Spinal Cord Injury: The track of stem cells.

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Therapeutic strategies to cure spinal cord injury have been so far largely unsuccessful, due mainly to the inability to translate into clinics experimental preclinical data. We report here two attempts at bridging this gap, based on the use of stem cells.

The presence in the nervous system of adult mammals of stem cells giving rise to neurons is now well accepted (Guenot et al.1982), and more recently it has been shown that such cells were also present in the brain of adult humans (Eriksson et al 1998). However, no such cells were ever found in the human adult spinal cord. Thanks to a special permission of "Etablissement Français des Greffes" we could collect ten spinal cords fragments from brain-dead patients, as early as two hours after interruption of artificial ventilation. Tissues were processed for ultrastructural examination, and for immunocytochemical detection of stem cells markers. We identified in the vicinity of the central canal cells with ultrastructural characteristics of B and C cells, already found by others in the subventricular zone. Stem cells markers such as Nestin and Sox2 were found in the same region. Some spinal cord fragments were dissociated and the resulting cells cultured as neurospheres. The same markers found in situ were present in the neurospheres, of which 15% were labelled with BrdU. Upon plating on an adhesive substrate, 15% of neurosphere cells exhibited markers of neurons such as Beta3 Tubulin and GAD, whereas others (80%) were GFAP-positive, and less than 1% O4-positive. These results indicate that there exist in the spinal cord of adult humans neural precursors which are able to differentiate in neurons, astrocytes and oligodendrocytes, thus raising the possibility of an auto therapy.

We developed in parallel another approach based on the use of foetal human neural progenitors genetically modified to express the proneural gene Ngn2, which is involved in neuronal differentiation. These cells were transplanted into the spinal cord of rats one week after a severe compression injury at T9 level, giving rise to a complete irreversible paraplegia. Control animals were transplanted with naïve human foetal neural progenitors. One month after grafting, animals transplanted with engineered cells had regained weight support, and some locomotion on a grid test, whereas animals grafted with naïve cells did not improve. Moreover, the scores of the latter were worse than those of injured-not grafted animals. Anatomical examination revealed that more than 90% of neural tissue was destroyed at the level of the injury. None of the grafted cells did survive in the cord after one month. However, we could detect, in Ngn2 grafted animals, caudally to the lesion, a massive re-innervation of motoneurons with serotonergic profiles, which was correlated with the clumping of 5HT2 receptors over plasma membranes. This indicates that engineered human neural progenitors may exert, one week after a severe spinal cord injury, a trophic influence stimulating the regeneration of serotoninergic axons which in turn can restore a significant locomotion. Conversely, naïve progenitors have a detrimental influence on functional recovery.

In summary, we demonstrate that there exist emerging tools based on the appropriate management of stem cells to contribute to the therapy of spinal cord injury. More work is needed to further refine these experimental approaches towards human therapy.

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