Best Practice & Research Clinical Obstetrics and Gynaecology 31 (2016) 69–81

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

7

Human neural progenitor cells in central nervous system lesions

Elisabet Åkesson, MD, PhD, Associate Professor,
Erik Sundström, PhD, Associate Professor *

Division of Neurodegeneration, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Novum 5th Floor, S-14157, Huddinge, and Stockholm Sjukhem Foundation, Box 12230, S-10226 Stockholm, Sweden

Keywords:
neural progenitor cells
stem cells
cell therapy
transplantation
nervous system lesions
neurodegenerative disease

Various immature cells can be isolated from human embryonic and fetal central nervous system (CNS) residual tissue and potentially be used in cell therapy for a number of neurological diseases and CNS insults. Transplantation of neural stem and progenitor cells is essential for replacing lost cells, particularly in the CNS with very limited endogenous regenerative capacity. However, while dopamine released from transplanted cells can substitute the lost dopamine neurons in the experimental models of Parkinson's disease, stem and progenitor cells primarily have a neuroprotective effect, probably through the release of trophic factors. Understanding the therapeutic effects of transplanted cells is crucial to determine the design of clinical trials.

During the last few years, a number of clinical trials for CNS diseases and insults such as amyotrophic lateral sclerosis (ALS), stroke, and spinal cord trauma using neural progenitor cells have been initiated. Data from these early studies will provide vital information on the safety of transplanting these cells, which still is a major concern. That the beneficial results observed in experimental models also can be repeated in the clinical setting is highly hoped for.

* Corresponding author. Division of Neurodegeneration, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Novum 5th Floor, S-14157, Huddinge, and Stockholm Sjukhem Foundation, Box 12230, S-10226 Stockholm, Sweden.
E-mail address: erik.sundstrom@ki.se (E. Sundström).

http://dx.doi.org/10.1016/j.bpobgyn.2015.11.020
1521-6934/

Human neural progenitor cells

Human first trimester embryonic and fetal tissue, retrieved from elective routine abortions after informed consent, is a source of stem and progenitor cells that may be used in experimental and clinical regenerative medicine as described later. However, there are ethical, practical, and immunological challenges and concerns due to the origin and derivation of these human cells. Human cell therapy application in the laboratory or clinic necessitates adherence to ethical guidelines, evaluation and approval of reproducible and transparent study protocols by regulatory authorities and the regional human ethical committee, biobank regulations, and informed consent from tissue donor and recipient host. A close and stable collaboration between the laboratory and clinic in charge is a prerequisite, including set protocols for collection, dissection, cell culture, and expansion, viral, bacterial, donor cell test batteries, and reporting procedures.

In this study, we will review the usage of neural cells derived from the central nervous system (CNS) in experimental studies for developing treatment approaches for diseases and insults of the CNS, with a particular focus on spinal cord injuries (SCIs). We will discuss a few clinical trials including these cells as treatment, the possible therapeutic effects of transplanted cells, and the immunological aspects of clinical application of cell therapy in the CNS.

Diseases and insults of the CNS

Diseases of the CNS and brain and spinal cord injuries arising from different types of insults have some unique characteristics. Neurons in the CNS may be very large in size; they play a pivotal role in the key functions of the CNS, the input of sensory information, information processing, and output of motor function control (including autonomic functions such as respiration and blood pressure). The primary motor neurons in the human cerebral cortex have axons of length $\geq$1 m. It has been suggested that such features may render neurons susceptible to disease. Small groups of these highly specialized neurons have specific functions. As a consequence, loss of even a rather limited number of cells, for example, after a stroke may result in pronounced neurological symptoms. Neurons lost due to pathological processes will not be replaced by neuron regeneration (see below), with few exceptions. The same limitation probably applies for oligodendrocytes, the cells responsible for the myelination of axons. However, the CNS is also characterized by a high degree of plasticity, and even significant neurological symptoms and deficits often improve for several years after an insult.

An increasing number of studies have shown that neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) represent disease processes that progress during decades, with a slow but steady degeneration of neurons. Eventually, this neuronal loss results in clinical symptoms, especially with the loss of affected neurons, and plasticity and other compensatory mechanisms do not suffice. In the case of PD, loss of 30% of the affected dopamine neurons in the ventral mesencephalon is estimated when symptoms start to occur [1,2]. Postmortem analyses showed a 60–70% reduction of the dopaminergic nerve terminals and the dopamine levels in the innervated caudate nucleus and putamen at this stage [3]; this was later verified in vivo using PET (positron emission tomography) imaging [4]. Due to the late onset of symptoms, the possible time for treatment is limited to a disease stage when most of the affected neural cells are already lost. This could change if presymptomatic patients could be identified with biomarkers and imaging techniques. At present, identification of presymptomatic patients with AD, PD, and ALS is practically possible only among members of families with known inherited variants of these disorders, typically only a few percent of the patients.

Another important aspect of neurodegenerative disorders is that although the degeneration may be limited to a small population of neurons at the early stages of disease, a more extensive degeneration often occurs at later stages. The involvement of different types of neurons in several locations has obvious implications for the possible strategies for cell therapy in these diseases. In AD, loss of cholinergic neurons in the subcortical forebrain is an early pathological change associated with the loss of spatial memory, but global brain atrophy always occurs as the disease progresses. During the first years of disease, PD patients mainly suffer from symptoms caused by the loss of dopamine neurons in the substantia nigra and often develop symptoms of dementia associated with cortical atrophy [5]. ALS