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Authors

Koliatsos, Vassilis E
Xu, Leyan
Cummings, Brian J

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Stem cell therapies for traumatic brain injury

Vassilis E. Koliatsos[1, 2, 3*], Leyan Xu[1], Brian J. Cummings[4]

[1]Department of Pathology, Division of Neuropathology, [2]Department of Neurology, [3]Department

of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine,

Baltimore, MD USA; [4]Departments of Physical and Medical Rehabilitation, Neurological

Surgery, and Anatomy and Neurobiology, Sue and Bill Gross Stem Cell Research Center,

University of California at Irvine, Irvine, CA, USA

* To whom correspondence should be addressed

The clinical problem

Traumatic brain injury (TBI) is a common problem with unmet therapeutic needs. In the US alone, there are 2-3 million new TBI cases requiring medical attention annually, most of them from falls, strike by/against an object, or motor vehicle crashes. Although most cases of TBI are concussions that usually resolve over a few weeks, a great number of patients will suffer chronic disability from TBI-associated encephalopathies. The prevalence of this chronic TBI is on the order of several millions. TBI-associated encephalopathies are usually caused by focal contusions usually related to low-impact falls and diffuse axonal injury (DAI) from ultra-fast loading of axons due to rotational acceleration in the course of motor vehicle crashes and other scenarios. Focal contusions are impact injuries featured by intraparenchymal hemorrhage with edema and ischemia in the inferior frontal and temporopolar regions leading to neuronal cell death and secondary axonal degeneration. DAI is an impulse injury associated with dynamic loading of axons and represents the commonest neuropathology across TBI cause and degree of severity. DAI evolves over hours-days, often leading to axotomy and disconnection at multiple CNS sites. Clinical problems caused by traumatic contusions and DAI have no satisfactory treatments besides symptomatic alleviation with physical/occupational/speech-language therapy and the empirical use of CNS-acting drugs. Clinical trials of small molecules have been unsuccessful (1). Inspired by some earlier success in models of ischemic brain injury, stem cell transplantation has shown some preclinical efficacy, primarily in models of focal TBI. However a number of limitations, including wide variance in transplanted cells and reported outcomes make it difficult to draw general conclusions at this time.

Stem cells from bench to bedside

Recent discoveries of the ability of exogenous neural stem cells to successfully incorporate into neural parenchyma (2) have refuted earlier conceptualizations of the mature nervous system as unfavorable to ongoing developmental events. It is now evident that neural stem cells and their more mature neuronal and oligodendrocyte precursor progenies can differentiate, survive

transplantation in the adult CNS, and integrate within the host nervous system (3). Neural stem cells used in preclinical transplantation scenarios were derived from fetal neural tissue, embryonic stem cells, or somatic cells induced to pluripotency with specific transcription factors. Scaling up for treatment of large numbers of patients is particularly challenging for fetal cells; such sources have limited expansion capacity and regulatory agencies require independent safety data for each new source. Embryonic stem cells and induced pluripotent stem cell sources are theoretically inexhaustible and extremely pliable and have been induced to a large number of neuronal or glial fates including motor (4) and dopaminergic (5) neurons as well as oligodendrocytes (6). Work with spinal cord-derived human neural stem cells in models of spinal cord injury and amyotrophic lateral sclerosis was instrumental in the initiation of pioneering clinical trials in motor neuron disease (NCT01348451, NCT01730716) and spinal cord injury (NCT01772810). Although it is too early to know the outcomes, these were landmark developments in regenerative neuroscience and are already followed by early trials in other neurological disorders. The therapeutic effects of neural stem cells in these conditions is presumambly due to a combination of synaptic physiological actions and the synaptic release of neuroprotective molecules (7). In an interesting turn of events, regenerative medicine based on stem cells may look more and more like regenerative medicine based on neurotrophins and trophic cytokines in the 90s, perhaps with the added benefit that stem cells can presumably produce these molecules indefinitely (*Fig. 1*).

Preclinical modeling of TBI

The last twenty-plus years have seen considerable efforts in modeling TBI by cause or mechanism. These models are usually classified into focal and diffuse. Focal models include the weight drop, controlled cortical impact injury, and midline fluid percussion injury. Diffuse models are produced via inertial or impact acceleration. Modifications of fluid percussion injury have both focal and diffuse elements. These models have not been adequately tested in nude rats or scid mice, i.e. subjects appropriate for stem cell transplantation, but this need has begun to be addressed in more recent studies. Controlled cortical impact and impact acceleration models offer complementary opportunities for regenerative medicine: the former is a primary contusional injury with secondary axonal degeneration, whereas the latter is a model of DAI with secondary effects on neurons. Based on paradigms worked out in spinal cord injury, the previous models can be used to optimize neuronal- versus oligodendrocyte-based cell therapies: Neuronal precursor transplants may be best optimized in models like controlled cortical impact, whereas oligodendrocyte precursor transplants may be best worked out in models of DAI. This contention does not imply that contusions are best treated with neuronal and DAI with oligodendrocyte precursor transplants. As in the case of spinal cord injury, both neurons and oligodendrocytes may need to be replaced and a mixed transplantation approach would probably work best in clinical TBI scenarios (8).

Stem cell transplantation as experimental therapy for TBI

Because of the complexity of TBI and its animal models, there is a need to identify specific repair targets based on key pathological mechanisms. Repair tasks include replacing dead neurons, supporting injured neurons, and protecting axons or assisting with axonal repair and regeneration (*Fig. 2*). Neuronal degeneration or death is encountered in both focal injury and in

the course of DAI. Neuronal cell death in focal TBI is acute with necrotic components, whereas in DAI it is slow with apoptotic features and may be associated with retrograde and transsynaptic effects. Although axonal repair/remyelination as a therapeutic target separate from neuronal regeneration is best established in spinal cord injury, demyelination may also contribute to degeneration of axons in DAI (9). Therefore, transplanting exogenous oligodendrocyte precursors in the case of DAI may assist in remyelination and prevent axonal degeneration and disconnection within brain circuits.

A growing number of studies with systemically administered stem cells may disclose novel mechanisms of neural injury and repair. Cells typically used in this approach are derived from bone marrow and include mesenchymal, multipotent adult, and mononuclear stem cells. Bone marrow-derived stem cells are easy to access, require simple or no manipulation, and have no attached immune rejection concerns if they are patient derived. Mononuclear cells have already entered several clinical trials: these cells are relatively small and hence not trapped in the lungs (first pass effect) after i.v. administration, whereas less than 4% of i.v. injected mesenchymal cells reaches arterial circulation (10). Bone marrow-derived cells have shown both biological and behavioral efficacy, primarily in stroke models. Because of questionable penetration into brain, one of the proposed mechanisms for therapeutic effects of these cells is the modulation of immune response (10), rather than integration in the host CNS. Consistent with this view, there is growing evidence for the role of spleen as a modulatory organ in neural injury, sometimes with impressive effects on neurodegenerative outcomes (11). The presumed trophic effects of systemically delivered bone marrow cells require further clarification. One study that has shown good blood-brain barrier penetration in controlled cortical impact injury also found an increase in levels of NGF, BDNF, NT-3, and VEGF in brain (12), whereas other studies have shown poor penetration (13). This discrepancy may be due to first-pass effects of different bone marrow cells or the particulars of experimental models. At any rate, it is unclear how trophic effects can be induced if these cells don't cross the blood-brain barrier (14).

Although administration of stem cells within lesions or i.v. in models of TBI and stroke is common, intrathecal or intraventricular delivery is also being used with some biological and functional benefits. The potential of such strategies, especially the intraventricular route, for diffuse or multifocal effects may be greater compared to that of intraparenchymal strategies, especially if stem cells can be enticed to migrate to the lesion sites and differentiate into neural cells (15). However, the consistency and comparative advantages of such effects are far from established.

The outcomes of preclinical testing of stem cells in various models of TBI have been reviewed by one of us (BJC) elsewhere (16) and a meta-analysis is in review. Positive effects were observed in most studies, with a small mean effect size that was more pronounced with modified or "enhanced" cells. Not surprisingly, transplantation within the lesion (for focal TBI) had a larger effect size than i.v. or ventricular delivery. Unfortunately, many of these studies have methodological problems. In addition, there is as yet no common standard for the assessment of outcome measures. Furthermore, a synthesis of studies using different cell populations is extremely difficult. Also, the majority of TBI studies using human stem cell do not quantify cell survival, thus clouding our understanding of potential mechanisms of action. Although

transplanted stem cell preparations such as neuronal precursors are fully capable of forming mature synapses with host structures in the brain and spinal cord (17), the physiological status of these synapses and their specific role in restoring function has not been characterized. Functionality of regenerated synapses is important not only for the purpose of conveying appropriate physiological signals, but also for transsynaptic trophic support. The application of optogenetic strategies may prove critical in solving this problem (18).

Special considerations for focal TBI and DAI

The vast majority of published stem cell experiments in TBI are on focal models: about half of published studies used some form of controlled cortical impact, and most of the rest are equally split between weight drop and fluid percussion. For reasons explained in the previous paragraph, the field is clearly behind stroke and spinal cord injury and results are difficult to synthesize. As in the field of stroke, although a variety of benefits have been reported, integration with the host has not been demonstrated. Also unresolved are the questions of optimal dosing and dose scaling to man; this is a tricky issue because, at least based on our experience on spinal cord injury, dose escalation alters the dynamics of engraftment, migration, and fate (19). Even less can be said about stem cell therapies for models of DAI, although the field can borrow from spinal cord injury that invariably involves trauma in axonal tracts. In contrast to spinal cord injury, where axons course in restricted areas, DAI involves disparate axon tracts that would be difficult to transplant at the same time. Therefore, in the case of DAI, the choice of transplantation route (systemic, ventricular, or parenchymal) and location of transplant (if we select parenchymal delivery) are critical. The selection of parenchymal sites for transplantation should be guided by factors such as concentration of axonal pathology or the importance of a specific DAI site for critical symptoms. A recent study has shown that human oligodendrocyte progenitors can survive and differentiate in experimental models of DAI. In sharp contrast to neuronal progenitors, oligodendrocyte progenitor cells do not colonize and differentiate locally but rather migrate massively along white matter tracts and remain within the white matter, often ensheathing themselves around host axons (20).

Conclusions

After multiple failures in clinical trials of single and combination agents, TBI is in dire need for effective treatments. The nature of some of the key lesions invites the consideration of the toolkit of regenerative medicine, including stem cell transplants. Important advancements in preclinical stem cell therapeutics and the popularity of TBI models create unprecedented opportunities for discoveries that may push this stalled field forward. Although there is no lack of interesting data and positive studies, a great disparity in models, cell preparations, and reported outcomes detract from an enthusiastic endorsement of stem-cell therapeutics for TBI at this time. Consortia to establish better guidelines for TBI modeling and NIH funding initiatives for collaborative and replication platforms are urgently needed: it makes no sense to fund more original research that will make little difference in and of itself and would be difficult to replicate or integrate with other studies. Beginning trials with infusions of bone marrow-derived stem cells and an

increasing recognition of the role of systemic factors in TBI outcomes are encouraging developments. In the course of experimenting with stem cell therapeutics, one of the greatest promises is the discovery of physiological molecular signals that afford protection or promote recovery in the adult brain.

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LEGENDS

Figure 1. The progression from trophic factor therapies in the 1990s (left) to stem cell therapies in the 2000s (right) and now to the realization that part of stem cell efficacy may be mediated via release and transduction of trophic signals targeted and amplified via synaptic contacts (bottom).

Figure 2. Sketch of repair targets for stem-cell based therapies in TBI. In upper panel, neuronal precursors support injured neurons (1) or, after they differentiate into nerve cells, they replace dead neurons (2). In lower panel, transplanted oligodendrocyte precursors support injured axons and prevent their degeneration (1) or facilitate the growth and maturation of axon sprouts (2). Immune signals related to systemically delivered bone marrow cells are not included.