NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 8 – Cell Replacement

Strategies of Cell Replacement in SCI to Improve Efficacy

Currently, animal experiments and clinical trials have demonstrated beneficial effect of using cell transplantations to treat spinal cord injury.

Cell transplantation is used to repair and/or replace damaged nerve cells and tissues from the injury. These new cells, which can include neurons and glial cells, help the integrity and reconstruction of nerve function. Additionally, cell transplants interact with surrounding damaged tissues to provide growth factors and alter the microenvironment to promote the growth of axons. We will talk about these internal and external factors more in depth in Module 9.

There are severable variables that can affect how well cell replacement works to treat SCI. These include:

- The level, severity, and mechanism of the injury
- The timing of the therapy (acute, subacute, chronic)
- The number of cells used
- The type of cells used

The level, severity, and mechanism of the injury

- Historically most cell transplantation studies in animal models have occurred in acute or sub-acute stages after spinal cord injury. While some experimental evidence does exist to suggest that transplanting in chronic stages of SCI may be helpful, better effects are observed with earlier intervention.
- Acute or sub-acute cell transplantations exert neuroprotective effects and can facilitate axon growth and plasticity more effective earlier after injury.
- However, most clinical trials are performed either exclusively in, or are including, transplantation in chronic SCI. There are several variables in clinical trials that make transplanting in chronic SCI more feasible. These include:
    - Knowing how well a participant can function after reaching a plateau which makes detecting changes caused by the transplants easier to identify. Acutely after an SCI, many people will regain some function spontaneously, so it is difficult to know if functional recovery was natural or induced by the transplant.
    - It is possible that intervening too early could cause physical displacement on the cord and potentially cause more damage. Observing a stable lesion can help guide where to transplant to avoid damaging healthy tissue.

The timing of the therapy (acute, subacute, chronic)

Transplantation of cells too early can result in the graft dying due to the harsh environment caused by secondary injury and inflammation. A brief delay of a couple weeks can promote better survival of transplanted cells when injected into the spinal cord. For cells that function mainly by producing anti-inflammatory effects or pro-survival effects, earlier transplantations may be better. Cell injections into the blood stream have been explored to avoid the harsh environment of the freshly damaged spinal cord. For cell transplantation approaches that require better survival of the graft, such as neuron replacement, a short delay may yield better survival to avoid the acute damaging inflammatory response. However, too long of a delay may result in missing a therapeutic window to promote plasticity or growth of axons from the transplant due to the formation of a glial scar. There are advantages and disadvantages to cell transplantations at any time point.

The number cells used

The number of cells transplanted is important aspect of the therapeutic effect, as insufficient number of cells that are transplanted will make it difficult to see any benefits. Similarly, the best route of administration is still debated (into the cavity, into healthy tissue, below the dura (intrathecal), or into the blood stream).

The types of cells used

There are two main types of cells transplants being tested and several different sources:

1) neural cells that can form new nervous system tissue; i.e. neural stem cells (NSCs).

2) non-neural cells that function to support the growth and survival of the spinal cord.

For use in humans, NSCs must be derived from a pluripotent cell such as an embryonic stem cell (ESC) or induced pluripotent stem cell (iPSC). iPSCs are favored over ESCs for two reasons. 1) iPSCs can come from a person's own body so the graft is not rejected by the immune system, and 2) there are ethical considerations with using ESCs that must come from embryonic sources. iPSCs act and function like an ESC and can be a source of new neurons.

iPSCs or ESCs can be differentiated into NSCs, and then into new neurons, oligodendrocytes, or astroctyes. (graphic showing skin biopsy to iPSC to NSC to neuron/oligo/Astro)

Non-neural cell transplantations have been extensively studied. Cells derived from many different sources possess different properties. The ultimate goal of using non-neural cells is to provide a growth permissive matrix for regeneration, the production of growth factors to encourage axon growth, and take advantage of anti-inflammatory properties to act as neuroprotective agents. Non-neural cell sources that are commonly used include, Schwann Cells, Olfactory Ensheathing Cells, and mesenchymal stem cells that can be derived from bone and fat amongst other locations.