Stem Cell Reviews and Reports
https://doi.org/10.1007/s12015-021-10222-x

Stem Cells for Aging-Related Disorders

Mia C. Borlongan[1] · Jeffrey Farooq[1] · Nadia Sadanandan[1] · Zhen-Jie Wang[1] · Blaise Cozene[1] · Jea-Young Lee[1] · Gary K. Steinberg[2]

Accepted: 12 July 2021

Abstract
This review captures recent advances in biological and translational research on stem cells. In particular, we discuss new discoveries and concepts regarding stem cell treatment of aging-related disorders. A myriad of stem cell sources exists, from hematopoietic to mesenchymal and neural cell lineages. We examine current applications of exogenous adult bone marrow-derived stem cells as an effective and safe transplantable cell source, as well as the use of electrical stimulation to promote endogenous neurogenesis for Parkinson's disease. We also explore the potential of transplanting exogenous umbilical cord blood cells and mobilizing host resident stem cells in vascular dementia and aging. In addition, we assess the ability of small molecules to recruit resident stem cells in Alzheimer's disease. Finally, we evaluate mechanisms of action recently implicated in stem cell therapy, such as the role of long non-coding RNAs, G-protein coupled receptor 5, and NeuroD1. Our goal is to provide a synopsis of recent milestones regarding the application of stem cells in aging.

Keywords Stem cells · Aging-related disorders · Transplantation · Regenerative medicine

Introduction

Developmental biology and adult neurology have both benefited from the advent of stem cells as a biological platform for studying cell fate and behavior, as well as being a robust biological material for the repair of injured and aging cells. Primarily because of its well-characterized pathological signature of nigrostriatal dopaminergic depletion [1, 2], Parkinson's disease (PD) served as the initial target for cell therapy. The striatal lesion that manifests in stroke presented as a logical next case to explore cell therapy for stroke repair. Circumventing the logistical hurdles in producing an ample supply of stem cells, coupled with technologies that harness mobilization and widespread deposition of stem cells in the brain, allowed for considering the use of cell therapy in the aging brain, such as Alzheimer's disease and vascular dementia. Although cell replacement was the initial overarching theme, the recognition that stem cells also secrete therapeutic molecules provided the basis for pursuing the concept of multi-pronged mechanisms of action medicating the therapeutic effects of cell therapy. Cognizant of the early beginnings of stem cells, specifically the laboratory-to-clinic challenges, have guided researchers and clinicians in pursuing cutting-edge discoveries towards the safe and effective applications of stem cells for aging-related disorders.

Parkinson's Disease

A hallmark pathology of PD features the nigrostriatal depletion of dopaminergic neurons leading to bradykinesia, tremor, and rigidity in patients. Postulated precipitating factors of PD include abnormal protein aggregation, exposure to environmental toxins, gut-brain dysbiosis, and genetic predispositions [1–4]. For example, trichloroethylene (TCE), a chemical compound routinely found in dry-cleaning, shoe polishers, and carpet cleaners, has been identified as a risk factor for PD [5]. Of note, TCE triggers protein aggregation especially in a genetically engineered PD model [6].

Mia C. Borlongan and Jeffrey Farooq contributed equally to this work.

✉ Gary K. Steinberg
gsteinberg@stanford.edu

[1] Department of Neurosurgery and Brain Repair, University of South Florida Morsani College of Medicine, Tampa, FL 33612, USA

[2] Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine, Stanford, CA 94305, USA

Published online: 10 August 2021

Developing appropriate animal models that mimic the clinical presentation of PD will allow a better understanding of the pathology and treatment of the disease [7, 8].

PD neurodegeneration also manifests a reduction in host stem cells in neurogenic niches [9, 10]. Therefore, as stem cells may be impaired in PD, an effective strategy that targets both stem cell survival and function likely will retard neurodegeneration. Along this line of developing stem cell-based regenerative medicine, transplanting exogenous stem cells or stimulating endogenous stem cells appears to be a promising strategy for PD treatment [11–14]. A minimally invasive procedure that allows stem cell enhancement in the brain may be feasible and directly applied in the clinic. Indeed, synergistic effects accompany electrical stimulation and mesenchymal stem cell transplantation in PD animal models have been observed [15]. Such therapeutic effects of electrical stimulation may be argued as partially rooted from the deep brain stimulation approach [16–18], but with modification on the target site and stimulation threshold and dosing parameters. The recent entry of portable electrical stimulators with peripheral instead of brain target sites advance their potential use in a clinical setting [19]. In particular, new spinal cord stimulators employ implantable electrodes to deliver controlled electrical signals to the spinal cord in PD experimental models [19]. The stimulation-induced dopaminergic circuitry normalization resembles that produced by a pharmacologic treatment such as Levodopa [19], a dopamine replacement agent; therefore, electrical stimulation can act as either as a stand-alone, or as an adjunct therapy, for PD.

Vascular Dementia and the Aging Brain

From fetal cells to embryonic stem cells and induced pluripotent stem cells, logistical and ethical concerns are of primary importance in developing safe and effective transplantable stem cells [20]. The use of adult tissue sources, including bone marrow and umbilical cord blood, meet two laboratory-to-clinic translational hurdles. Despite the limited cell cycle division associated with these adult tissue-derived stem cells, ample supply of the viable and transplantable cells still can be harvested for research purposes and clinical applications [20]. While the preference remains for lineage or phenotypic differentiation of the cells (i.e., dopaminergic cells in the case of PD), naive stem cells have been widely accepted as transplantable cells because of demonstrated cellular bystander effects [21]. With the recognition that PD (and other neurologic disorders) has a major peripheral component to its pathology, targeting the stem cells to non-brain organs — such as the spleen, lung and gut — proves to be a promising therapeutic approach. Indeed, umbilical cord blood-derived stem cells delivered intravenously to target both gut and brain promote therapeutic effects in animal models of PD [22]. That stem cells migrate to injured tissues, likely due to inflammatory signals, demonstrates the cells' potential to hone to the vasculature where the cells may confer neuroprotective effects in diseases characterized by inflamed vasculature, such as PD, stroke, and vascular dementia [23]. Because these neurologic disorders entail stem cell dysfunction due to "aging" as the common denominator [24], cell transplantation has been considered as an anti-aging treatment, at least in attenuating the cognitive deficits associated with aging [23]. As noted above, functional recovery of the injured and aging brain can be augmented by transplantation of exogenous stem cells or stimulation of endogenous stem cells [11–14]. We have noted electrical stimulation as a potential method of enhancing resident stem cells [19], however small molecules are also deemed equally effective in affording host brain repair [25]. By exploiting the inflammation pathway — specifically the intercellular neuro-immune signaling process — molecules that induce endogenous stem cells to secrete anti-inflammatory factors may also represent a robust strategy to treat inflammation-plagued disorders such as multiple sclerosis, stroke and traumatic brain injury [25]. Among the many therapeutic molecules, estradiol promotes hippocampal neurogenesis coincident with improved hippocampal dependent cognitive behaviors, suggesting the potential of enhancing resident host stem cells for treating Alzheimer's disease [26]. These laboratory studies provide compelling evidence that stem cell-based regenerative medicine may have direct application to aging-related disorders.

Mechanisms of Action Mediating Stem Cell Therapy

Stem cells behave as biologics, and may act as drugs mediated by a ligand-receptor mechanism in conferring their therapeutic benefits. With this in mind, the host tissue brain and the stem cells may serve as the ligand and receptor or vice versa. We have noted that stem cells may migrate to the vasculature via inflammatory cues; additionally, stem cells may also use long non-coding RNAs in their migration towards impaired brain tissues [27]. In stroke for example, long noncoding RNAs closely approximate the temporal and spatial evolution of the pathology of ischemic stroke and intracerebral hemorrhage [27]. Long noncoding RNA-based diagnostic tools can approximate the severity and progression of the disease [27]. Similarly, measurement of long noncoding RNAs can provide an index of functional recovery following therapeutic intervention [27]. Accordingly, these modalities may benefit stroke, as well as other disorders with alterations in distinct long noncoding RNAs.

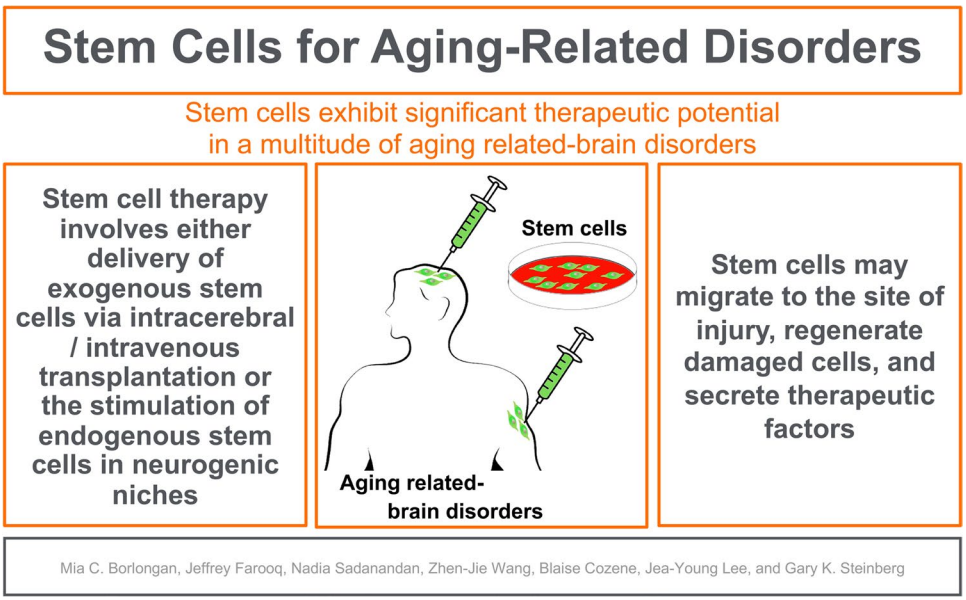

Fig. 1 Stem cells for aging-related disorders. Cell replacement therapy, via exogenous stem cell transplantation or stimulation of endogenous stem cells, stands as a potent mechanism of regnerative medicine for age-related brain disorders. Additionally, the by-stander mode of action of stem cells poses as an equally effective brain repair process that involves the secretion of therapeutic molecules by the grafted cells

A G-protein coupled receptor interacting with Notch represents another mechanism which could be targeted via stem cell therapy. Noteworthy in PD and few other brain disorders, the sense of smell deteriorates, which may signal an early manifestation of the disease [28]. Similarly, aging manifests a deterioration of the olfactory sensory neurons in the olfactory epithelium, which interestingly can be remedied by regenerating the olfactory epithelium via Notch signaling pathway through stimulation of G-protein coupled receptor 5-positive cells [29]. Such a Notch and G-protein coupled receptor may serve as a target mechanism for stem cell proliferation.

Probing transcriptional processes represent another potential strategy in examining stem cell communication with the host tissue. To this end, neuronal transcription factor NeuroD1 may harness the conversion of astrocytes into neurons following stroke cells [30]. Stroke and other brain disorders cause dysfunction to the neurovascular unit; therefore, targeting neurons, astrocytes, glia, and endothelial cells will potentially improve the disease outcomes. Transcriptomic profiling of the impaired tissues may reveal potent targets for stem cell therapeutics [31, 32].

Conclusion

From petri dish to bedside, stem cells have advanced innovative platforms for the investigations of developmental cell biology and for therapeutic applications of regenerative medicine in debilitating brain disorders. Logistical laboratory-to-clinic translational hurdles hindered finding an unlimited supply of safe and effective transplantable stem cells. We do, however, have ample access to embryonic stem cells, neural stem cells, induced pluripotent stem cells, and adult tissue-derived stem cells. Clinical trials are ongoing in many age-related brain disease indications including PD, stroke, and traumatic brain injury [33–35]. Targeting stem cell delivery into the aging brain was logical for these conditions. With the new knowledge that many brain disorders entail a peripheral component, especially the inflammation-enriched organs, targeting stem cells into these tissues have now become common approaches in cell therapy. Whether the ultimate goal is to transplant exogenous stem cells or enhance endogenous stem cells, our mechanism-directed understanding of the brain and non-brain stem cell niches, as well as elucidating inflammation cues may reveal novel candidate modalities for stem cell-based regenerative medicine in aging-related disorders (Fig. 1).

Authors' Contributions Mia C. Borlongan: Writing (original draft, review, and editing).
Jeffrey Farooq: Writing (original draft, review, and editing).
Nadia Sadanandan: Writing (original draft, review, and editing).
Zhen-Jie Wang: Writing (review, and editing).
Blaise Cozene: Writing (review, and editing).
Jea-Young Lee: Writing (review, and editing).
Gary K Steinberg: Conceptualization, Writing (original draft, review, and editing), Supervision.

Funding This work was Supported in part by NIH NINDS R01 NS058784 (GKS).

Availability of Data and Material No specific data sets are associated with this study.

Code Availability Not Applicable.

Declarations

Conflicts of Interest/Competing Interests The Authors declare no conflicts of interest, nor competing interests, in relation to this manuscript.

Ethics Approval Not Applicable.

Consent to Participate Not Applicable.

Consent for Publication Not Applicable.

References

1. Argyrofthalmidou, M., Spathis, A. D., Maniati, M., Poula, A., Katsianou, M. A., Sotiriou, E., et al. (2021). Nurr1 repression mediates cardinal features of Parkinson's disease in alpha-synuclein transgenic mice. *Human Molecular Genetics, 30*(16), 1469–1483.
2. Maitra, U., Harding, T., Liang, Q., & Ciesla, L. (2021). GardeninA confers neuroprotection against environmental toxin in a Drosophila model of Parkinson's disease. *Commun Biol, 4*(1), 162.
3. Tan, A. H., Chong, C. W., Lim, S. Y., Yap, I. K. S., Teh, C. S. J., Loke, M. F., et al. (2021). Gut Microbial Ecosystem in Parkinson Disease: New Clinicobiological Insights from Multi-Omics. *Annals of Neurology, 89*(3), 546–559.
4. McQuade, R. M., Singleton, L. M., Wu, H., Lee, S., Constable, R., Di Natale, M., et al. (2021). The association of enteric neuropathy with gut phenotypes in acute and progressive models of Parkinson's disease. *Scientific Reports, 11*(1), 7934.
5. De Miranda, B. R., Castro, S. L., Rocha, E. M., Bodle, C. R., Johnson, K. E., & Greenamyre, J. T. (2021). The industrial solvent trichloroethylene induces LRRK2 kinase activity and dopaminergic neurodegeneration in a rat model of Parkinson's disease. *Neurobiology of Disease, 153*, 105312.
6. Keane, P. C., Hanson, P. S., Patterson, L., Blain, P. G., Hepplewhite, P., Khundakar, A. A., et al. (2019). Trichloroethylene and its metabolite TaClo lead to degeneration of substantia nigra dopaminergic neurones: Effects in wild type and human A30P mutant alpha-synuclein mice. *Neuroscience Letters, 711*, 134437.
7. He, J., Huang, Y., & Hu, Z. (2020). Effect of bone marrow stromal cells in Parkinson's disease rodent model: A meta-analysis. *Frontiers in Aging Neuroscience*, *12*, 539933.
8. Van Den Berge, N., Ferreira, N., Mikkelsen, T. W., Alstrup, A. K. O., Tamguney. G., & Karlsson, P., et al. (2021). Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. *Brain*, *144*(6), 1853–1868.
9. Marchetti, B., Tirolo, C., L'Episcopo, F., Caniglia, S., Testa, N., Smith, J. A., et al. (2020). Parkinson's disease, aging and adult neurogenesis: Wnt/beta-catenin signalling as the key to unlock the mystery of endogenous brain repair. *Aging Cell*, *19*(3), e13101.
10. Napoli, E., & Borlongan, C. V. (2017). Cell Therapy in Parkinson's Disease: Host Brain Repair Machinery Gets a Boost From Stem Cell Grafts. *Stem Cells, 35*(6), 1443–1445.
11. Daadi, M. M., Grueter, B. A., Malenka, R. C., Redmond, D. E., Jr., & Steinberg, G. K. (2012). Dopaminergic neurons from midbrain-specified human embryonic stem cell-derived neural stem cells engrafted in a monkey model of Parkinson's disease. *PLoS One*, *7*(7), e41120.
12. Yasuhara, T., Matsukawa, N., Hara, K., Yu, G., Xu, L., Maki, M., et al. (2006). Transplantation of human neural stem cells exerts neuroprotection in a rat model of Parkinson's disease. *Journal of Neuroscience, 26*(48), 12497–12511.
13. Rosati, J., Ferrari, D., Altieri, F., Tardivo, S., Ricciolini, C., Fusilli, C., et al. (2018). Establishment of stable iPS-derived human neural stem cell lines suitable for cell therapies. *Cell Death & Disease, 9*(10), 937.
14. Steinbeck, J. A., Choi, S. J., Mrejeru, A., Ganat, Y., Deisseroth, K., Sulzer, D., et al. (2015). Optogenetics enables functional analysis of human embryonic stem cell-derived grafts in a Parkinson's disease model. *Nature Biotechnology, 33*(2), 204–209.
15. Yang, C., Qiu, Y., Qing, Y., Xu, J., Dai, W., Hu, X., et al. (2020). Synergistic effect of electric stimulation and mesenchymal stem cells against Parkinson's disease. *Aging (Albany NY), 12*(16), 16062–16071.
16. Pahwa, R., Lyons, K. E., Wilkinson, S. B., Simpson, R. K., Jr., Ondo, W. G., Tarsy, D., et al. (2006). Long-term evaluation of deep brain stimulation of the thalamus. *Journal of Neurosurgery, 104*(4), 506–512.
17. Okazaki, M., Sasaki, T., Yasuhara, T., Kameda, M., Agari, T., Kin, I., et al. (2018). Characteristics and prognostic factors of Parkinson's disease patients with abnormal postures subjected to subthalamic nucleus deep brain stimulation. *Parkinsonism & Related Disorders, 57*, 44–49.
18. Habets, J. G. V., Heijmans, M., Kuijf, M. L., Janssen, M. L. F., Temel, Y., & Kubben, P. L. (2018). An update on adaptive deep brain stimulation in Parkinson's disease. *Movement Disorders, 33*(12), 1834–1843.
19. Kuwahara, K., Sasaki, T., Yasuhara, T., Kameda, M., Okazaki, Y., Hosomoto, K., et al. (2020). Long-Term Continuous Cervical Spinal Cord Stimulation Exerts Neuroprotective Effects in Experimental Parkinson's Disease. *Front Aging Neurosci, 12*, 164.
20. He, J. Q., Sussman, E. S., & Steinberg, G. K. (2020). Revisiting stem cell-based clinical trials for ischemic stroke. *Frontiers in Aging Neuroscience*, *12*, 575990.
21. Weiss, M. L., Medicetty, S., Bledsoe, A. R., Rachakatla, R. S., Choi, M., Merchav, S., et al. (2006). Human umbilical cord matrix stem cells: Preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. *Stem Cells, 24*(3), 781–792.
22. Lee, J. Y., Tuazon, J. P., Corey, S., Bonsack, B., Acosta, S., Ehrhart, J., et al. (2019). A Gutsy Move for Cell-Based Regenerative Medicine in Parkinson's Disease: Targeting the Gut Microbiome to Sequester Inflammation and Neurotoxicity. *Stem Cell Rev Rep, 15*(5), 690–702.
23. Venkat, P., Culmone, L., Chopp, M., Landschoot-Ward, J., Wang, F., Zacharek, A., et al. (2020). HUCBC Treatment Improves Cognitive Outcome in Rats With Vascular Dementia. *Front Aging Neurosci, 12*, 258.
24. Broxmeyer, H. E., Liu, Y., Kapur, R., Orschell, C. M., Aljoufi, A., Ropa, J. P., et al. (2020). Fate of hematopoiesis during aging. What do we really know, and what are its implications? *Stem Cell Reviews and Reports*, *16*(6), 1020–1048.
25. Nicaise, A. M., Willis, C. M., Crocker, S. J., & Pluchino, S. (2020). Stem Cells of the Aging Brain. *Front Aging Neurosci, 12*, 247.
26. Qin, Y., An, D., Xu, W., Qi, X., Wang, X., Chen, L., et al. (2020). Estradiol Replacement at the Critical Period Protects Hippocampal Neural Stem Cells to Improve Cognition in APP/PS1 Mice. *Front Aging Neurosci, 12*, 240.
27. Fan, J., Saft, M., Sadanandan, N., Gonzales-Portillo, B., Park, Y. J., Sanberg, P. R., et al. (2020). LncRNAs stand as potent biomarkers and therapeutic targets for stroke. *Frontiers in Aging Neuroscience*, *12*, 594571.
28. Jankovic, J., & Tan, E. K. (2020). Parkinson's disease: Etiopathogenesis and treatment. *Journal of Neurology, Neurosurgery and Psychiatry, 91*(8), 795–808.

29. Li, X., Tong, M., Wang, L., Qin, Y., Yu, H., & Yu, Y. (2020). Age-dependent activation and neuronal differentiation of Lgr5+ basal cells in injured olfactory epithelium via notch signaling pathway. *Frontiers in Aging Neuroscience*, *12*, 602688.
30. Jiang, M. Q., Yu, S. P., Wei, Z. Z., Zhong, W., Cao, W., Gu, X., et al. (2021). Conversion of reactive astrocytes to induced neurons enhances neuronal repair and functional recovery after ischemic stroke. *Frontiers in Aging Neuroscience*, *13*, 612856.
31. Shah, P. T., Stratton, J. A., Stykel, M. G., Abbasi, S., Sharma, S., Mayr, K. A., et al. (2018). Single-cell transcriptomics and fate mapping of ependymal cells reveals an absence of neural stem cell function. *Cell*, *173*(4), 1045–1057 e9.
32. Sun, J., Huang, Y., Gong, J., Wang, J., Fan, Y., Cai, J., et al. (2020). Transplantation of hPSC-derived pericyte-like cells promotes functional recovery in ischemic stroke mice. *Nature Communications, 11*(1), 5196.
33. d'Angelo, M., Cimini, A., & Castelli, V. (2020). Insights into the Effects of Mesenchymal Stem Cell-Derived Secretome in Parkinson's Disease. *International Journal of Molecular Sciences, 21*(15), 5241.
34. Sameri, S., Samadi, P., Dehghan, R., Salem, E., Fayazi, N., & Amini, R. (2020). Stem Cell Aging in Lifespan and Disease: A State-of-the-Art Review. *Current Stem Cell Research & Therapy, 15*(4), 362–378.
35. Yu, Y. (2018). Application of Stem Cell Technology in Antiaging and Aging-Related Diseases. *Advances in Experimental Medicine and Biology, 1086*, 255–265.