NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 7 – Neurorepair

Hurdles / Controversies

While there are seemingly hundreds to thousands of pre-clinical research papers that demonstrate different strategies for regeneration, it is important to note that the time post-SCI that these treatment strategies are deployed may play a key role in their success.

After an SCI there is a short window of opportunity where axon growth is more permissive. This is best exemplified by early research studies which observed successful regeneration of sensory axons across a spinal cord lesion when those axons were coerced to regenerate immediately after injury. If neurons are primed to regenerate before or shortly after SCI, they can growth more readily into and beyond the lesion. However, if the neurons are stimulated to regenerate long after SCI, axons do not regenerate.

These findings point to what is now understood: 1) inhibitory molecules increase around the lesion increase with time and 2) growth promoting molecules decrease with time.

One reason that regeneration success diminishes in chronic SCI is the formation of a net around neurons and axon terminals and stop them from growing.

Breaking down CSPGs can open a window for axons to grow and improve outcomes.

As we mentioned earlier, several inhibitory molecules are increased after SCI and are sustained chronically. Some of these inhibitory molecules, as well as other proteins existing in the extracellular matrix, begin to form a thick net around neurons and their processes, even at distances far away from the lesion. This net has been called the peri-neural net, and its presence and increased thickness in chronic SCI is believed to be one of the reasons that strategies aimed at inducing regeneration and plasticity in chronic SCI is significantly more challenging.

CSPGs are only one inhibitor in chronic SCI. We still do not know all sources of inhibition or reasons that regeneration therapies work less efficiently in chronic SCI.

Ultimately, we do not yet fully understand all of the inhibitors that make inducing regeneration and axon growth more challenging in chronic SCI. The acute and chronically injured spinal cord are two significantly different environments.

Regrowing axons through a lesion and down the spinal cord is only the first challenge. We still need to figure out how to get them to connect where they are supposed to without making inappropriate connections.

Finally, we are still at a point in regenerative medicine where we are trying to identify the best, most robust, and most clinically relevant ways to induce regeneration within the spinal cord.

The threat of unspecific growth is a major hurdle for the use of growth promoting proteins. Once the mysteries of regeneration are better understood, we will then enter a stage where we can begin asking and answering questions about how to get axons to grow where we want them to grow and connect to where we want them to connect.