and reside in the lesion chronically.

Other types of cells also divide and enter into, or around, the lesion and contribute to the glial scar. Collectively each of these cells are key players in the glial scar and can exert different influences over axon growth and regeneration. While it is believed that the density of all of these non-neural cells can act as a physical barrier to growth and regeneration, each of these cells can also produce inhibitory molecules that act as chemical barriers as well.

Probably the most extensively studied cells within the glial scar that contributes to regenerative failure are astrocytes and the expression of chondroitin sulfate proteoglycans (CSPGs), which are known to stop axon growth. It should be noted that not all astrocytes complicate regeneration, as some are in fact permissive to axonal growth.

CSPGs are produced on a variety of cell types but are increased on astrocytes around the glial scar.

CSPGs exert their inhibitory influence on axon growth by binding to receptors on growing axons and acting as a stop signal.

Importantly, these CSPGs remain increased within the glial scar chronically and are believed to be an ongoing contributor to the failure of regeneration and plasticity within the nervous system.

Oligodendrocytes, which form insulation (known as myelin) around axons, also produce several molecules that inhibit axon regeneration which makes it difficult for a growing axon to grow long distances down a spinal cord.

Within the mature and healthy central nervous system, oligodendrocytes form myelin around axons to support their function and spread of signals to other cells. One of the functions of myelin is to also help anchor axons in place so that they do not form abnormal connections.

Myelin inhibitors are a type of protein that inhibit axon growth and are believed to contribute to regenerative failure around and beyond the lesion. Let’s talk about a hypothetical. If researchers learn how to coerce damaged axons to regenerate across the lesion and through all of the sources of inhibition just outlined, the axon that now emerges on the other side of the lesion still needs to grow and extend long distances through otherwise healthy tissue that is filled with myelin inhibitors. Many of these myelin

inhibitors act in a similar way to CSPGs, by binding to receptors on axons and telling the growing axon to stop.

It is important to understand the difference between axons in the central nervous nervous system and in the peripheral nervous system. Damaged axons in the spinal cord do not turn on necessary genetic programs needed to regenerate. Additionally, these injured axons, produce proteins that stop growth from occurring. Damaged axons in the peripheral nervous system do turn on genetic programs that allow them to regenerate.

In order for a neuron to grow it needs more than just a growth permissive substrate, the molecules that directly grow the neuron inside of the cell need to be both:

1) present and produced by the neuron, and 2) activated to grow.

In mature neurons within the brain and spinal cord, there are several continuously active molecules that stop neurons from growing. Most neurons within the spinal cord do not produce the proteins that are required to regenerate after they are injured, and there are proteins that are continuously preventing axons from growing and responding to environmental cues that may otherwise produce growth.

Unlike neurons in the brain or spinal cord, neurons in the peripheral nervous system (PNS) have an innate capacity to regenerate. When PNS neurons are damaged we see the damaged tips of these neurons act differently from when CNS neurons are damaged.

Specifically, in the PNS we see the tip form a complex structure filled with short processes that are extending to survey the environment. This structure has been called the growth cone and has been identified to be essential for axon regeneration to occur. In contrast, damaged axon tips in the CNS are observed to be short bulbous structures.

When a growth cone meets an extracellular inhibitor such as a CSPG or myelin inhibitor, the processes collapses the growth cone and forms a bulbous end termed a retraction bulb.

In order for neurons to form a growth cone and start to regenerate, neurons need to be aware that they have been damaged so they can mount an appropriate genetic response. Regeneration of axons is as much about the extracellular environment as it is the intracellular environment and require genetic programs to be activated in a neuron.

Neurons of the PNS undergo a genetic response to being injured and begin to turn on genes and produce proteins that are associated with regeneration; or regenerative associated genes.

Neurons injured in the CNS do not show a very strong response to injury, if any at all, and do not undergo a regenerative shift in their genetic response.