Received: 5 May 2021 | Accepted: 5 May 2021

DOI: 10.1002/sctm.21-0168

PREVIEWS

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

STEM CELLS TRANSLATIONAL MEDICINE

Stuart P. Atkinson

Centro de Investigación Príncipe Felipe, Valencia, Spain. Email: satkinson@cipf.es

The progressive onset of abnormal movements, psychiatric problems, and cognitive deficits characterize Huntington's disease,[1] an autosomal-dominant neurodegenerative disorder that affects approximately 5 of every 100 000 people in the United States, Europe, and Australia.[2] A trinucleotide CAG repeat expansion in the Huntingtin (*HTT*) gene prompts the production of a mutated protein (mHTT) that misfolds and forms clumped, rigid aggregates[3] that prompt the degeneration of efferent medium spiny neurons in the striatum (which coordinates multiple aspects of cognition), a decline in striatal volume, and whole-brain atrophy. Cellular and molecular features of inflammation, including alterations to cytokine levels and microglial activation,[4] have also been reported as features of Huntington's disease; however, inflammation may represent a protective mechanism during early stage disease,[5] with neuroinflammatory mechanisms only inducing neuronal death during subsequent progression.[4,5] Current research aims include the development of stem cell therapies to inhibit disease progression or treat specific pathologies and the generation of animal models of Huntington's disease to accelerate the clinical translation of said therapies. In the first of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Dahlenburg et al describe the generation and characterization of an immunodeficient mouse model of Huntington's disease and the subsequent development of a humanized strain to define how the human immune system impacts pathogenesis.[6] In a Related Article published in *STEM CELLS*, Yoon et al demonstrated how the intracerebral transplantation of clinical-grade neural stem cells (NSCs) in a rat model of Huntington's disease prompted significant improvements in behavioral and pathological deficits by replacing lost cells and inducing endogenous regeneration.[7]

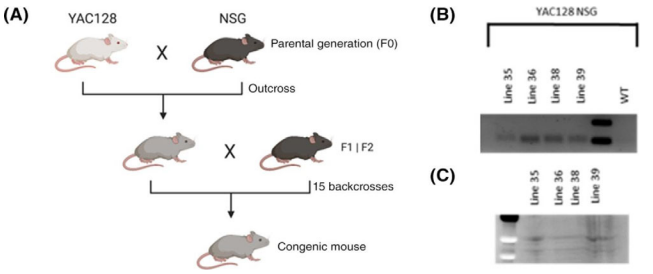
MicroRNAs (or miRNAs) are short noncoding RNAs of 20 to 25 nucleotides in length that constitute a crucial part of the post-transcriptional regulatory machinery that fine-tunes gene expression.[8] miRNA-mediated regulation impacts crucial physiological processes, such as development, proliferation, differentiation, and apoptosis, and also participates in disease pathogenesis and aging. miRNAs bind to complementary sequences within target mRNAs to silence expression by cleaving mRNA, destabilizing mRNA, or inhibiting mRNA translation. Alongside proteins, lipids, DNA, and other RNA species, miRNAs comprise one of the major cargos carried by extracellular vesicles, a heterogeneous group of lipid bilayer-delimited particles released by most cells for cell-to-cell communication purposes. Our current appreciation of miRNAs now supports their role as crucial regulators of the self-renewal and differentiation of various stem/progenitor cell populations.[9] Furthermore, recent research has tightly linked the presence of extracellular vesicle-associated miRNAs to the therapeutic output of stem cell therapies in a range of distinct diseases and disorders.[10,11] In the second of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Ragni et al report on the characterization of the extracellular vesicle-derived miRNA profile of human amniotic membrane-derived MSCs in the hope of accelerating their development into a treatment for diseases such as osteoarthritis.[12] In a Related Article published in *STEM CELLS*, Channakkar et al described how a brain-enriched miRNA enhanced the differentiation of induced pluripotent stem cell (iPSC)-derived NSCs by altering mitochondrial function in a study that the authors hoped would facilitate the design of treatments for aging-associated neurodegenerative diseases.[13]

FEATURED ARTICLES

New Huntington's Disease Mouse Model May Support the Development of Cell Therapies

Research from the laboratory of Kyle Fink (University of California, Davis, Sacramento, California) had previously demonstrated that MSCs only survived for seven days in the absence of immunosuppression in the YAC128 transgenic mouse model of Huntington's disease,[14,15] thereby hindering an evaluation of how cell therapy may modulate neuroinflammation and inhibit disease progression. To solve this problem, the team recently generated an immunodeficient/xenotolerant Huntington's disease mouse model by crossbreeding immunodeficient NSG and YAC128 mouse strains to create the YACNSG immunodeficient Huntington's disease mouse model. The team also explored the relevance of the human immune system through the intrahepatic transplantation of human umbilical cord blood CD34+ cells after sublethal irradiation of the YACNSG strain. As reported in *STEM CELLS Translational Medicine*,[6] Dahlenburg et al confirmed the lack of circulating T, B, and natural killer cells in non-humanized YACNSG mice and employed in vivo imaging to highlight the extended retention time of fluorescently labeled MSCs compared to immunocompetent YAC128 mice. Functional assessments of

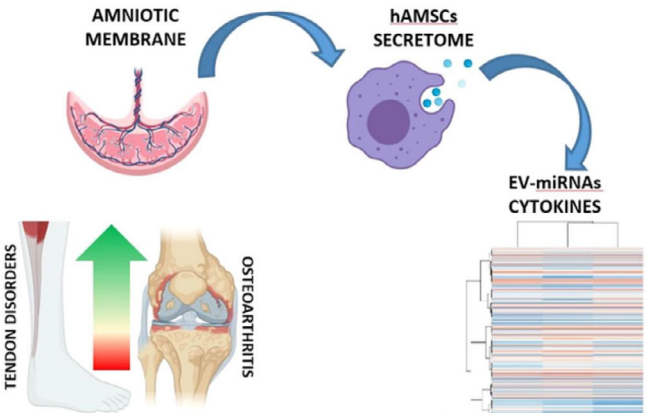
both YACNSG strains suggested the development of the expected disease-associated motor phenotypes, while subsequent histological analysis demonstrated that non-humanized YACNSG mice displayed a reduced level of striatal atrophy compared to YAC128 mice. Interestingly, humanized YACNSG mice displayed a level of atrophy similar to YAC128 mice, thereby suggesting that the immune system/neuroinflammation plays a significant role in disease progression. Future research efforts from the authors will aim to characterize the extent of humanization and evaluate the role of neuroinflammation in responses to cell-based therapeutics.



https://doi.org/10.1002/sctm.20-0431

Detailed Characterization of Amniotic Membrane MSC-Secreted Factors Seeks to Advance Clinical Translation

The success of human amniotic membrane-derived MSCs (or hAMSCs) as a treatment for osteoarthritis of the human knee[16] is thought to derive from the therapeutic activity of a wide range of secreted cytokines, growth factors, and miRNA-containing extracellular vesicles.[17,18] In the hope of accelerating the clinical development of these MSCs into an effective musculoskeletal disease treatment, researchers led by Laura de Girolamo (IRCCS Istituto Ortopedico Galeazzi, Milan, Italy) recently profiled the presence of 200 secreted factors and 754 miRNAs from the MSC secretome and purified extracellular vesicles. As reported in their recent *STEM CELLS Translational Medicine* article,[12] Ragni et al first highlighted the abundant secretion of 37 cytokines/chemokines of relevance to osteoarthritis, including those involved in the chemotaxis and homeostasis of inflammatory cells and extracellular matrix remodeling. The subsequent analysis of the top 51 extracellular vesicle-derived miRNAs highlighted the abundant expression of teno- and chondro-protective species that induced M2 macrophage polarization, inhibited inflammatory T cells, and promoted T regulatory cell function. Finally, the authors demonstrated that the administration of the human amniotic membrane-derived MSC secretome to chondrocytes and tenocytes pretreated with the pro-inflammatory cytokine Interleukin-1β induced the downregulation of inflammation-associated gene expression. Overall, these findings lay the groundwork for the exploration of the impact of stem cell-derived miRNAs on other pathologies and the definition of clinically efficient secretome-based therapeutic products.



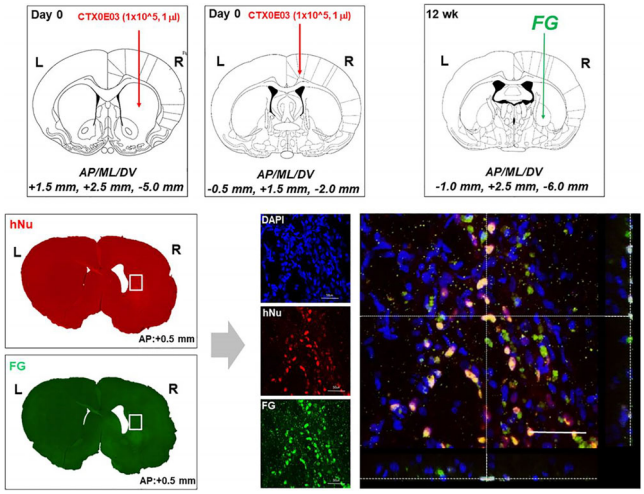
https://doi.org/10.1002/sctm.20-0390

RELATED ARTICLES

Clinical-Grade Human NSCs Rescues Huntington's Disease-Associated Deficits

Previous research had established how intracerebral implantation of CTX0E03, a good manufacturing practices-manufactured conditionally-immortalized human NSC line,[19,20] in a mouse model of ischemic stroke prompted the recovery of behavioral deficits by stimulating reparative mechanisms, such as angiogenesis and neurogenesis.[19,21] Given these encouraging previous findings, researchers from the laboratory of Jihwan Song (CHA University, Gyeonggi-do, South Korea) hypothesized that the transplantation of CTX0E03 NSCs might represent an effective treatment option for Huntington's disease. As reported in their recent *STEM CELLS* article,[7] Yoon et al investigated the consequences of intracerebral NSC transplantation into a quinolinic acid-lesioned rat model of Huntington's disease. Encouragingly, the authors established significant behavioral improvements at 8 and 12 weeks post-transplantation (rotarod, stepping, and staircase tests to assess motor coordination, akinesia, and fine motor reaching skills, respectively) when compared to sham- or human fibroblast-transplanted model rats. Said improvements associated with robust survival and stable engraftment of NSCs and efficient region-specific differentiation in the striatum and the cortex and increased expression of brain-derived neurotrophic factor (BDNF). Furthermore, the study highlighted the formation of connections between NSC-derived striatal medium spiny neurons and GABAergic neurons with host brain tissues, a reduction in glial scarring and inflammation, and an increase in endogenous regeneration mechanisms, including neurogenesis and angiogenesis. Overall, this exciting study provided evidence that CTX0E03 transplantation improved the behavioral and pathological deficits associated with

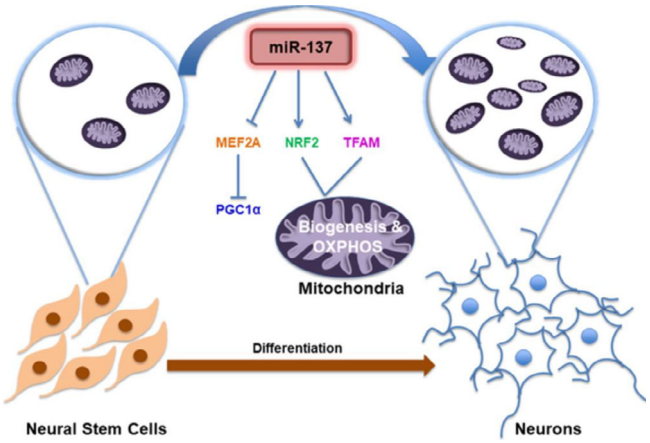
Huntington's disease via cell replacement and the induction of host cell regeneration mechanisms.



https://doi.org/10.1002/stem.3191

Human NSC Fate Modification by a Brain-Enriched miRNA

Previous research into the brain-enriched miR-137 in mouse cell models had linked miRNA expression to neural differentiation and the inhibition of cell proliferation,[22,23] thereby suggesting that miR-137 regulates the fate of human NSCs. Researchers led by Yogita K. Adlakha (National Brain Research Centre, Manesar, India) recently explored this hypothesis and reported their results in a fascinating *STEM CELLS* article.[13] Channakkar et al initially discovered that the ectopic expression of miR-137 in human induced pluripotent stem cell-derived NSCs reduced their proliferation and accelerated both neuronal differentiation and migration. Detailed in silico analyses and subsequent confirmatory in vitro assays established that miR-137 targeted the 3′ untranslated region of myocyte enhancer factor-2A (*MEF2A*) transcription factor mRNA to reduce expression levels. This mechanism then prompted the reduced transcription of peroxisome proliferator-activated receptor-gamma coactivator (PGC1α), a direct target of MEF2A, to accelerate mitochondrial biogenesis, fusion, fission, and oxidative phosphorylation to support the metabolic requirements associated with neuronal differentiation. The study also highlighted that ectopically expressed miR-137 prompted the elevated expression of OCT4 and SOX2 in hiNSCs, with these pluripotency-associated factors then binding to regions within the *miR-137* gene promoter to establish a feed-forward self-regulatory loop. Given these exciting findings, the authors proposed that the modulation of NSCs fate by miR-137 expression may represent the basis of reparative/regenerative strategies for the treatment of aging-associated neurodegenerative diseases.



https://doi.org/10.1002/stem.3155

REFERENCES

1. Kremer B, Goldberg P, Andrew SE, et al. A worldwide study of the Huntington's disease mutation: the sensitivity and specificity of measuring CAG repeats. *N Engl J Med*. 1994;330:1401-1406.
2. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. *Mov Disord*. 2012;27:1083-1091.
3. MacDonald ME, Ambrose CM, Duyao MP, et al. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971-983.
4. Crotti A, Glass CK. The choreography of neuroinflammation in Huntington's disease. *Trends Immunol*. 2015;36:364-373.
5. Rocha NP, Ribeiro FM, Furr-Stimming E, et al. Neuroimmunology of Huntington's disease: revisiting evidence from human studies. *Mediators Inflamm*. 2016;2016:8653132.
6. Dahlenburg H, Cameron D, Yang S, et al. A novel Huntington's disease mouse model to assess the role of neuroinflammation on disease progression and to develop human cell therapies. *Stem Cells Translational Medicine*. 2021;10:1033-1043.
7. Yoon Y, Kim HS, Jeon I, et al. Implantation of the clinical-grade human neural stem cell line, CTX0E03, rescues the behavioral and pathological deficits in the quinolinic acid-lesioned rodent model of Huntington's disease. *Stem Cells*. 2020;38:936-947.
8. Lai EC. Micro RNAs are complementary to 3′ UTR sequence motifs that mediate negative post-transcriptional regulation. *Nat Genet*. 2002;30:363-364.
9. Li N, Long B, Han W, Yuan S, Wang K. microRNAs: important regulators of stem cells. *Stem Cell Res Ther*. 2017;8:110.
10. Harrell CR, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal stem cell-derived exosomes and other extracellular vesicles as new remedies in the therapy of inflammatory diseases. *Cell*. 2019;8:1605.
11. Keshtkar S, Azarpira N, Ghahremani MH. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. *Stem Cell Res Ther*. 2018;9:63.
12. Ragni E, Papait A, Perucca Orfei C, et al. Amniotic membrane-mesenchymal stromal cells secreted factors and extracellular vesicle-miRNAs: anti-inflammatory and regenerative features for musculoskeletal tissues. *Stem Cells Translational Medicine*. 2021;10:1044-1062.
13. Channakkar AS, Singh T, Pattnaik B, Gupta K, Seth P, Adlakha YK. MiRNA-137-mediated modulation of mitochondrial dynamics regulates human neural stem cell fate. *Stem Cells*. 2020;38:683-697.

14. Pollock K, Dahlenburg H, Nelson H, et al. Human mesenchymal stem cells genetically engineered to overexpress brain-derived neurotrophic factor improve outcomes in Huntington's disease mouse models. *Mol Ther*. 2016;24(5):965-977. https://doi.org/10.1038/mt.2016.12.
15. Slow EJ, van Raamsdonk J, Rogers D, et al. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. *Hum Mol Genet*. 2003;12:1555-1567.
16. Vines JB, Aliprantis AO, Gomoll AH, Farr J. Cryopreserved amniotic suspension for the treatment of knee osteoarthritis. *J Knee Surg*. 2016;29:443-450.
17. Eleuteri S, Fierabracci A. Insights into the secretome of mesenchymal stem cells and its potential applications. *Int J Mol Sci*. 2019;20:4597.
18. Witwer KW, Van Balkom BWM, Bruno S, et al. Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J Extracell Vesicles*. 2019;8:1609206.
19. Stroemer P, Patel S, Hope A, Oliveira C, Pollock K, Sinden J. The neural stem cell line CTX0E03 promotes behavioral recovery and endogenous neurogenesis after experimental stroke in a dose-dependent fashion. *Neurorehabil Neural Repair*. 2009;23:895-909.
20. Kalladka D, Sinden J, Pollock K, et al. Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study. *Lancet*. 2016;388:787-796.
21. Hicks C, Stevanato L, Stroemer RP, Tang E, Richardson S, Sinden JD. In vivo and in vitro characterization of the angiogenic effect of ctx0e03 human neural stem cells. *Cell Transplant*. 2013;22:1541-1552.
22. Sun G, Ye P, Murai K, et al. miR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells. *Nat Commun*. 2011;2:529.
23. Jiang K, Ren C, Nair VD. MicroRNA-137 represses Klf4 and Tbx3 during differentiation of mouse embryonic stem cells. *Stem Cell Res*. 2013;11:1299-1313.