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Transfer and reprogramming of neural stem cells in spinal cord injury

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Spinal cord injury affects 11.000 Europeans/year and there are 300.000 victims in Europe. Two decades ago, repair of the spinal cord was regarded as an impossible task. This gloomy outlook is slowly yielding to cautious optimism. To protect from secondary damage, replace and repair what has been lost, cell and tissue grafting strategies have shown promise.

Injury to the spinal cord will immediately lead to vascular damage and local ischemia. This and the extracellular spreading of contents from damaged cells will exacerbate initial damage. Inflammatory and immune responses will become activated. The consequences of these responses are presumably partly necessary and beneficial, but also include negative effects that may vary significantly between individuals, depending on genetic disposition. The end result of a spinal cord injury is typically an area at the site of injury with major grey and white matter damage, scar tissue and often the formation of cysts. Typically, the cellular losses include loss of many of the myelin-forming oligodendroglial cells, since they depend on local nutrition for survival, while some of the passing axons that were not severed by the traumatic insult, may remain, since they can survive by nutrition via axonal flow from their cellular origin in nerve cells residing in non-injured areas above or below injury. This will lead to a number of demyelinated axons, with severely impaired axon potential conduction properties. Due to the loss of protective myelin such axons also are at risk to become directly damaged and degenerate. Unlike the situation in a peripheral nerve, in which the myelinating Schwann cells can proliferate, stimulate axon regeneration and provide remyelination when needed, oligodendroglial cells do not promote regeneration and do not provide remyelination to any significant degree. To make matters worse, the remaining intact myelin sheaths actively inhibit nerve fiber growth by a system of membrane-bound molecules such as Nogo, MAG and OMgp, that all activate the Nogo receptor complex on nerve fibers to cause growth cone collapse.

Current thinking in spinal cord injury has two focuses. First, in cases where intervention can be initiated soon after injury (hours - about 2 weeks) protective protocols may help minimize secondary degenerative events, negative immune responses and losses of oligodendroglial cells. Second, for those descending and ascending axon pathways that have been interrupted by the injury, a plethora of experimental strategies have been tested to allow axon regeneration with reestablishment of functional connectivity.

Stem cells and stem cell-like cell lines of various origin may prove useful to achieve both the first and the second goal. While initial efforts were perhaps more focused on the use of stem cells to replace cells that had been lost, it is being increasingly realized that the delivery of stem cells to a site of CNS injury (be it the brain or the spinal cord) may also help host tissue by providing trophic support and/or counteracting some of the negative consequences of inflammatory/immune reactions. Of note, the alternative approach to stimulate intrinsic stem cell proliferation, rather than transplanting cells has also shown promise recently.

One readily available stem cell population is bone marrow stromal cells, which can be harvested from bone marrow, and probably also from blood. Protocols have been developed to proliferate marrow stromal cells into large quantities, sufficient for therapeutic purposes, within less than 4 weeks, thus closing in on the window of opportunity for using cells proliferated from an individual patient with spinal cord injury for treatment that may help protect from secondary injury. We have shown that marrow stromal cells, given one week after impact injury to the rat spinal cord survive, form bridges that nerve fibers associate with, and improve functional outcome (Hofstetter et al 2002).

Neural stem cells are particularly interesting for CNS protection and repair purposes. When naive adult neural stem cells, grown into neurospheres, are grafted the injured site of the rat spinal cord, we recently detected that positive effects were accompanied by the development of allodynia. Transduction of Neurogenin-2 before engraftment changed the fate of grafted cells, alleviated allodynia, and improved sensory recovery (Hofstetter et al 2005). A detailed analysis of the fate of the grafted neural stem cells showed that a majority of naive cells become astrocytes. We found that incoming CGRP-immunoreactive sensory nerve fibers proliferated pathologically in the vicinity of such newly formed astrocytes, probably explaining the allodynia. If instead neurogenin2-transduced cells were grafted, few became astrocytes and many more developed into oligodendroglial cells, capable of remyelinating nude host axons. Thus, while uncritical implantation of pluripotent cells carries risk, genes may be used to control cell fate leading to better and safer future treatment protocols. Our experiments also show the importance of using a multitude of outcome assessments, focusing not only on gait, and not only relying on behavior outcomes to determine sensory functions. Using a combination of gait assessment and functional MRI we have for instance shown that numb rats can walk (Hofstetter et al 2003).

No single method will allow for robust repair of the injured spinal cord. The combination of several strategies, including disinhibition of the Nogo signaling system, delivery of trophic support and cells that may help guide growing axons and remyelinate axons in need of a myelin sheaths may eventually lead to experimental results good enough to make it unethical not to carry the methods to clinical trials.

References:

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