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Mini Review

One step at a time, stem cell therapy for traumatic brain injury needs two more breakthroughs

Abstract

Traumatic brain injuries often result in disability in survivors. Unresolved inflammation and ongoing neurodegeneration underlies the disability. Human neural stem cells (NSCs) are attractive candidates that can address both issues at once. Despite several preclinical studies and start-up companies over the past two decades, the approach is not yet in the clinic. In this mini review, I present two steps that brought the NSCs from lab to Phase I/II trials and final two breakthroughs that may be necessary to facilitate clinical application.

Keywords: traumatic brain injury, neurodegeneration, human neural stem cells, firearm injury, neuro imaging

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Introduction

Firearm injury is a serious public health problem in the United States (US) costing more than $70-75 billion annually.[1,2] Non-fatal gunshot injuries in the US have increased from 20.5 per 100,000 Americans in 2002 to 23.7 per 100,000 by 2011, mainly due to increased assaults.[3] Despite increasing incidence, timely neurosurgical intervention aided with improved neuro imaging and advances in acute trauma management have lowered the firearm fatality rate.[4–6] Thus, among the estimated 5.3 million people living in the US with traumatic brain injury (TBI)-related disability, the proportion of gun-shot wound survivors has been rising steadily.[3,7–11] Among head injuries, penetrating injuries (PTBI) are associated with the worst outcomes.[12,13] and no effective restorative treatment beyond physical therapy is currently available to mitigate post-TBI disability.[12–14] Therefore, there is an urgent need to explore additional treatment options to address long term TBI related disabilities. Studies with preclinical models have demonstrated that failure of injury-induced regenerative neurogenesis; chronic inflammation and atrophy underlie poor outcomes.[15–17] Loss of neurons and consequent brain atrophy is a consistent neuro pathological finding in TBI survivors and may underlie long-term functional deficits, resulting in reduced executive and integrative capability.[18–20] Human PTBI neuro pathological findings support neuronal and axonal loss with significant brain atrophy.[21] The milestones in neural stem cell (NSC) research were outlined in a review by Gage and Temple, pioneers of the field.[22] NSCs afford the plasticity to generate, repair, and change nervous system function thus are of great interest to basic scientists as well as clinicians. NSCs have not blossomed into a therapeutic as yet and in this article some the issues that underlies the dormancy are discussed. The cell therapy field needed to address four main issues before clinical trials can be started. Firstly, production of the cell therapy candidate under good manufacturing conditions (GMP), second discovery of efficient immunosuppression, third demonstration of therapeutic benefit under controlled conditions. Three decades of basic science has managed to address first two issues.

Step I Cell therapy candidate

Neural stem cells have several characteristics that make them ideal candidates for brain repair, including a relatively high potential for neuronal differentiation.[1,23–25] Several preclinical studies have evaluated the efficacy of rodent neural precursor cells in TBI rodent models.[22,26–30] The culturing NSCs *in vitro* started as an attempt to grow multipotent embryonic cortical tissue (the word neural stem cells was not yet coined) and successfully accomplished in 1989 at the University of Miami.[31] This work evolved when Martin Raff, a Canadian born Boston neurologist decided to move to England and chose to leave the United States (US) than fight in Vietnam War and to pursue immunology.[32] After elucidating the properties of T-cells and B-cells, in a bid to stay on a new research plan was hatched. It was to raise antibodies against cells of the nervous system and use them to distinguish and separate the different cell types so that their development and interactions could be studied, albeit mainly in a culture dish.[32] One his students was Sally Temple, she worked on have a cell-intrinsic mechanism that helps determine when precursor cells should stop dividing and differentiate into oligodendrocytes. She published her work during her brief stop at University of Miami before heading off to Albany, NY from where she still contributes to the NSC field.[22,33] Attempts to identify the growth factors required for culturing these cells was pioneered at NIH under Ron McKay. Initially the group misidentified NGF.[34,35] as a NSC growth factor only to come back later with the right one.[36] This set stage for two companies namely Neural stem Inc., and Stem cells Inc. Both have produced stable cells under good manufacturing practice "GMP standard" conditions, secured FDA approval to use the cells in human clinical trials. In the past decade, Neural stem Inc. had developed NSI-566, an epigenetically expanded bank of NSC derived from 8-week human fetal spinal cord, which is not on the Federal moratorium list for funding.[37] These cells have been subject to extensive preclinical safety testing and characterization, by multiple independent labs with multiple immunosuppression regimens.[38–44] The cells are produced under stable good manufacturing practice "GMP standard" conditions, and have been recently tested in several animal models. They are subject of three ongoing FDA approved clinical trials including a Phase II study for amyotrophic lateral sclerosis (ALS), a trial for ischemic stroke, and a Phase I study for chronic spinal cord injury.[26] As of 2015, a total of 49 ALS patients have received NSI-566 cells. Both the cells and surgery were well tolerated and the ALS studies reported a 47% responder rate with decline in disease progression and improved grip strength. Stem cells inc., on the other hand lost a patent dispute to NSI and recently closed operations.

Step 2 Immunosuppression

Transplantation of the cells conferred benefits such as restoration of injured neuronal morphology[45] and cognitive function.[46] even without immunosuppression. Transient immunosuppression was shown to be sufficient to support engraftment and transplanted derived neurons were reportedly present 6 months post transplantation.[47] However, no data quantifying either engraftment or behavior modification were presented. Such studies were limited by cyclosporine mediated immunosuppression which resulted in persistence of barriers to engraftment and demonstration of effectiveness of the approach.[48–50] The initial optimism was replaced by skepticism if the therapeutic potential of neural stem cells: greater in people's perception than in their brains.[51,52] The US Food and Drug Administration (FDA; Rockville, MD) guidelines on preclinical assessment of cell therapies in the publication "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products".[53,54] A review of literature shows human cell therapy in rat TBI that measure cognitive benefit have not addressed donor cell fate past one-month post-transplantation.[1,55] Further the experts in the field recommended that 8-week survival period prior to assessments would allow sufficient time for differentiation and integration of human neural stem cells with the host and possibly validate the presumed mechanism of action.[1,26] The successful preclinical ALS, SCI and stroke studies.[40,41,44,56] have employed a different immunosuppression technique that was pioneered by Hefferan et al.[40] This technique relies on three agents namely: mycophenylate mofetil, tacrolimus and methyl prednisolone. The combination has been found to be superior to cyclosporine, a standard immunosuppressant between 1999-2012.

Step 3 Mechanism of action

However, due to the lack of exact mechanism of action still precludes attempts to move neural stem cell therapy to the clinic.[26] Paul Lu et al.[41] demonstrated the mechanism of regeneration in spinal cord injury models.[41] Axonal growth was partially dependent on mammalian target of rapamycin (mTOR), but not Nogo signaling. Grafted neurons supported formation of electrophysiological relays across sites of complete spinal transection, resulting in functional recovery. The recovery was lost subsequent to re-transection of the spinal cord. With modern sophisticated methods such as functional connectivity under optogenetic control would provide necessary evidence for mechanism of action.[57]

Step 4 safety

Variety of companies have derived and developed human fetal neural stem cells.[58] Some companies have closed (REF JSRT-16-NWS-125), others made little progress, while Neural stem Inc., has remained viable. However as not NSCs are equal is evident from various outcomes of the transplantations. At least three adverse reaction cases have been reported to date.[59–61] In contrast cells from Stem cells Inc, Neural stem Inc and in an Italian study have been found to be safe.[42,58,62] The difference may be attributed to quality of cells. With unregulated clinical use rampant all over the World,[58,63–66] the research scientists need to heed the advice given by Prof. Knoepfler.[67]

Among the non-neural stem cells from which NSCs have been derived, AMP have exhibited the best neural differentiation potential.[68] Mesenchymal origin neural stem cells (mNSCs) and AMP derived NSCs (AM-NSCs) differentiated, expressed some neural markers, and were associated with cognitive benefits early after transplantation, post-TBI. However, AM-NSCs did not survive in the brain injury site 1 month after transplantation.[69] Few reports have demonstrated integration of such cells into host tissues, thus suggesting this cell type to be a poor candidate for cell replacement.[70–73]

A recent study with athymic rat TBI and hNSCs ~38% of the transplanted cells expressed NeuN.[74] The duration of differentiation of hNSCs into NeuN positive cells is consistent with a published report that showed ~6-8 weeks were sufficient to induce transplant derived neurogenesis.[1,75]

Transplantation of viable fetal neural progenitor cells (as early as 24h post TBI) attenuated host neuronal degeneration (as assessed on day 6 post transplantation), also guided host microglia/macrophages towards an anti-inflammation phenotype indicating that a potentially beneficial effect of progenitor cell transplantation on adjacent host cells.[30,76–78]

In other TBI and stroke models, cells have been delivered via intravenous (IV), intra-arterial carotid (IAC) or intraparenchymal (IP) injections. However, IV administration causes loss of the majority (~95%) of the cells during lung passage,[55,79–81] whereas IAC injection carries the risk of causing embolic brain infarction and fails to deliver sufficient cells across the vascular wall barrier to the brain parenchyma, which is the major barrier for putative clinical use of this route. Engraftment after IAC injection is also dependent on cell type and adhesion molecule expression. IAC has been developed with bone marrow MSCs into a clinical trial for stroke.[82,83] However, in all TBI studies exploring human cell therapies with neural or non-neural origin hNSCs/progenitors no engraftment has yet been detected with either IV or IAC.[84,85] Direct transplantation of hNSCs to replace damaged neural networks may be a viable approach in the treatment of severe TBI. According to "The International Society for Stem Cell Research and Center for Biologics Evaluation and Research/ Office of Cellular, Tissue and Gene Therapies" 54 FDA guidelines, translation of cell transplantation approach in TBI requires evidence supporting: (1) lack of hNSCs tumorigenecity in TBI models, (2) cell dose dependence of behavior alterations in TBI, (3) best site and time for transplantation after TBI, and lastly (4) to establish feasibility, and scalability of the approach to both normal and TBI animals with longer gyrencephalic brains, such as pig or primate.[53,54,86]

Conclusion

In conclusion albeit the NSC holds great promise the final two steps described above hold key to application in the clinic, To help with this The International Society for Stem Cell Research (ISSCR)' has presented its 2016 Guidelines for Stem Cell Research and Clinical Translation. The 2016 guidelines reflect the revision and extension of two past sets of guidelines and demand rigor, oversight, and transparency in all aspects of practice, providing confidence to practitioners and public alike that stem cell science can proceed efficiently and remain responsive to public and patient interests.[87–89]

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Conflict of interest

The author declares no conflict of interest.

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