Stem Cell Therapy for Spinal Cord Repair: A Current Status Report

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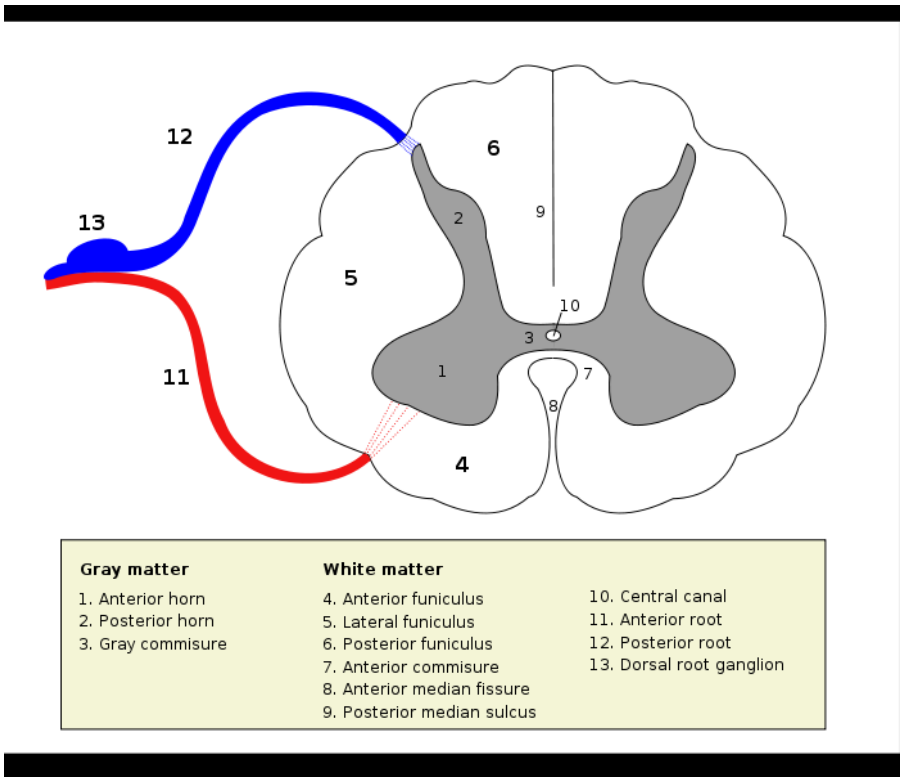

Figure 1; Schematic of the Spinal Cord indicating the Grey and White Matter. blue=sensory neurone, red=motor neurone (**GNU Free Documentation License**, User:Polarlys, 2006, from http://commons.wikimedia.org/wiki/File:Medulla_spinalis_-_Section_-_English.svg)

The hope of medical research is that one day the world's worst illnesses and most debilitating injuries will be cured. Spinal cord injury (SCI) affects around 2.5 million people worldwide with an estimated 130 000 incidences occurring each year (Thuret et al., 2006). In the past prognosis for SCI patients was poor, but with advances in technology and scientific research SCI patients now reach a normal life expectancy, albeit living with a severely reduced quality of life. As such, there has been a wave of interest investigating the long-term treatment and management options. As the number of individuals with SCI increases, the social and economic implications this has on the British health care system is huge, with an estimate of 500 million pounds spent annually (Adams and Cavanagh, 2004).

For patients, not only do they suffer with their disability, but the costs of primary care and loss of income also lead to financial burden (Thuret et al., 2006). SCI is both devastating and life altering and thus investigating its treatment is essential.

Spinal Cord Injury

SCI is defined as any trauma to the spinal cord which leads to sensory and motor dysfunction (Hulsebosch, 2002). The causes can either be traumatic due to direct insult or non-traumatic as a secondary injury due to a diseased state.

Variability in physiological damage and level of disability after SCI is due to differences in the composition of grey and white matter in the spinal cord (McDonald and Sadowsky, 2002)(*see figure 1*).

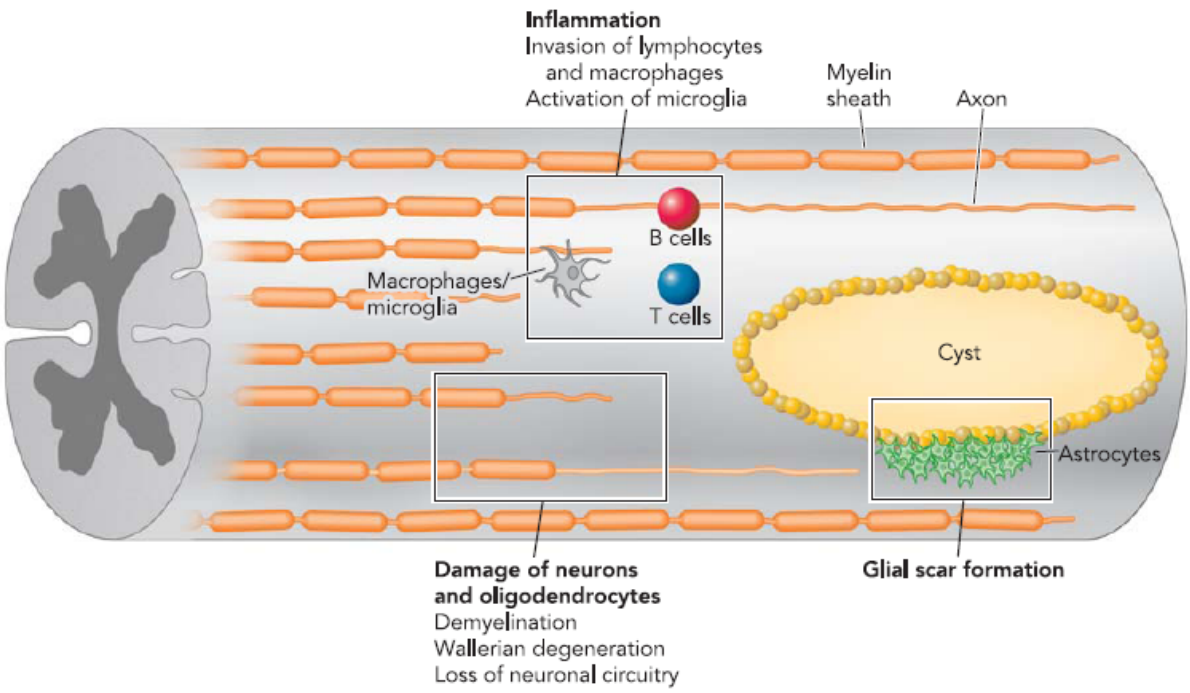

Figure 2 Schematic of SCI, note the physical damage, inflammation and scar formation
(**from** Obermair *et al*, Physiology, Vol. 23, No. 5, 296-304, October 2008 © 2008 Int. Union Physiol. Sci./Am. Physiol. Soc.. Many thanks to the American Physiological Society for educational access to their material).
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The grey matter consists of cell bodies, dendrites, unmyelinated axons and the nerve support cells the glia, whilst the white matter that surrounds it contains bundles of myelinated axons acting as pathways running up and down the spinal cord. Lesions affecting solely the grey matter at a particular level will affect only the motor and sensory innervations in that area, if a lesion were to extend toward the white matter, long tracts may be affected leading to paralysis. In addition, as the spinal cord innervates all autonomic organs of the body, any damage also affects these autonomic functions.

Problems Repairing the Spinal Cord

Physical disruption of nerve tissue and the retraction and degeneration of the axons have to be repaired (*see figure* 2). The damage also leads to glial scarring. The glial scar creates an inhibitory environment suppressing axonal regeneration and remyelination (Hu et al., 2010).

In addition to the physical disruption caused by the trauma, biochemical effects further damage the tissue and limit the ability of the nerve cells to repair themselves. Excitotoxic amino acid neurotransmitters are released and further contribute to cell death, whilst immune cells and inhibitory molecules surround the growth cones of neurones (Ramer et al., 2005). Other factors alter gene expression and the regulation of proteins involved in the inflammatory and regenerative response (Liverman et al., 2005) and inhibit myelin repair (Houle and Tessler, 2003).

Why do Stem Cells offer hope?

Current treatment to minimise the traumatic lesion usually involves; removing large fragments that cause further damage; application of drugs to restrict the damage from excitotoxicity (free radical inhibitors and steroids); and the use of extracellular matrix modifiers to minimise scarring.

More radical and experimental treatments focus on the replacement of tissue, using peripheral nerve and support cells and now stem cells.

The discovery of mouse stem cells in 1967, led to a flurry of research investigating the medical possibilities of their use (*see figure* 3).

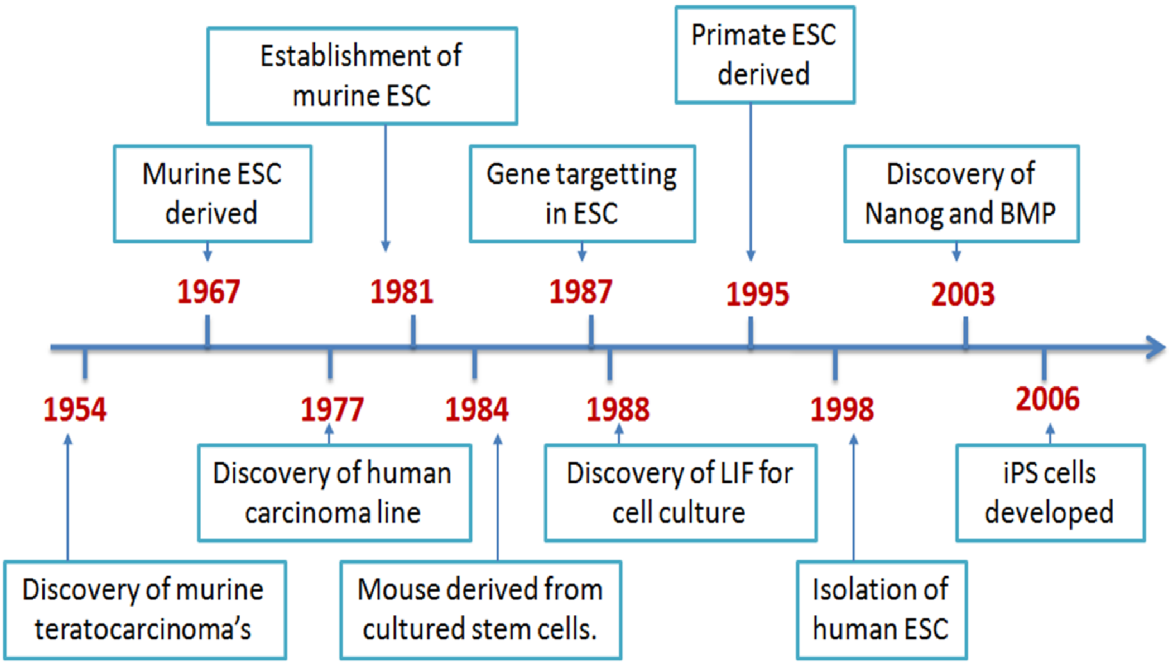

Figure 3; Brief Timeline of Stem Cell Research. Abbreviations: ESC- Embyonic Stem Cells; iPS- Induced Pluripotent Stem Cells; LIF-leukemia inhibitory factor (required for successful in vitro murine ESC growth); Nanog- A gene expressed in ESC which maintains pluripotency and self-renewal; BMP- Bone Morphogenic Protein (an anti-neural factor that maintains pluripotency). Timeline produced from data in Friel et al. (2005) and Solter (2006).

Interest was sparked by their unique properties; they can divide, proliferate and renew for long periods of time without differentiation; and they are unspecialised but can give rise to specialised mature cells.

Stem Cell Therapy (SCT) for Spinal Cord Repair

The ability to manipulate stem cells and their inherent characteristics set them apart from other forms of cellular therapy.
The goals of stem cell therapy are in:

- cell replacement,
- neuroprotection,
- axonal regeneration,
- and as a vector to transport therapeutic factors.

(Enzmann et al., 2006; Tewarie et al., 2009; Kan et al., 2010; Zhang et al., 2010).

Cell replacement

McMahon et al. (2010) transplanted neural stem cells into immune-suppressed mice with a bruising injury to the spinal cord. These cells demonstrated the ability to integrate with host cells and migrate towards the site of the lesion, expressing markers for neurones and support cells at 2 weeks post injury.

A pre-clinical study examining neural stem cell transplantation in marmosets has further corroborated these findings. In this study Iwanami et al. (2005) transplanted human stem cells into the lesion site and progress was examined behaviourally, electrophysiologically and histologically. Nine days post transplantation the cells differentiated into neurones and support cells, and behavioural tests showed that there was a significant improvement in function. In addition, microscopic analysis of injured spinal cords indicated that cavities were smaller. This demonstrated that replacement of lost cells could aid in functional recovery.

Neuroprotection

Stem cells are also thought to attenuate further damage to the spinal cord. An *ex vivo* experiment using organotypic murine cultures from 8 day old rats, demonstrated that when neural stem cells were present, the neurones were protected against glutamate induced excitotoxicity (Llado et al., 2004).

Axonal regeneration

Axonal regeneration and neuroprotection both rely on the ability of stem cells to secrete factors that create a local environment favourable to nerve repair and growth, whilst avoiding glial scarring.

Experimentally, mouse stem cells have been shown to produce nerve growth factors. These factors supported extensive growth of axons in adult rats with spinal cord lesions (Lu et al., 2003; Llado et al., 2004). Human umbilical cord cells transplanted into rats reduced the formation of the glial scar allowing for growth, regeneration and repair (Veeravalli et al., 2009).

Vector

Another more recent theory for the use of stem cells is as a vector for the delivery of therapeutic factors, such as neurotrophins, cytokines and fibroblast growth factors. Studies have indicated that stem cells are capable of migrating to the lesion site (Pal et al., 2010). This has lead to the genetic modification of stem cells to produce particular trophic factors that will enhance axonal regeneration.

Problems with Stem Cells

Although stem cells (SC) have the potential to be successful as a cellular therapy for SCI, there are a number of problems which need to be overcome. These include the propensity to form tumours, differentiation to an undesired lineage and pain generation (Zhang et al., 2010).

This risk of tumour formation is particularly evident with less differentiated cells (Ronsyn et al., 2007). This might be avoided by using stem cells from the host.

Some stem cells will preferentially differentiate into an undesired lineage, neurones particularly. Neural stem cells predominantly give rise to support cells which contribute to glial scar formation (Hofstetter et al., 2005).

Pain in response to a stimulus which is normally not noxious is termed allodynia, thought to be caused by an increase in astrocytes (Dworkin et al., 2003). Stem cell implantation also causes spontaneous pain (Perrin et al., 2010).

Conclusion

The use of stem cells as a routine treatment for SCI is distant but slowly becoming a reality. In the meantime, further research must be conducted to create reliable and reproducible stem cell lineages capable of sustaining the SCI population. As studies are reaching clinical testing we can only wait with anticipation to see the results of these trials, and hope that success is seen.

Author Profile

"Gabrielle is 21 years old and after completing her International Baccalaureate decided to study at the School of Biosciences graduating in 2011 with a first class degree, BSc. Animal Science. Throughout her degree Gabrielle became interested in molecular genetics and neurophysiology, deciding to pursue this interest through her dissertation".

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