Neural stem cells for myelin repair in MS

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What are neural stem cells?

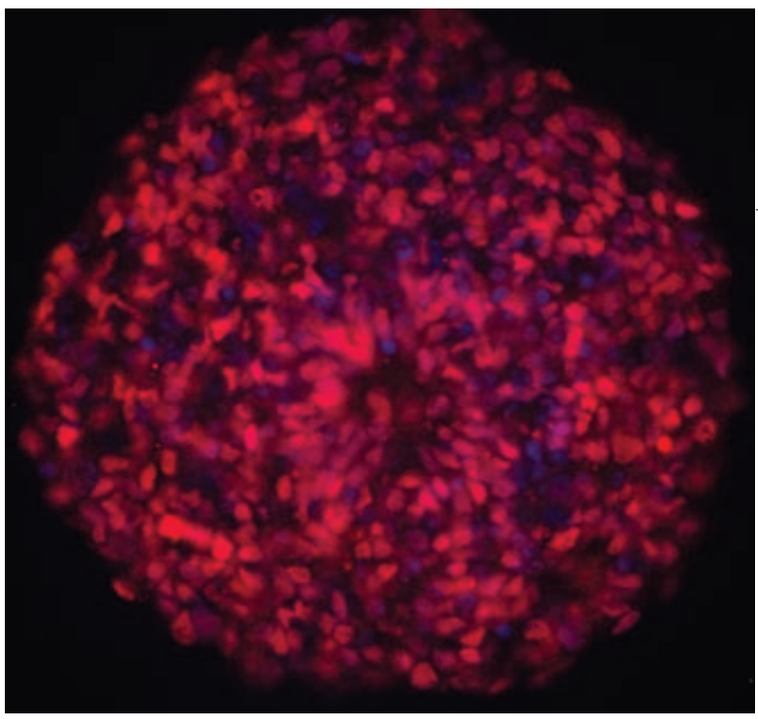
The very first indication of the existence of stem cells dates back to the end of the 19th century. At that time, scientists were able to hypothesise that stem cells were present in both embryos and in the blood. Nevertheless, the notion that stem cells were present in the mature brain was neglected until the early 1960s when new neurons generated from a population of dividing cells, thereafter named neural stem/progenitor cells (NPCs), were first observed. Further studies conducted through the early 1980s demonstrated that NPCs were self-renewing cells capable of giving rise to a limited number of multipotent cell types in a laboratory environment, owing to their capability to alter into the three main cell types of the nervous system: neurons, astrocytes and oligodendrocytes.

Since the identification of NPCs, protocols aimed at obtaining large numbers of NPCs *in vitro* have been successfully established. These harvesting protocols support the concept that these cells might represent a source of ready-to-use cells for transplantation purposes in virtually any CNS disorder including myelin disorders such as MS.

Neural stem cell therapy in MS – where are we and where are we headed?

Encouraging preliminary results have been obtained by transplanting NPCs into rodents affected by EAE, the experimental model of MS. However, there are still some issues we need to consider before any potential application of such therapies in people with MS:

- the ideal stem cell source for transplantation
- the route of cell administration
- the integration of the transplanted cells into the targeted tissue.



Neural progenitor cells might represent the ideal cell source for cell-based therapies in myelin disorders.

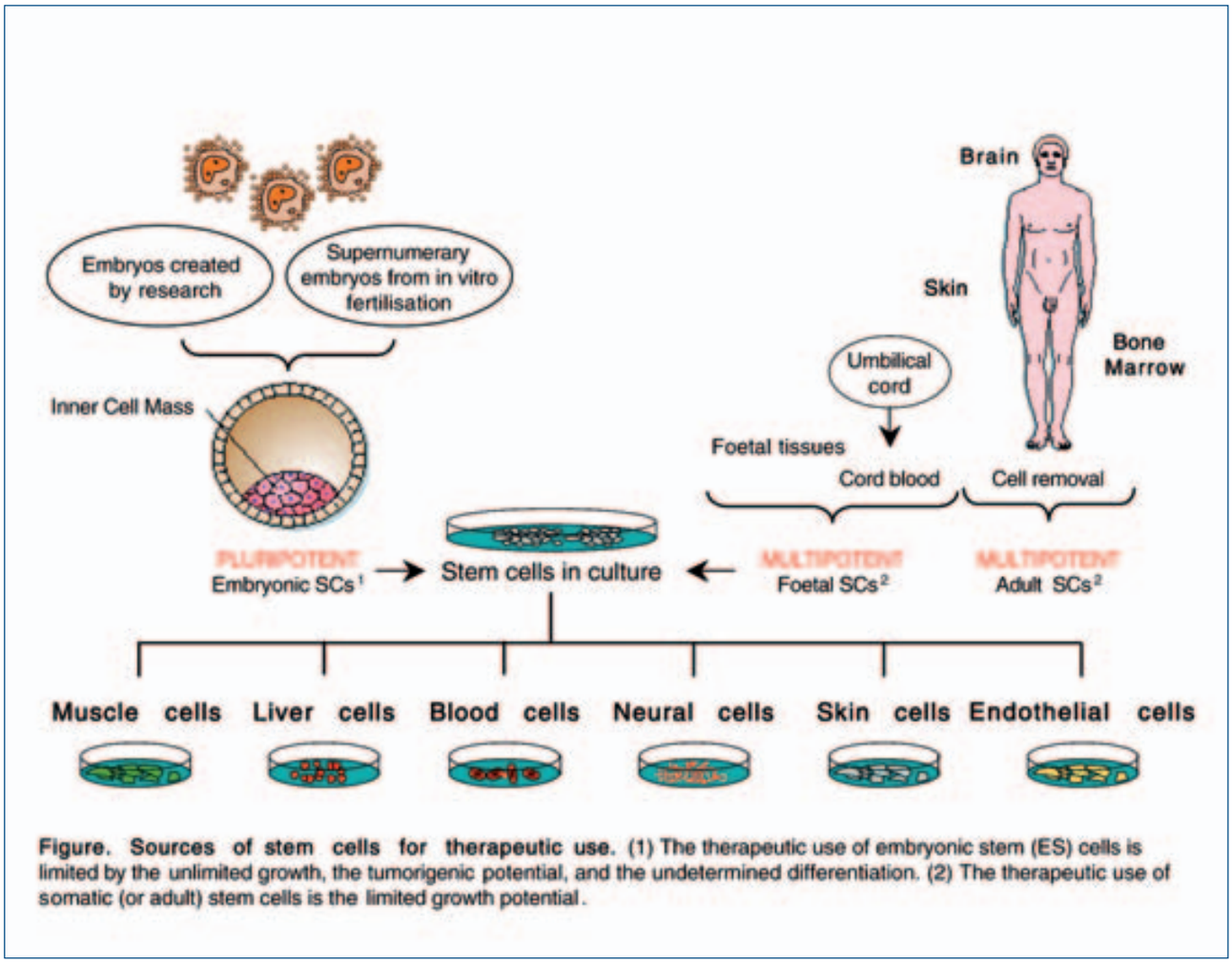


Figure. Sources of stem cells for therapeutic use. (1) The therapeutic use of embryonic stem (ES) cells is limited by the unlimited growth, the tumorigenic potential, and the undetermined differentiation. (2) The therapeutic use of somatic (or adult) stem cells is the limited growth potential.

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Stem cell source

Both embryonic stem cells (ES) and NPCs might represent the ideal cell source for cell-based therapies in myelin disorders. These cells are able to differentiate into myelin-forming cells and re-ensheath, *in vivo*, demyelinated nerves when transplanted in animals with EAE. But each of these potential sources has complications. Ethical issues are not the only cause for concern surrounding ES. Further studies have shown that the cells have a tendency to form tumours once transplanted. The use of NPCs is complicated by the difficulty in obtaining these cells for transplant to the person with MS without rejection. So far, the only available and reliable source of NPCs is from a human foetus but this renders the transplantation procedure difficult because the recipient would need chronic immunosuppression, to avoid complications caused by the incompatibility between the donor's cells and the recipient's cells.

Route of cell administration

The route of cell administration represents another key issue for stem cell transplantation. While direct cell transplantation into lesions can be instrumental in CNS disorders characterised by a single, well-identifiable area of damage, such as in Parkinson's disease or a spinal cord injury, alternative approaches have to be established in a disease like MS where multiple areas of damage are a typical feature. Multiple cell injections into the brain are unrealistic. Some recent experiments have partially overcome this

latter limitation. In animal models of MS, it has been shown that NPCs may reach the most areas of myelin damage when injected intravenously (IV) or into the cerebrospinal fluid (IC) circulation.

Cell integration

Three steps are necessary to lead to a permanent restoration of nerve conduction. Transplanted NPCs should integrate into areas of myelin damage, differentiate into myelin-forming cells and re-ensheath the damaged nerves with newly formed myelin. NPCs can differeniate into myelin-forming cells once transplanted *in vivo*, but their capacity to reconstruct the actual complex brain architecture and to give rise to properly operating cells capable of long-lasting functional integration into the brain circuits still remains unproven.

On the other hand, recent data in animals with EAE suggests that NPCs may still be effective via therapeutic mechanisms. IV and IC injection of NPCs has been shown to prevent myelin damage by exerting a potent anti-inflammatory activity leading to the death of the blood-borne inflammatory cells invading the CNS and damaging the myelin sheath. This therapeutic effect – which prevents secondary neurodegeneration and irreversible neurological impairment – does not rely on NPCs' ability to differentiate into myelin-forming cells. The effect is exerted mainly by NPCs that have not differentiated. Actually, the study showed that less than 5-10 percent of the transplanted NPCs differentiated into myelin-forming cells in the rodents with EAE that benefited from cell transplantation.

How scientists are using stem cells to understand MS

Since NPCs residing in the adult brain are considered to be self-renewing, multipotent cells capable of repairing brain lesions, it is not clear why such cells fail to promote stable remyelination in MS spontaneously over time. Preliminary experimental and human studies in MS indicate that the inflammatory process leading to myelin damage might also cause selective damage to endogenous NPCs, or NPCs already present in the organism itself. The most striking evidence supporting this hypothesis is that the vast majority of brain lesions irreversibly progressing in MS are located within the periventricular area, the very same area where NPCs accumulate during adulthood. Thus, NPC damage can be, at least in part, responsible for the failure of remyelination in people with MS. Understanding the interactions between cells and how the interactions are regulated might lead to therapeutic strategies aimed at re-establishing NPCs' capacity to spontaneously regenerate in MS.

Safe and controlled development will have a profound impact.

The future of stem cell research

Before conducting small, phase I, safety trials using NPCs in MS, the scientific community would need to agree on important preliminaries such as:

- the establishment of common patient enrolment criteria and outcome measures (to compare results, etc)
- the establishment of a common registry of transplanted patients
- the development of reproducible and traceable procedures for stem cell production (source of the cells, traceability of the donor, etc).

The future of this research also depends upon the development of biomarkers, which are molecules that allow for the detection and isolation of a particular cell type, and of MRI techniques aimed at assessing efficacy/toxicity of transplanted cells. Although it will take years before neural stem cell therapy will become a routine therapy in MS, its safe and controlled development will certainly have a profound impact on the therapeutic options for this disease.