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Review Article

Cell-Based therapy for traumatic brain injury

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Abstract

Traumatic brain injury is a major economic burden to hospitals in terms of emergency department visits, hospitalizations, and utilization of intensive care units. Current guidelines for the management of severe traumatic brain injuries are primarily supportive, with an emphasis on surveillance (i.e. intracranial pressure) and preventive measures to reduce morbidity and mortality. There are no direct effective therapies available. Over the last fifteen years, pre-clinical studies in regenerative medicine utilizing cell-based therapy have generated enthusiasm as a possible treatment option for traumatic brain injury. In these studies, stem cells and progenitor cells were shown to migrate into the injured brain and proliferate, exerting protective effects through possible cell replacement, gene and protein transfer, and release of anti-inflammatory and growth factors. In this work, we reviewed the pathophysiological mechanisms of traumatic brain injury, the biological rationale for using stem cells and progenitor cells, and the results of clinical trials using cell-based therapy for traumatic brain injury. Although the benefits of cell-based therapy have been clearly demonstrated in pre-clinical studies, some questions remain regarding the biological mechanisms of repair and safety, dose, route and timing of cell delivery, which ultimately will determine its optimal clinical use.

Key words: cell-based therapy; stem cells; traumatic brain injury

Editor's key points

- The authors review the mechanisms of traumatic brain injury and the potential place for the use of cell-based therapies.
- They conclude that there is a clear potential for benefit, but substantial work remains in optimising cell-based therapy.

In the United States between 2001 and 2010, severe traumatic brain injury (TBI) was responsible for up to 2 200 000 emergency department visits, 300 000 hospitalizations and 55 000 deaths each year. Traumatic brain injuries contributed to 30% of all injury-related deaths in the USA. Their economic burden, including direct medical and indirect costs, was estimated in 2010 to be approximately $76 billion dollars.[1] In 2007, the Brain Trauma Foundation and the American Association of Neurological Surgeons published the third edition of evidence-based guidelines for the management of severe TBI.[2]

However, because of the severe morbidity and mortality associated with TBI, innovative therapies are needed. Based on promising pre-clinical studies and a few completed clinical trials, cell-based therapy may be such a new, innovative, therapeutic approach. In this review, we describe the pathophysiology of TBI and give a comprehensive overview of the pre-clinical studies on the use of cell-based therapy for TBI. We present the different

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cell types used for treatment, their main biological basis of action, the various animal models utilized, and outline the main results. We also discuss the few published and ongoing clinical trials. This review was created by searching PubMed for relevant studies, considering the following MeSH terms: stem cell, cell-based therapy, and traumatic brain injury, from the first published studies on this topic in 2000 until 2014, and examining the clinicaltrial.gov database and major published reviews. Of 896 articles initially selected, we eliminated articles not directly focused on brain trauma or cell-based therapy and finally reviewed 89 articles, among which, 68 were pre-clinical studies.

Pathophysiology of traumatic brain injury

Time dependent injury, neuronal loss and the inflammatory micro-environment

TBI can result from direct impact or from extreme acceleration-deceleration and rotational forces. The injury evolves over two phases. The primary phase corresponds to immediate damage to the central nervous system with massive depolarization of brain cellular components, resulting in a major release of inflammatory neurotransmitters, inducing monocyte/macrophage-mediated phagocytosis and complement-mediated cytolysis, and diffuse neuronal dysfunction.[3] Initial forces can also disrupt the blood brain barrier, further aggravated by early expression of high concentrations of glucose transporter-1 and synthesis and release of nitric oxide.[4] Consequently, the resulting cerebral haemorrhage and oedema can increase intracranial pressure and lead to cerebral ischaemia. The secondary phase starts a few hours after the injury and can last several days. It is mostly characterized by an intracellular influx of calcium, free radical generation with lipid peroxidation, and mitochondrial dysfunction,[4] leading to apoptosis and necrosis of neuronal cells.

The neuronal loss after TBI is both focal and diffuse as a consequence of the primary and secondary phases of the injury. The hippocampus is especially vulnerable to the neuronal loss, even in the absence of elevated intracranial pressure,[5] explaining why many studies have been interested in this cerebral region. Apoptotic neurones have been observed in the hippocampus even up to 12 months after TBI, correlating with memory impairment both in animal models and humans.[6] TBI is responsible for an acute inflammatory environment, with monocyte/macrophage-mediated phagocytosis and complement-mediated cytolysis, which can persist several weeks after the injury.[7] Although TBI can up-regulate neuronal growth factor (NGF) and brain derived neurotrophic factor (BDNF) and down-regulate neurotrophin-3, this inflammatory environment may impede the function of endogenous stem cells in repair.[8]

Neurogenesis and angiogenesis

Neurogenesis and angiogenesis are stimulated after TBI. After a short proliferation phase, neural stem cells (NSC) migrate from the sub-ventricular zone (SVZ) to the site of injury and differentiate into neuronal and glial cells, stimulated by growth factors released by endothelial cells (Fig. 1). In animal models, the ipsilateral SVZ proliferation increases two to four-fold after TBI, while contralateral SVZ proliferation increases to a lesser extent.[9] Also, active angiogenesis has been observed three days after an ischaemic insult. Nevertheless, even if neuroblasts have been shown to migrate to areas of injury, their ability to replace neuronal loss is uncertain.[9] Furthermore, the reparative mechanisms are often overwhelmed by the resulting inflammatory neurotransmitters, cerebral haemorrhage and oedema after TBI. Multiple investigators have studied the effect of various stem and progenitor cells as therapy in this injury environment, to minimize the severity of TBI.

Pre-clinical studies using stem and progenitor cells as treatment for traumatic brain injury

Reported mechanisms of action

Various cell types have been used as potential therapy for TBI: mesenchymal stem cells (MSC), NSCs, neural progenitor cells (NPC), NTera2 (NT2) cells, embryonic stem cells, multipotent adult progenitor cells, and endothelial progenitor cells (Supplementary Table). Currently, several different mechanisms of action have been postulated to explain the therapeutic effects of transplanted stem and progenitor cells delivered after TBI (Fig. 2). The promotion of cell replacement by the differentiation of NSCs and MSCs was first hypothesized to be an essential mechanism of action of stem and progenitor cells after TBI.[10 11] But our current knowledge suggests that improvements after TBI may essentially result from paracrine and systemic effects, via the secretion of chemokine and growth factors,[12–14] decreasing oedema and inflammation caused by TBI, and enhancing endogenous neurogenesis, angiogenesis and vasculogenesis.[15] Stem and progenitor cells may also stabilize damage cells via gene and protein transfer, by inter-cellular contact or fusion,[16] and may develop pathways between the SVZ and the site of injury by a 'biobridge,' enhancing the migration of host neurogenic cells.[17]

Mesenchymal stem cells

Cells origin, dose, and potency

MSCs were the most frequently used stem cells for therapy in experimental TBI (Supplementary Table). Previously, cell-based therapy with MSCs was shown to be safe clinically, when administered in patients with various acute organ injury such as myocardial infarction, acute kidney injury, stroke, etc.[18] For pre-clinical studies in TBI, MSCs were mainly isolated from rat and human bone marrow,[19 20] but were also isolated from human umbilical cord,[21] rat and human adipose tissue,[22 23] and human amniotic membrane.[24] No study compared the effects of MSCs on TBI according to their site of isolation (i.e. bone marrow, adipose tissue, placenta). The primary mechanism of action proposed initially was the ability of MSCs to differentiate into neural cells, but there is little evidence that these cells can transform into functional neurones.[25 26] Most mechanistic studies now deal with the ability of MSC to secrete paracrine soluble factors, which stabilize the endothelium preventing excessive permeability and suppress cells of the innate and adaptive immune system.

The administration dose of MSCs used in experimental TBI models in rodents varied from 1.5×10^5 [27] to 2×10^7 [28] cells per kg body weight, with the average dose being mostly between 10^6 and 10^7. Lower doses were reserved for stereotactic injection,[14 17 21 24 27] or internal carotid artery,[29] or lateral ventricle[30 31] delivery. In studies with i.v. administration, higher cell dose was associated with higher cell survival rate, but without better functional improvement.[32 33]

Transplanted MSCs were cultured without growth factors in the large majority of pre-clinical studies. However, some groups cultured MSCs with NGF and BDNF[23 34 35] or epidermal growth factor (EGF) and fibroblast growth factor (FGF)-2.[21 24] NGF and BDNF increased the survival rate and the microtubule-associated