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EDITORIAL

Recent Advances in Stem Cell-Based Therapeutics for Stroke

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Regenerative Medicine Circumvents Short Therapeutic Window of Stroke

Regenerative medicine has advanced the efficacy of exogenous and endogenous stem cells in restoring central nervous system disorders (CNS) in the aged and diseased brain [1–3]. Stem cell therapy has been examined in numerous neurological disorders, with highly encouraging results suggesting its indication as a stroke treatment [4–6]. In this regard, despite the availability of the thrombolytic agent tissue plasminogen activator (tPA) for stroke, its narrow therapeutic window and associated adverse events have not resolved the disease stigma as a major cause of mortality and morbidity around the world. Because stem cell therapy targets the subacute and chronic phases of stroke, thereby significantly extending the effective time of intervention, many patients are likely to benefit from this treatment. Several types of transplantable cells have been tested in the laboratory, with a few reaching clinical trials for cell therapy in stroke, including fetal cells, NT2N cells, CTX0E3, embryonic stem cells, neural stem/progenitor cells, umbilical cord blood, amnion, adipose, and induced pluripotent stem cells [7–12]. Primarily, due to solid safety profile in other disease indications, preclinical studies and ongoing clinical trials have given special attention to bone marrow and its cellular derivatives [13, 14]. Direct intracerebral implantation and peripheral transplantation, such as intravenous, intra-arterial, and intranasal, have documented the functional benefits of bone marrow-derived stem cells [13, 15–18]. Clinical trials have been initiated, and preliminary reports have demonstrated safety, although efficacy warrants additional investigations [14]. Here, we discuss the various sources and profiles of stem cells, with particular interest in the adult tissue-derived mesenchymal stem cells, their use in cell transplantation, translational challenges, and putative need for adjunctive therapies. Finally, we reflect on the current societal views that stem cell therapy in general has provoked in the public domain. Our goal is to assess the science behind regenerative medicine in an effort to advance the safe, effective, and mechanism-based application of cell therapy for stroke.

So Many Choices, but We Need to Identify the Best Stem Cell

Among the several factors such as cell route, dose, and timing of administration, the specific type of stem cells is key to the outcome of cell transplantation [19–21]. From the initial study of fetal cell transplantation into stroke animals, varying levels of histological and behavioral recovery have been demonstrated in NT2N, CTX0E3, embryonic stem cells, hematopoietic stem cells, neural stem cells, adult tissue-derived stem cells, and induced pluripotent stem cells [7–11, 22]. The quest for the optimal cell type for transplantation therapy has largely been dictated by ethical and logistical issues [23, 24]. Fetal and embryonic cells have been primarily hampered by the ethics governing their isolation, while the generation of an ample supply of cells that truly recapitulate "stemness" has been the logistical challenge for the other cell types. Because of the adult tissue origin and the resemblance with many of the stem cell phenotypic features, bone marrow-derived stem cells have emerged as leading transplantable cell type for CNS disorders,

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including stroke [25]. Specialized subsets or populations, as well as engineered stem/progenitor cells, have been derived from the bone marrow, including mesenchymal stem or stromal cells (MSCs), endothelial progenitor cells (EPCs), SB623, multipotent adult progenitor cells (MAPCs), multilineage-differentiating stress enduring (Muse), among many others [26–30]. Among these bone marrow-derived cells, MSCs have been extensively studied in stroke animal models. MSCs have been shown to exhibit adult multipotency characteristics, capable of differentiation toward various cell lineages both in vitro and in vivo [13, 16, 31–34]. Following their transplantation in stroke models, MSCs produced functional recovery, including reduction in brain damage and improvement of motor and cognitive performance [35]. Postulated mechanisms of action include cell replacement, growth factor secretion, and promotion of endogenous brain repair processes, including neurogenesis, angiogenesis, and synaptogenesis, which are triggered by the grafted MSCs themselves or their secreted factors or exosomes [36–40]. Although stem cells are considered biologics, assessment of their clinical applications seemed initially influenced by the ligand-receptor mechanism usually ascribed to drugs. Accordingly, a reductionist single regenerative pathway accompanied the quest for determining the mode of action underlying cell therapy for stroke. However, we now recognize the multipronged cell death processes that plague stroke that likely will be best sequestered by the stem cells' multiple regenerative functions [41–43]. This complexity of the disease process will also necessitate not a stand-alone cell therapy, but a combination of therapies, including potent drugs and biomaterials which in tandem may facilitate the functional outcomes of stem cell-based therapeutics (to be discussed in detail below).

The Jury Has Partially Spoken: MSCs Are Safe, but Their Efficacy Remains Inconclusive

Intravenous administration of autologous MSCs has been tested in limited clinical trials. Improvements in neurological outcomes, including Barthel index and Rankin scale, were noted following delayed (initial infusion at 4 weeks after disease onset) autologous transplantation of 100 million MSCs (SH-2 and SH-4 positive) in five stroke patients, although the functional benefits appeared to wane by 12 months post-transplantation [44]. No adverse events were observed in this randomized trial [44]. A similar autologous intravenous bone marrow transplantation, but this time using 7–10 million mononuclear cells (MNCs) per kilogram delivered acutely (24 and 72 h after stroke), produced more robust improvements in Barthel index, modified Rankin scale, and National Institutes of Health Stroke Scale (NIHSS) over a 6-month period in many of the transplanted patients [45]. No adverse events were also reported in this open-labeled study [45]. Building upon this initial bone marrow-derived MNC stroke trial, a phase II, multicenter, parallel group, randomized trial with blinded outcome assessment that included 120 patients was conducted in India [15]. Results revealed that stroke patients (n = 58) who received a mean of 280.75 million MNCs at median of 18.5 days after stroke onset did not differ in the Barthel index score, modified Rankin scale shift analysis, NIHSS score, or infarct volume compared to non-transplanted stroke patients at 6-month post-transplantation [15]. This randomized study showed that intravenous transplantation MNCs is safe but not effective for subacute stroke. A smaller population of bone marrow MNCs which are CD34+ was the basis of another stroke trial that involved intra-arterial delivery of 100 million autologous, immunoselected CD34+ stem/progenitor cell in stroke patients (n = 5) presenting within 7 days of onset with severe anterior circulation ischemic stroke (NIHSS score of ≥8) [46]. All transplanted stroke patients exhibited improvements in the modified Rankin scale and NIHSS score, coupled with reductions in lesion volume during a 6-month follow-up period. The procedure was well tolerated in all patients, and no significant treatment-related adverse effects occurred. This open-labeled study revealed that intra-arterial delivery of bone marrow MNC-derived CD34+ cells is safe [46].

A careful review of these clinical trials revealed that transplantation of MSCs and their cellular derivatives (including MNCs) is safe in stroke. However, with small number of patients and the open-labeled approach (except the Prasad study), the efficacy of MSCs in stroke remains to be determined. Further scrutiny of the trials also exposed discrepancies across the trials themselves that limit direct cross-study evaluations. Equally disappointing is the disconnection between the laboratory and clinical transplant regimens. Apparent from these clinical transplant protocols are the differences in donor cells, which as noted in our overarching premise is likely to dictate the functional outcomes of stem cell therapy. Bang and colleagues have used the SH-2 and SH-4 as released criteria of their cells [44], Savitz and collaborators used an extensive panel of antibodies (CD3, CD14, CD16, CD19, CD20, CD34, CD45, CD56, Lin 1, CD133-2) for flow cytometry to define MNCs [45], Prasad and co-workers also used flow cytometry to identify MNCs but focused only on CD34 and CD45 [15], and Banerjee and colleagues used magnetic cell isolation procedure to harvest purified CD34+ cells [46]. Clearly, based on this donor cell starting material alone, comparisons of the outcomes from the four trials will be inconclusive. Moreover, the timing of intervention significantly varied across trials: 4 weeks, days 1–3, 18.5 days, and within 7 days of stroke onset for Bang, Savitz, Prasad, and Banerjee trials, respectively. Additionally, the route of delivery differed, being intravenous route for the Bang, Savitz, and Prasad, and intra-arterial for Banerjee. Compared with

the preclinical studies of many stem cells, MSCs included, the effective dose range of intravenous delivery is about 4 million cells in a 250 g rat which translates to around 840 million cells in a 75 kg human being [47] indicating that the dose these clinical trials utilized are well below the threshold to recognize any efficacy readout. An exception is the Savitz's trial that closely approximated the preclinical cell dose and resulted in many patients showing clinical improvement, although efficacy needs to be cautiously interpreted as this was an open-labeled study. A search of the literature revealed scarce reported studies supporting the characterization of safety, efficacy, and mechanism of action, along the Stem cell Therapeutics as an Emerging Paradigm for Stroke (STEPS) lab-to-clinic translational guidelines [19], for each defined donor type used in each clinical trial except for the Savitz's group. Adherence to the STEPS guidelines of future clinical trials, allowing the science to form the basis of the clinical trial design, is likely to enhance the successful translation of stem cell-based therapeutics for clinical applications.

Cell Therapy: from Standing Alone to Synergic Regenerative Processes

Driving Stem Cells Under the Influence of Drugs

The safety and efficacy of tPA as stroke therapeutics are confined to a relatively small population of ischemic stroke patients because of its narrow therapeutic window, within 4.5 h of stroke onset. Extending this limited effective window for intervention has proven a challenge for many chemicals, peptides, or trophic factors; thus, many pharmaceutical companies have avoided research and development of drugs for stroke. However, two major new breeds of drugs targeting the subacute and chronic phases of the disease appear to revive excitement in drug therapy for stroke, namely biological compounds that enhance neurogenesis/angiogenesis/synaptogenesis and those that abrogate inflammation [48–50]. Among these candidate drugs tested in stroke models, and a few reaching limited clinical trials, are statins [51–53], G-CSF [8, 54, 55], erythropoietin [56–59], candesartan [51, 52], metformin [60, 61], minocycline [62], apurinic/apyrimidinic site-repairing enzyme endonuclease-1 [63], isoxazole-9 [64], arachidonic acid metabolites such as lipoxin A4 [65], and recombinant T cell receptor ligands [66, 67]. Of note, MSCs have been shown to induce both neurogenesis and anti-inflammation [18, 68, 69], suggesting that an additive effects may be achieved by combining MSCs and drugs that act on these two regenerative pathways. Indeed, this stem cell-drug combination therapy has been a recent topic of much interest in cell therapy for stroke [8]. Recent non-pharmacological approaches shown to augment neurogenesis and to dampen inflammation in stroke have involved remote ischemic conditioning [70–75] and localized cerebral hypothermia [76]. Rigorous preclinical studies will be needed to translate combination therapies for clinical applications in stroke.

Cradling Stem Cells in a Microenvironment Conducive for Regeneration

The ischemic brain arising from stroke is characterized by hostile neural tissue that is not conducive for exogenous and endogenous stem cells to survive and to initiate regeneration. The use of hydrogels and other biomaterials in neural tissue regeneration may aid in remodeling the ischemic brain [77]. Acellular extracellular matrix has been shown to stimulate the infiltration of host brain cells while sequestering necrotic debris from the injury. Such hydrogel treatment is capable of promoting an endogenous stem cell-mediated repair response [77] but could also induce a favorable microenvironment for improved survival of exogenous stem cells that could be vital for initiating regeneration of the stroke brain [78]. In particular, hydrogels can serve as scaffolds to support interactions between the host and transplanted tissues, occupy the tissue cavity or necrotic core, and regulate localized delivery of stem cell-secreted therapeutic molecules [77, 79]. This biomaterial modifies the post-stroke microenvironment to become suitable for implantation of exogenous stem cells and also nurtures endogenous stem cells towards creating a niche for neurogenesis [80]. Similar to drugs, the use of biomaterials as an adjunct treatment to cell-based therapeutics will require translational research to find the optimal fabrication that is safe and effective in harnessing regenerative medicine in stroke.

Challenges in Stem Cell Therapy: Missing Controls and Public Perception

Rehabilitation therapy is the standard treatment for stroke survivors [81, 82]. Surprisingly, rehabilitation therapy has been neglected as a control arm for most, if not all, of the preclinical studies and ongoing clinical trials of cell therapy for stroke. In order to fully capture the therapeutic benefits of cell therapy, incorporation of rehabilitation therapy will be paramount in both transplanted stroke animals and patients.

The ascent of stem cell use in science has been accompanied by a public concern about their tissue origin and commercialization [24]. The media has exploited the ethical controversy surrounding the fetal and embryonic origin stem cells, fostering public fear and misperception of commercialization of stem cells that has contributed to medical tourism. A consortium that will convene the layman public with stem cell experts is likely to resolve many concerns about the bioethics of stem cells [23].

Conclusion

The aging and diseased brain can be regenerated. Stem cell therapy for stroke has garnered sufficient scientific evidence to proceed towards limited clinical trials. Solid safety profiles of MSCs in other disease indications make these cells appealing as donor cells for transplantation in stroke. Rigorous preclinical studies further support MSC transplantation in stroke patients. However, preliminary reports from completed and ongoing clinical trials of cell therapy in stroke indicate safety but not efficacy owing in large part to obvious deviations of the clinical protocols from the optimal transplant regimen established in the laboratory. In particular, the current dose in the clinic is at least eightfold lower than the dose observed to be effective in stroke animals. Allowing science to guide the clinical trial design is likely to improve the outcome of cell therapy in stroke. A vis-à-vis comparison between stem cell therapy and rehabilitation therapy, which is the current gold standard of stroke care, will provide stringent assessment of the therapeutic effects of this regenerative medicine. The public concern on the bioethics of stem cells needs to be addressed as we move forward with both laboratory and clinical investigations of cell therapy for stroke.

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Compliance with Ethical Standards

Conflict of Interest CVB received research grants from NIH, NeuralStem, Karyopharm, SanBio Inc. and has patent applications related to stem cell therapy with Athersys Inc. and SanBio Inc. EN declares that she has no conflict of interest.

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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