Received: 28 January 2021 | Accepted: 28 January 2021

DOI: 10.1002/sctm.21-0036

PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

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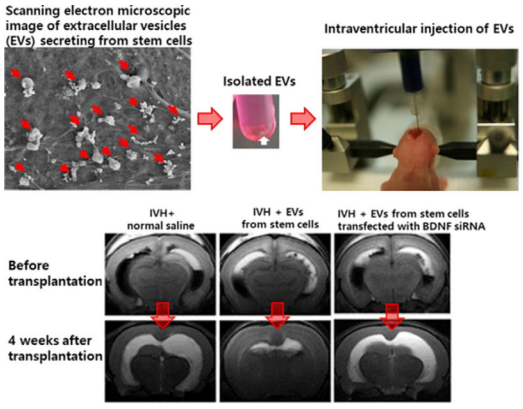
Brain-derived neurotrophic factor (BDNF), a member of the mammalian neurotrophin family of growth factors, supports the survival and differentiation of neuronal cells during development and regulates synaptic transmission and neural plasticity in the adult brain.[1] Importantly, age-related declines in cognitive performance, the increased incidence of pathological conditions such as Alzheimer's disease and Parkinson's disease, and the onset of neuropsychiatric disorders have all been linked to a reduction in BDNF levels or altered BDNF signaling. The transplantation of BDNF-expressing stem cells, such as mesenchymal stem cells (MSCs),[2,3] as a therapeutic strategy aims to afford neuroprotection and halt neurodegeneration in the central nervous system; as an example, the transplantation of MSCs engineered to express higher levels of BDNF can inhibit neurodegenerative processes, increase neurogenesis, and improve behavioral deficits in a murine model of Huntington's disease.[4,5] Studies such as these have fostered the ongoing development of BDNF-targeted stem cell therapies to mitigate the sequelae of various forms of brain injury and prompted the exploration of the mechanisms controlling BDNF release and the therapeutically relevant signaling pathways affected by secreted BDNF. In our first Featured Article published this month in *STEM CELLS Translational Medicine*, Ahn et al. report that the transplantation of MSC-derived extracellular vesicles can attenuate the brain injuries associated with severe intraventricular hemorrhage by transferring BDNF.[6] In a Related Article published recently in *STEM CELLS*, Zheng et al. demonstrated that administered MSCs provide neuroprotection following hypoxia-ischemia-associated brain damage by enhancing autophagy through the BDNF/mammalian target of rapamycin (mTOR) signaling pathway.[7]

Brachyury is a transcription factor within the T-box family of genes, which play crucial roles in embryo development in a range of organisms.[8] The brachyury gene (symbol *T* or *TBXT*) was discovered through the analysis of a spontaneously-occurring mouse mutant that presented with a short-tail phenotype. Brachyury plays a key role as a master regulator of the specification/differentiation of the mesoderm, a germ layer that gives rise to a number of critical structures and organs within the developing embryo, contributing to the skeletal, muscular, excretory, circulatory, lymphatic, and reproductive systems. Of note, Brachyury represents the primordial factor controlling the very earliest stages of cardiovascular differentiation through the regulation of downstream cardiopoietic transcription factors.[9,10] Recent research has hoped to take advantage of the transcriptional activity of brachyury to endow tissue-resident stem cells with a mesodermal-like fate and extend their therapeutic ability. In contrast, other research has aimed to understand the epigenetic regulation of mesoderm-associated transcription factors such as brachyury and how this influences cell fate. In our second Featured Article published this month in *STEM CELLS Translational Medicine*, Li et al. describe how transfection with microencapsulated-modified-brachyury mRNA can induce MSCs to adopt a cardiopoietic fate that promotes enhanced cardioreparative activity.[11] In a Related Article published recently in *STEM CELLS*, Bai et al. reported how a histone lysine methyltransferase regulates the differentiation of human embryonic stem cells (ESCs) by binding to and altering the chromatin landscape at the regulatory regions of crucial mesendodermal transcription factor genes, including brachyury.[12]

FEATURED ARTICLES

BDNF Transfer by MSC-Derived Extracellular Vesicles Mediates Neuroprotection in the Preterm Brain

Previous research from the laboratory of Won Soon Park (Sungkyunkwan University, Seoul, South Korea) reported the critical role of BDNF secretion from transplanted MSCs in mediating neuroprotection and improving myelination and neurogenesis in a rat pup model of intraventricular hemorrhage-induced brain injuries.[13,14] In the hope of creating a stem cell-free therapy for intraventricular hemorrhage, researchers from the Park laboratory next sought to explore the

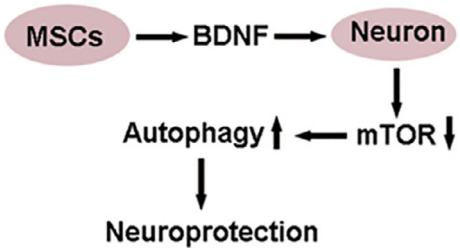


potential of MSC-derived extracellular vesicles as a safe and effective alternative therapeutic approach. Reporting in a recent *STEM CELLS Translational Medicine* article,[6] Ahn et al. compared MSCs and MSC-derived extracellular vesicles in the presence or absence of BDNF (via small interfering RNA expression) in rat cortical neuronal cells challenged with thrombin and intraventricular hemorrhage model rat pups. The authors established the comparable ability of MSCs and MSC-derived extracellular vesicles to significantly attenuate thrombin-induced neuronal cell death and rescue severe intraventricular hemorrhage-associated defects (such as the increases in apoptotic cell death, inflammatory responses, oxidative stress, and astrogliosis and the reduction in brain myelination and neurogenesis); however, these positive outcomes only occurred in the presence of BDNF expression. Overall, the authors suggest BDNF transfer by MSC-derived extracellular vesicles may represent a safe and effective means of attenuating severe intraventricular hemorrhage-induced brain injuries. Their future studies will include the establishment of the optimal timing, administration route, and dosage of MSC-derived extracellular vesicles required to improve the treatment outcomes.

https://doi.org/10.1002/sctm.20-0301

Brachyury Expression Transforms MSCs into Cardioreparative Stem Cells

Recent studies have sought to improve the treatment of ischemic heart failure with patient-derived MSCs by optimizing cardioreparative capacity through co-instruction with specific cocktails of growth factors; however, this approach remains expensive due to the need for recombinant proteins and represents a significant challenge to scale. This vexing problem prompted researchers led by Atta Behfar (Mayo Clinic, Rochester, Minnesota, USA) to explore an alternative strategy - the induction of enhanced cardiopoiesis (the production of cardiac muscle tissue) by MSCs through targeted gene delivery employing microencapsulated-modified-messenger RNA technology.[15,16] In their recent *STEM CELLS* article, Li et al.[11] employed a screening of known mesodermal and pre-cardiac transcription factors to highlight brachyury expression as a potentially exciting means of engineering a cardiopoietic phenotype in adipose-derived MSCs. Brachyury mRNA transfection of MSCs (non-integrating and viral-free) induced the elevated expression of cardiopoietic markers such as Nkx2.5 and Mef2c and afforded cells with protective antioxidant, vasculogenic-secretome driven angiogenic, and immunomodulatory properties in vitro. These advantages translated into improved cardiac performance and protection from decompensated heart failure via a paracrine mechanism following the intramyocardial delivery of brachyury-transfected MSCs in a murine model of myocardial infarction. Overall, the authors highlight what they term a "minimalistic approach for predelivery optimization of a regenerative cell product" that could prompt the development of a safe and effective means of treating conditions such as ischemic heart failure.

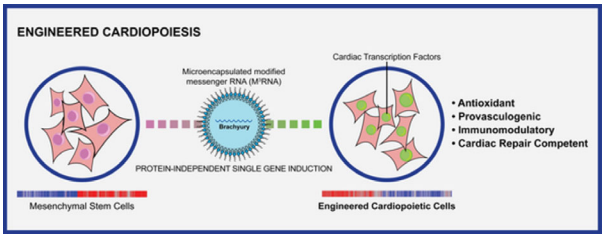


https://doi.org/10.1002/stem.2808

RELATED ARTICLES

MSCs Protect Against Hypoxia-Ischemia-Associated Brain Damage by BDNF-Induced Autophagy

Recent studies from researchers led by Dezhi Mu and Yi Qu (Sichuan University, Chengdu, Sichuan, China) revealed that altered mTOR signaling, a key regulator of autophagy, induced neuronal cell death following hypoxia-ischemia-associated brain damage in developing rats.[17] As MSC administration can enhance autophagy and exert a neuroprotective effect,[18] Zheng et al. sought to explore the effect of MSC administration on autophagy and recovery in affected rat pups. Writing in a recent *STEM CELLS* article,[7] researchers from the Mu and Qu laboratories provided evidence that MSC administration can prompt an increase in BDNF levels, which acts to inhibit mTOR pathway activation to then increase autophagy and neuroprotection. Their initial in vitro analysis employing rat cortical primary neurons exposed to hypoxia-ischemia revealed that MSC coculture prompted the increased expression of BDNF and autophagy-associated markers and reduced cell death. Subsequent in vivo analysis revealed the existence of similar mechanisms following MSC transplantation in a rat hypoxia-ischemia model; however, the authors also underscored the MSC-mediated attenuation of associated behavioral deficits. The team strengthened the importance of BDNF and the inhibition of mTOR signaling by highlighting the reversal of the observed MSC-induced neuroprotective effects via the addition of a BDNF-neutralizing antibody. Overall, the authors anticipated that their findings would open

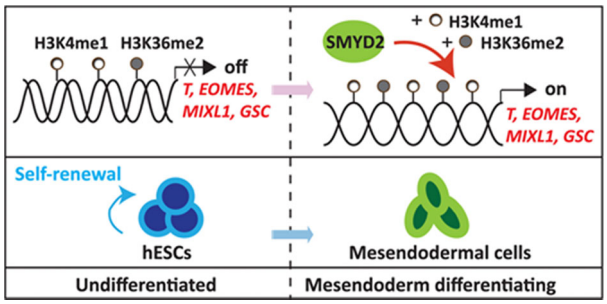


new avenues of exploration that may foster the development of novel treatments for hypoxia-ischemia-associated brain injury in neonates.

https://doi.org/10.1002/sctm.20-0193

Histone Lysine Methyltransferase Mediates the Mesendodermal Differentiation of ESCs

Understanding the mechanisms controlling the differentiation of human ESCs into cells representative of the three germ layers may provide insight into early human development. ESCs pass through an intermediate mesendodermal stage as they differentiate into endoderm and mesoderm that coincides with the expression of key transcription factors, including brachyury. In a recently published *STEM CELLS* article,[12] researchers led by Huang-Tian Yang (University of Chinese Academy of Sciences, Shanghai, China) sought to explore the epigenetic control of gene expression during in vitro mesendodermal differentiation mediated by studying the SMYD2 histone lysine methyltransferase, which supports the dimethylation of histone 3 lysine 36.[19,20] Bai et al. initially discovered low-level SMYD2 expression in self-renewing ESCs; however, expression levels specifically and significantly increased during mesendodermal differentiation. In agreement, loss of SMYD2 expression failed to influence ESC self-renewal (or early neuroectodermal differentiation) but did block mesendodermal lineage commitment. Subsequent chromatin-based analysis revealed that SMYD2 bound to the regulatory sequences of essential mesendodermal genes, such as brachyury, where an increase in the levels of dimethylated histone 3 lysine 36 (H3K36me2) and mono-methylated histone 3 lysine 4 (H3K4me1) was observed. This chromatin profile supported mesendodermal gene expression and mesendodermal differentiation, thereby providing evidence of the previously unrecognized and crucial role of SYMD2 in mesendodermal lineage commitment. Overall, this exciting study highlighted the potential role of histone lysine methyltransferase activity during the very earliest stages of human development.



https://doi.org/10.1002/stem.3068

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How to cite this article: Atkinson SP. A PREVIEW OF SELECTED ARTICLES. *STEM CELLS Transl Med*. 2021;10:333–336. https://doi.org/10.1002/sctm.21-0036