NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 7 – Neurorepair

Current Strategies to Promote Regeneration

There are various strategies that many researchers are focusing in on to help promote neurorepair. These include:

1) Eliminating sources of inhibition
2) Providing growth promoting cues
3) Blocking intracellular inhibitors of growth/ enhancing pro-regenerative programs

Breaking down inhibitory molecules in the glial scar, such as CSPGs, or stopping them from interacting with neurons is a research focus to help axons grow into or around the lesion. Similar strategies can be applied to myelin inhibitors.

To begin, research has supported the role that many CSPGs are inhibitory to axon regeneration by delivering an enzyme not native to humans called chondroitinase ABC into the spinal cord of rodents, which acts to digest and disable CSPGs. Digestion of CSPGs around the lesion leads to axon growth into, and in some instances beyond the lesion.

Further, other recent clinical trials have developed approaches to mask the receptors on neurons that respond to myelin inhibitors, which has shown some benefits when applied to animal models.

Delivering proteins or molecules that directly cause axons to grow can provide enough growth signals to overcome the inhibition within the scar and spinal cord.

We have so far discussed the role of inhibitory molecules in the extracellular environment that lead to the collapse of the growth cone and regenerative failure.

However, just as there are growth inhibitors, there are also growth promotors.

One of several reasons that neurons of the PNS regenerate so efficiently is because glial cells in the PNS called Schwann cells secrete proteins and guide the regenerating axon towards them. Schwann cells are not present in the brain or spinal cord.

There are many secreted proteins that are known to induce axon growth,

and in some situations that growth response can be strong enough to overcome other sources of inhibition.

Ultimately, while the delivery of these and other growth promoting proteins can induce axon growth, either via regeneration or sprouting, there have been several risks proposed with the exogenous delivery of growth factors for the treatment of SCI.

Delivering proteins to cause axon growth can potentially cause growth of other neurons/axons within the spinal cord that can give rise to pain, autonomic dysreflexia, or other complications. More on this complication will be discussed in Module 9, neuroplasticity.

There is a need to control the genetic programs of neurons within the spinal cord to regulate growth and regeneration. In 2009, scientists identified an important molecule inside of neurons that prevents their growth. This molecule is called PTEN for short.

When a growth-promoting molecule interacts with a receptor on the surface of a neuron, that receptor initiates a cascade of intracellular molecular interactions to allow growth. PTEN directly interferes with this pathway and prevents growth promotors from functioning.

Deleting/blocking PTEN allows the cascade pathway to activate.

An analogy for this is, deleting/blocking PTEN is like taking the parking brakes off a car allowing it to move forward.

Future experiments are aiming to identify what genes are essential to turn on for an axon to regenerate, what intracellular inhibitors are acting to stop axon growth, and to develop genetic and pharmaceutical strategies aimed at inducing a pro-regenerative intracellular environment.