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The future of stem cells in neurodegenerative disorders of the central nervous system

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There is an ever-growing expectation that stem cells will provide substantial benefit to people living with neurodegenerative disorders of the central nervous system such as Alzheimer disease, Parkinson disease, Huntington disease, and motorneuron disease. Globally, these conditions affect millions of people, and they are set to become more common as our society ages. However, is this expectation realistic?

Stems cells are cells that can self renew, produce progeny and differentiate. Neural cells can be generated from a number of embryonic, fetal and adult sources, including skin, using induced pluripotent stem cell and induced neuronal cell technologies.[1,2] The cells so generated include neurons and astrocytes, and the relative proportion of each varies as a function of the cell of origin, time and manipulation in culture, as does the phenotypic identity of the neurons. But how can these cells, which are grown with ever-increasing sophistication in vitro, be usefully employed in the treatment of neurodegenerative disorders?

Stem cells as models of disease

The recent discovery that adult somatic cells can be "dedifferentiated" back to neurons or to a more pluripotent state and from there driven into neuronal lines has yielded the possibility of using patient-derived cells for disease modelling. In theory, this could allow the disease process to be followed in vitro. Alternatively, neurons or astrocytes could be derived for cell replacement, assuming that the replacement cells do not undergo the same fate as neurons affected by the disease.[3]

Although induced pluripotent stems cells hold great potential, the limitations of their use are only now becoming recognized. There remain a number of critical issues that must be addressed. First, can one truly hope to recapitulate a disease process in vitro that takes decades to develop in vivo? Second, how can one interrogate the spread of disease and the dialogue between populations of various cells (e.g., neurons, microglia and astrocytes) when one is intent on driving the system to a particular cellular fate? Third, the reason why a single biopsy generates so many different cell lines is unknown, and induced pluripotent stem cells contain a range of genetic and epigenetic abnormalities that may critically affect their behaviour and ability to faithfully reproduce what happens in vivo.[4]

Modifying the local environment

An alternative strategy is to use stem cells and their progeny to provide supportive factors to the diseased brain. This could be in the form of neurotrophic factors, immune modulation or buffering excitotoxic transmitters. Indeed, stem cells may be uniquely able to produce benefits by acting through a synergistic array of mechanisms. Such an approach has been pursued in the treatment of multiple sclerosis,[5] although whether the benefits provided by stems cells translate into a clinically meaningful effect for patients or whether such therapy is competitive over more conventional treatment options is unknown. Furthermore, in motorneuron disease, engineering stem cells into supportive transplantable astrocytes may be more useful than treatments that involve neuronal replacement as, at least in some cases, the loss of motorneurons involves aberrant excitotoxic glutamate transmission.[6]

Cell replacement

The rationale behind cell replacement is that all neurodegenerative disorders have a relatively localized pathology that would have substantial

Key points

- Neural stem cells can be generated from multiple sources, each of which has its own merits and difficulties.
- Each neurodegenerative disease has its own challenges for stem cell biology and therapy; as such, stem cells may be used differently in the treatment of these various disorders.
- Stem cells could be used to model the neurodegenerative disease process, to modify the local central nervous system environment and thus promote innate repair, or to serve as a source of replacement cells targeting the core pathology.
- Extravagant claims have been made of these cells, and it is critical that we understand the limitations of the technologies at our disposal.

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clinical effects when treated. Although this is a gross oversimplification, it has proven a useful starting point in the treatment of Parkinson disease. Pharmacologic replacement of the dopaminergic nigrostriatal projection results in long-term clinical benefits, which has led to a range of dopaminergic cell therapies, the most successful of which involves the grafting of fetal dopaminergic neuroblasts derived from the developing human ventral mesencephalon into the brains of patients with Parkinson disease. In some instances, though not all, the grafted dopaminergic cells have survived for more than 10 years, and patients have received substantial functional benefits.[7,8] Of interest, recent studies have shown that the transplanted cells can acquire the pathology of Parkinson disease,[9] which could conceivably compromise their effectiveness.

Interestingly, in the case of Huntington disease, attempts at fetal striatal allografts have shown disease-like degeneration that compromises their long-term survival. This may be because the disease process affects all of the cells of the central nervous system to some degree, thus creating a hostile environment in which the transplanted tissue is ultimately unable to survive.[10]

The different responses of grafts to the local environment in these two situations highlights how each neurodegenerative disorder presents its own challenges such that stem cells cannot be seen as a generic treatment for all diseases. Furthermore, these neurodegenerative conditions have diverse pathologies, and any strategy that focuses on cell replacement is never going to cure the patient.

Conclusion

Stem cells and their derivatives will face a number of additional hurdles before they can be considered useful in clinical settings. First, can they differentiate appropriately when placed in the environment of a diseased, adult central nervous system? Second, can they be shown not to migrate or integrate into circuits away from the site of the graft? Third, can they be shown not to significantly proliferate once grafted? Finally, can they survive in their differentiated state once grafted, without reverting to the stem cell state?

Stem cells may offer great potential in furthering our understanding and treatment of neurodegenerative disorders of the central nervous system. However, exactly how much of a contribution they can make remains unclear. Extravagant claims have been made of these cells, especially when commercial interests are attached to them. It is therefore critical that we understand the limitations of the technologies at our disposal, as well as the inherent difficulties in trying to take an in vitro cell culture system to the heterogeneous complexities of patients in the clinic.

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