Mini Review

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Safety of neural stem cell therapy for traumatic brain injury

Abstract

Traumatic brain injuries (TBI) often result in disability in survivors. Unresolved inflammation and ongoing neurodegeneration are thought to underlie injury-induced disability. Central nervous system in mammals is incapable of self-repair and the reasons are poorly understood. Apart from rehabilitation, there is no therapeutic modality to mitigate disability after TBI. Human neural stem cells (NSCs) are attractive candidates as both modulators of inflammation and candidate for cell replacement. One agent to address two goals. Over the past two decades, several preclinical studies at academic institutions and academic-industry partnership clinical trials have contributed significantly to our knowledge base. However, such efforts are not yet relevant in the clinic. While it takes time to bring a preclinical product to clinic, certain members of the community set aside their medical training principles and rush to offer unproven, often hazardous cell therapies to desperate patients. Such behavior is distraction and this article focuses on an impediment to clinical application of human neural stem cells to mitigate TBI effects.

Keywords: traumatic brain injuries, nscs, firearm injury, ptbi, ipsc

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Introduction

Firearm injury is a serious public health problem in the United States (US) costing more than $70-75billion annually.[1,2] Despite increasing incidence, timely neurosurgical intervention aided with improved neuroimaging and advances in acute trauma management have lowered the firearm fatality rate {Joseph, 2014 #42;Lin, 2012 #164;Young, 2008 #56}. Thus, among the estimated 5.3million people living in the US with traumatic brain injury (TBI)-related disability, the proportion of gun-shot wound survivors has been rising steadily.[3–8] Among head injuries, penetrating injuries (PTBI) are associated with the worst outcomes,[9,10] and no effective restorative treatment beyond physical therapy is currently available to mitigate post-TBI disability.[9–11] There is an urgent need to explore additional treatment options to address long-term TBI related disabilities. Since the demonstration of ability to culture, expand human fetal neural stem *in vitro*, their genetic modification and engraftment in rodents post transplantation[12–15] multiple insights into how embryonic transplant derived neurons integrate into adult circuits (Gotz 2016) and technical advances studies have supported clinically relevant studies in immuno compromised or immuno suppressed animal.[16,17] Athymic rats with TBI (Haus 2016), or Parkinson disease (Snyder 2016) have been used with neural stem cells derived from induced human pluripotent stem cells to demonstrate the viability of the approach.

A variety of companies have derived and developed human fetal neural stem cells.[18] Due to lack of uniform standards across the globe and varying extent of regulations of the cell therapy approach adverse reaction cases have been reported to date.[19–21] Additional bad press for autologous stem cells came in 2017[22,23] and the untimely termination of the Pathway Trial.[24,25] In contrast, NSCs from other unrelated sources have been found to be safe.[18,24,26–28] There are big differences between cells that produced tumors and those deemed safe. The tumorigenic potential of cells is highest in embryonic stem (ES) cells and diminishes in its progeny and is lowest in fetal neural stem cells. However, there is a strong focus on inducible pluripotent stem cell (iPSC) derived NSCs due to the obvious advantage that it would be patient's own cells, hence rendering it an autologous intervention that circumvents need for immunosuppression. To lower the tumorigenic potential of iPSCs researchers have taken to thorough neuralization protocols and screening of any undifferentiated ES cells,[29] or pre-treating cells with known anti-cancer drugs such as gamma secretase inhibitors (SfN 2016 Okano Hideyuki). Data presented by Andres Persson at SfN 2016 suggests that astrocytes are the origin of brain tumors.[30] Taken together unlike the proneuronal cultures of fetal week 8-16 NSCs (give rise exclusively to neurons for several weeks post transplantation), the heterogeneity of iPSC or ES cells derived NSCs (give rise to multiple cell types following transplantation) may contribute to their tumor potential. The pretreatment of ES or iPSC derived NSCs with anti cancer drugs may mitigate the tumor incidence from such transplants. Stem cell tourism as defined by CRIM (https://www.cirm.ca.gov/patients/stem-cell-tourism) should be discouraged as the unregulated clinical use of cell therapy rampant all over the World[18,31–34] is yet to provide a cure. The research scientists need to heed the advice given by academic scientist[35,36] and not oversell their findings to lay public/private practices as this often fuels unregulated clinical applications.

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"[37] 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 the establishment of feasibility and scalability of the approach to both normal and TBI animals with longer gyrencephalic brains, such as pigs or primates.[37–39]

Conclusion

In conclusion while the NSC holds great promise, the final two steps described above hold key to application in a clinical setting. To help with this The International Society for Stem Cell Research (ISSCR)' has presented its 2016 Guidelines for Stem Cell Research and Clinical Translation. These guidelines reflect the revision and extension of two previous sets of guidelines and demand rigor, oversight, and transparency in all aspects of practice, providing confidence to practitioners and the public that stem cell science can proceed efficiently and remain responsive to public and patient interests.[40-42]

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Conflict of interest

The author declares no conflict of interest.

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