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How to use stem cells for repair in stroke patients

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ABSTRACT

Regenerative cell therapy is a promising therapeutic strategy in neurology, most notably to improve stroke recovery. Although tolerability and feasibility have apparently been validated, many questions remain as to what is the best type of cells to use, the best route and the post-stroke delay for administration. Two main strategies have currently emerged: intravenous injection of mesenchymal stem cells with systemic trophic support; and intracerebral grafting of neural stem cells with brain repair effects at the lesion site. Multicenter clinical trials have just begun and are starting to assess the efficacy of these treatments on functional recovery. However, experimental studies also need to be conducted in parallel to precisely identify the mechanisms of action regarding the pathophysiology of brain plasticity, notably when stroke occurs with comorbidities. Such studies should also evaluate the potential of cell grafting combined with injectable biomaterials.

1. Introduction

Stroke affects approximately six million people in the European Union (EU), with 1.1 million new cases every year. The stroke burden is expected to increase due to aging of the population and diabetes. Thus, interventions to alleviate residual post-stroke impairment are urgently needed. Current treatment options are limited to intravenous (IV) thrombolysis by alteplase within 4.5 h, thrombectomy, aspirin within 48 h, decompressive craniectomy for large strokes, and management in stroke care units for intensive care and rehabilitation. Yet, while thrombolysis together with improved acute care has decreased mortality, surviving patients are often left with sensorimotor and cognitive disability. Despite spontaneous recovery, more than 60 % of stroke patients have residual impairment, causing a huge burden on patients, their relatives and society in general. Thus, effective treatments beyond prevention and acute care are urgently needed. However, this requires a sophisticated understanding of stroke pathophysiology. It is well known that stroke effects are not limited to neurons, but involve both brain cells and the surrounding extracellular matrix in a ''glioneurovascular niche'' that interacts with the peripheral immune system. For these reasons, new therapies, such as cell therapies (for review and bibliography, see Detante et al. [1]), should target all of these systems, rather than only individual damage processes, to perhaps avoid the failures of past clinical translational attempts to develop specific neuroprotection.

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2. Pathophysiology of brain repair and plasticity

Early after stroke and in addition to possible reperfusion via collateral arteries or fibrinolysis, several endogenous protective mechanisms are spontaneously engaged. The adult brain has a capacity for self-repair that often results in re-emergence of childhood organizational patterns. During stroke recovery and beyond phenomena related to adaptive functional compensation, there is ''structural'' brain plasticity [2,3] based on the participation of surviving tissue in the reorganization of damaged networks, including synaptogenesis with axonal sprouting that may persist for several months. This form of post-stroke plasticity is notably seen in elderly human brains [4]. Stroke also increases neurogenesis from neural stem cells (NSCs) of the subventricular zone (SVZ) and hippocampal dentate gyrus, generating neuroblasts that migrate to the lesion and differentiate into mature neurons. This post-stroke neurogenesis is closely linked to angio- and vasculogenesis and glial function, leading to the concept of a glioneurovascular niche [5] as a favorable ''stem cell niche''. For several months following stroke, neuroblasts from the SVZ migrate close to vessels through an area exhibiting early vascular remodelling [6] stimulated by the release of neurotrophic factors, such as angiopoietin 1 (Ang1), stromal-derived factor (SDF1), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and metalloproteases. Neuroblasts also enhance angiogenesis with the release of VEGF [7], a relationship underlining the bi-directional link between microvascular and neuronal remodelling. In addition, glial cells play a key role during post-stroke recovery, with astrocytes removing excitatory neurotransmitters (glutamate) and K^+, thereby limiting excitotoxic damage. Astrocytes also modulate synaptogenesis by enhancing the formation of functional synapses [8]. Furthermore, oligodendrocyte progenitors resident in white matter or derived from SVZ NSCs differentiate after stroke into mature oligodendrocytes, thereby enabling axonal remyelination and contributing to brain repair processes [9]. Microglia contribute to this post-stroke remodelling process, acting to modulate inflammation, and also to encourage synaptogenesis and neurite outgrowth by releasing trophic factors such as BDNF [10].

Although the effects of these complex processes comprising post-stroke plasticity are reinforced by rehabilitation, post-stroke neurogenesis from endogenous NSCs is relatively weak and many new neurons die, often resulting in incomplete functional recovery. Thus, a deeper understanding of how post-stroke brain remodelling is affected by the integration of neurons into their ''gliovascular'' microenvironment is crucial for developing more effective regenerative therapies.

3. Cell therapy in stroke: stem cells for regenerative medicine

A promising approach in the treatment of stroke is activation of the brain repair mechanisms and enhancement of spontaneous functional recovery. The major advantage of such restorative therapies is the extension of the therapeutic time window to up to several weeks or months after the initial insult. Cell-based restorative therapies have emerged as particularly attractive approaches. Transplanted cells, which are examples of ''plastic'' biological products, can adapt to different local conditions in damaged brain tissue while not being limited to a specific target. This means they can act in a wide range of endogenous protective and brain repair processes, including immunomodulation, and neuronal, vascular and glial remodelling. Traditionally, two main treatment strategies are recognized: paracrine trophic support using ''peripheral'' stem or stromal cells; and direct neural replacement using neural stem/progenitor cells or mature cells such as neurons. However, the route, dose and timing of such cell administration after stroke remains subjects of debate, depending on the chosen cell product and expected therapeutic effect.

4. Cell sources

These repair cells can be sorted by their adult, fetal (extraembryonic) or cell-culture origin in vitro. While adult sources, such as bone marrow, are widely used in clinical trials, adipose tissue containing mesenchymal stromal/stem cells (adipose-derived stem cells [ADSCs]), peripheral blood, olfactory mucosa, menstrual blood, brain tissue, breast milk and dental tissue are all interesting alternatives for reparative therapy. Fetal sources, such as umbilical cord, are relatively easy to collect for banking, and can provide cell products for stroke therapy from either the cord itself (Wharton's jelly) or from cord blood samples. Placental, amniotic fluid and fetal brain samples, including striatal and first-trimester cerebral cortex, are already used as cell sources in current clinical trials, and sources in vitro, such as NSCs and neural cell cultures, have already been used in clinics. From cultures in vitro, pluripotent cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) from adult tissue cannot be directly used due to their associated high tumorigenic risk. However, as sources, ESCs and iPSCs can be expanded over many passages, thereby providing a virtually unlimited supply of multipotent and mature derived cells appropriate for cell therapy.

5. Cell therapy products

Products harvested from these different cell sources can be used for xenogenic, allogeneic and autologous treatments. Three main therapeutic cell categories can be distinguished:

- mesoderm-derived stromal or stem cells;
- ectoderm-derived neural stem/progenitor cells;
- hematopoietic/endothelial stem cells.

Stromal/stem cells isolated from bone marrow, umbilical cord or blood and ADSCs are widely used in cell-therapy trials for stroke.

Mesenchymal stem cells (MSCs) and multipotent adult progenitor cells (MAPCs) [11] can also be used under allogeneic conditions without immunosuppressant drugs owing to their

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