NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 6 – Neuroprotection

Immunomodulation

One experimental neuroprotection strategy is called "immunomodulation." In SCI, immunomodulation means manipulating immune cells so that they carry out their restorative functions but not their damaging inflammatory functions.

Cells called macrophages and neutrophils are two of the potential targets of this approach.

Macrophages are specialized immune cells that enter the injured spinal cord from the blood stream, and remain in the injured cord for very long periods after an SCI. Their main job is to ingest dead cells, debris, and foreign pathogens such as bacteria and viruses, and break them down safely in a process called "phagocytosis."

Some macrophages have pro-inflammatory functions, while others have anti-inflammatory functions. And we have learned from basic research that it is possible to manipulate macrophages to switch back and forth between pro-inflammatory and anti-inflammatory functions.

Neutrophils are short-lived immune cells that act as the first line of defense against infectious pathogens. Like macrophages, they also clear debris through phagocytosis. And they also play a major role in mounting an inflammatory response.

Researchers have tested several different ways of modulating the immune response after an SCI. **Methylprednisolone** was the first immunomodulatory neuroprotective agent to be used routinely in SCI; it inhibits macrophages and neutrophils from infiltrating into the spinal cord. At the end of this module, we will talk about important lessons that can be learned from the way methylprednisolone was studied.

Minocycline, a drug that is approved as an antibiotic, may tackle inflammation and several other biological processes that damage neurons in the aftermath of an SCI through mechanisms that are not yet understood and are not yet proven to work in SCI. So far, basic research and preclinical studies suggest that minocycline:

- Inhibits the activation of macrophages and microglia to reduce damaging inflammatory processes;
- Scavenges free radicals and inhibits the production of nitric oxide (NO);
- Prevents apoptosis (programmed cell death) of neurons and oligodendrocytes; and

- Prevents excitotoxicity (damage to neurons caused by over-active signaling).

We will discuss excitotoxicity, free radicals, and apoptosis in more detail later.

Granulocyte colony-stimulating factor (or "G-CSF"), is another experimental immunomodulatory therapy for SCI. G-CSF is a biologic drug that is approved as a treatment for neutropenia (or low neutrophil count). It is a protein that our bodies make naturally that helps keep inflammation in balance.

On the one hand, it acts as a growth factor that stimulates the body to produce more neutrophils. But G-CSF also counteracts some of the inflammatory signals that neutrophils and other immune cells send. Therefore, G-CSF helps preserve neutrophils' ability to clear debris while lessening their inflammatory effects.

G-CSF also promotes macrophages to transition from pro-inflammatory to anti-inflammatory functions.

Several different types of **cell replacement therapy**--including bone marrow mesenchymal stem cells (or "BMSCs"), neural stem cells, and neural progenitor cells--can switch macrophages from pro- to anti-inflammatory functions. While this means they may work as immunomodulators, cell replacement therapies have special qualities and unique challenges that make them different from the other examples. We will talk more about this research in the Cell Replacement module.