Received: 30 July 2020 | Accepted: 31 July 2020

DOI: 10.1002/sctm.20-0357

PREVIEWS

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

Stuart P. Atkinson

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

Long non-coding RNAs (lncRNAs), a large, diverse class of transcribed RNA molecules with a length of more than 200 nucleotides that do not encode proteins, represent important regulators of gene expression that impact a wide range cellular processes. LncRNAs mediate transcriptional regulation or chromatin modification both in cis and in trans, bind to complementary RNA to affect processing, turnover, and localization, and interact with proteins to impact function and localization and form riboprotein complexes.[1] While the exact function of the vast majority of the 30 000 estimated lncRNAs present in the human genome remains uninvestigated, there exists ample evidence that lncRNAs play crucial roles in stem cell differentiation and cell fate determination. Examples include the RMST lncRNA, which physically interacts with SOX2 and acts as a transcriptional coregulator to modulate the fate of neural stem cells,[2] and LNCRNA-HIT, which promotes the expression of multiple genes that foster the formation of cartilage in the mouse embryo limb mesenchyme.[3] What other examples of stem/progenitor cell-specific lncRNAs exist, and how do they control stem cell differentiation and cell fate? In the first of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Chen et al. report on the identification of a new lncRNA highly expressed in adipose-derived mesenchymal stem cells (ASCs) undergoing differentiation into adipocytes that may aid the development of novel therapeutics for metabolic disorders.[4] In a Related Article published recently in *STEM CELLS*, Tang et al. identified a novel osteogenesis-associated lncRNA in differentiating bone marrow mesenchymal stem cells (MSCs) that regulates the activation of the bone morphogenetic protein (BMP) signaling pathway by interacting with an RNA binding protein.[5]

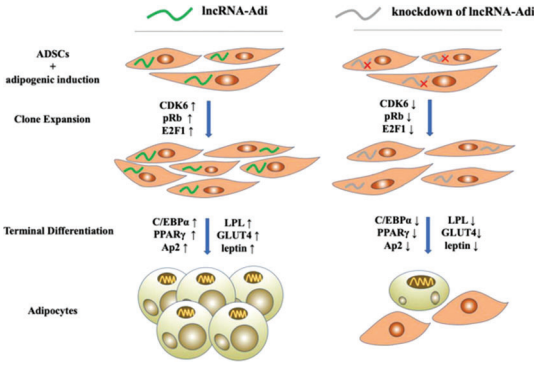
The progressive degeneration of the central nervous system characterizes Alzheimer's disease, the most common form of age-related dementia. Neuropathological hallmarks include the presence of extracellular beta-amyloid plaques and neurofibrillary tangles containing a hyperphosphorylated microtubule-associated protein, inflammation, synaptic and neuronal dysfunction, and neural degeneration.[6] Microglia-mediated neuroinflammation can exacerbate Alzheimer's disease-related pathologies to drive neuronal injury,[7] and studies have also established that microglia express many Alzheimer's disease risk genes.[8] Studies such as these highlight microglial targeting and the reduction of neuroinflammation as a potentially efficient treatment approach; can we take advantage of the well-known immunomodulatory and anti-inflammatory abilities of MSCs to develop an effective treatment for Alzheimer's disease? Oxidative stress also contributes to the development of Alzheimer's disease by reducing neural proliferation, differentiation, and survival and hence negatively impacting neurogenesis. The increased oxidative stress associated with beta-amyloid toxicity can induce the inflammation and the subsequent pathological and cognitive abnormalities observed in Alzheimer's disease patients.[9] Furthermore, this inhospitable environment can inhibit the proper function of resident or exogenously administered stem/progenitor cells; can we provide said cells with a means to protect themselves to improve outcomes in Alzheimer's disease patients? In the second of our Featured Articles published this month in *STEM CELLS Translational Medicine*, Losurdo et al. demonstrate that the intranasal administration of extracellular vesicles derived from MSCs dampens pathogenic inflammation and induces neuroprotective effects in a triple transgenic mouse model of Alzheimer's disease.[10] In a Related Article published recently in *STEM CELLS*, Kärkkäinen et al. reported the involvement of a transcription factor associated with the oxidative stress response in the neuronal differentiation of neural progenitor cells (NPCs), the regulation of injury-induced neurogenesis, and protection against the development of Alzheimer's disease .[11]

FEATURED ARTICLES

Novel Long Non-Coding RNA Regulates the Adipogenic Differentiation of ASCs

While studies have established that the lncRNA Plnc1 promotes adipogenic differentiation by regulating peroxisome proliferator-activated receptor-gamma (PPARγ)[12] and the lncRNA GAS5 inhibits adipogenic differentiation by modulating the microRNA (miR)-18a/connective tissue growth factor (CTGF) axis,[13] researchers led by Lei Liu (Sichuan University, Chengdu, Sichuan, China) believed these examples to represent the mere tip of the iceberg regarding the number of lncRNAs that influence adipogenesis.[14] In their new *STEM CELLS Translational Medicine* article,[4] Chen et al. now report on their full transcriptome microarray analyses that

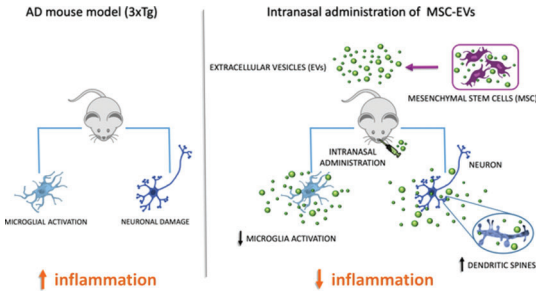
highlights the specific and elevated expression of lncRNA-Adi during the mitotic clonal expansion phase of ASCs (or ADSCs) undergoing differentiation into adipocytes. The authors first evaluated the knockdown of lncRNA-Adi through RNA interference, finding that this impairs the adipogenic differentiation of ASCs. Next, they established that lncRNA-Adi normally resides in the ASC cytoplasm and interacts with miR-449a, which itself acts to enhance the expression of cyclin-dependent kinase 6 (CDK6) during adipogenesis. Specifically, lncRNA-Adi competitively interacts with miR-449a regarding binding to the CDK6 mRNA 3′ untranslated region to prevent its degradation, and increase CDK6 translation. This mechanism subsequently promotes the activation of the pRb-E2F1 pathway—a crucial step in cell proliferation and PPARγ expression during adipogenesis. While these findings delineate the role of lncRNA-Adi in ASCs, the authors hope that this study will also foster the development of therapeutic advances for metabolic disorders such as obesity and diabetes.



https://doi.org/10.1002/sctm.19-0438

Intranasally Administered MSC-Derived Extracellular Vesicles as a Novel Alzheimer's Disease Treatment

The modulation of neuroinflammation by the administration of extracellular vesicles derived from MSCs represents a potentially exciting means to inhibit the acceleration of pathogenic processes in conditions such as Alzheimer's disease. Related studies chose to administer extracellular vesicles systemically[15] or by intracerebroventricular injection,[16] with the partial rescue of Alzheimer's disease pathology observed in these cases. Recently, researchers led by Silvia Coco (University of Milano-Bicocca, Monza, Italy) evaluated the potential of cytokine-preconditioned (tumor necrosis factor-alpha and interferon-gamma treatment for 48 hours) MSC-derived extracellular vesicles after intranasal administration in a triple-transgenic mouse model of Alzheimer's disease in the hope of developing a safe and effective treatment for human patients. Reporting in their new *STEM CELLS Translational Medicine* article,[10] Losurdo et al. establish that extracellular vesicles administered via this minimally-invasive route rapidly reach the brain where they dampen the activation of microglia (the macrophages of the central nervous system) and increase dendritic spine density without any unwanted side effects. in vitro analysis then demonstrated that MSC-derived extracellular vesicles polarize murine primary microglia into an anti-inflammatory phenotype, suggesting that the neuroprotective effects observed in vivo derive from the modulation of inflammation. Overall, the authors of this fascinating new study hope that their findings will provide a platform for the exploitation of MSC-derived extracellular vesicles as a treatment for Alzheimer's disease in human patients.



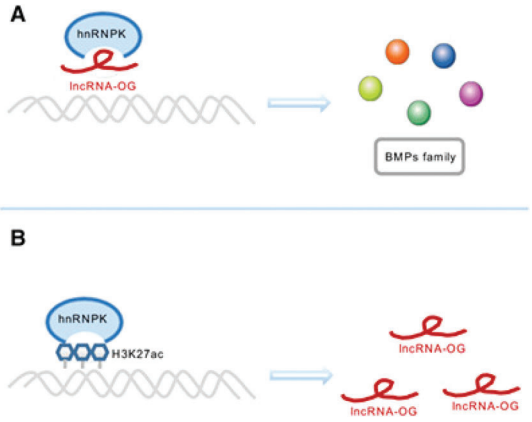
https://doi.org/10.1002/sctm.19-0327

RELATED ARTICLES

Induced Osteogenic Differentiation of Bone Marrow MSCs via a Novel Long Non-Coding RNA

Researchers from the laboratory of Huiyong Shen and Yanfeng Wu (Sun Yat-sen University, Shenzhen, Guangdong, China) previously analyzed lncRNA expression profiles during the osteogenic differentiation of bone marrow MSCs.[17] While they identified multiple important RNAs, they lacked an understanding of mechanisms underlying the lncRNA-mediated regulation of osteogenic differentiation. In a recent *STEM CELLS* article,[5] Tang et al. identified a novel highly-transcribed osteogenesis-associated lncRNA (lncRNA-OG) during their comparison of lncRNA expression profiles in MSCs before and during osteogenic differentiation employing customized microarrays. Functional assays confirmed that lncRNA-OG promoted MSC osteogenesis, and their inquiries into the mechanisms controlling this phenomenon suggested that lncRNA-OG interacts with the heterogeneous nuclear ribonucleoprotein K (hnRNPK) RNA binding protein to activate the BMP signaling pathway. hnRNPK controls cellular processes such as mRNA transcription, mRNA splicing, and chromatin remodeling[18] and interacts with lncRNAs to regulate the expression of various genes.[19] In this study, the authors established that hnRNPK positively regulated lncRNA-OG transcriptional activity by promoting the acetylation of H3K27, a permissive histone modification, within the lncRNA-OG promoter.

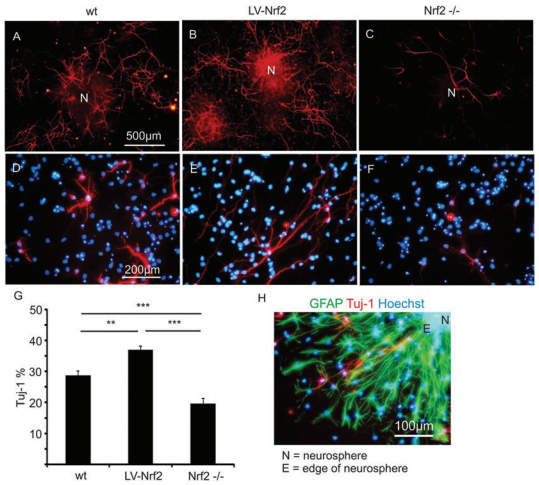
This fascinating study identified lncRNA-OG as a possible target to induce MSC osteogenesis and improve their clinical applicability in conditions such as osteoarthritis while also providing further insight into the relationship between hnRNPK and lncRNA. Moving forward, the authors noted their desire to understand just how lncRNA-OG interacts with hnRNPK to regulate downstream genes in their subsequent research.



https://doi.org/10.1002/stem.2937

Targeting Nrf2 in the Battle Against Alzheimer's Disease

While previous studies had provided evidence that the stabilization of nuclear factor erythroid 2-related factor (Nrf2), a transcription factor induced in response to oxidative stress, could protect NPCs against oxidative stress-induced cell death,[20,21] a possible role for Nrf2 in NPC proliferation, migration, maturation, and protection against beta-amyloidtoxicity, and hence the neurodegeneration and cognitive abnormalities associated with Alzheimer's disease, remained relatively unexplored. This knowledge gap prompted researchers from the laboratory of Jari Koistinaho (University of Eastern Finland, Kuopio, Finland) to undertake a detailed evaluation of the physiological role of Nrf2 in NPCs using knockout mice models. Reporting their findings in a recent *STEM CELLS* article,[11] Kärkkäinen et al. first revealed that Nrf2-null mice exhibited a deficit in the ischemia-induced increase in newborn neurons in the subgranular zone of the dentate gyrus, suggesting that Nrf2 regulates the proliferation and neuronal differentiation of NPCs but not their migration. Moving in vitro, the authors confirmed that the overexpression or overactivation of Nrf2 increased the neuronal differentiation of NPCs, and, excitingly, they also discovered that Nrf2 protected NPCs from the toxic effects of the Alzheimer's disease-associated beta-amyloidpeptide. Overall, these encouraging findings provided evidence that Nrf2 may represent a therapeutic target in the development of novel treatments for Alzheimer's disease.



https://doi.org/10.1002/stem.1666

REFERENCES

1. Wilusz JE, Sunwoo H, Spector DL. Long non-coding RNAs: functional surprises from the RNA world. *Genes Dev*. 2009;23:1494-1504.
2. Ng S-Y, Bogu Gireesh K, Soh Boon S, et al. The long non-coding RNA RMST interacts with SOX2 to regulate neurogenesis. *Mol Cell*. 2013;51:349-359.
3. Carlson HL, Quinn JJ, Yang YW, Thornburg CK, Chang HY, Stadler HS. LncRNA-HIT functions as an epigenetic regulator of chondrogenesis through its recruitment of p100/CBP complexes. *PLoS Genet*. 2015;11:e1005680.
4. Chen Y, Li K, Zhang X, et al. The novel long non-coding RNA lncRNA-Adi regulates adipogenesis. *Stem Cells Translational Medicine*. 2020;9:00-00.
5. Tang Sa XZ, Wang P, et al. LncRNA-OG promotes the osteogenic differentiation of bone marrow-derived mesenchymal stem cells under the regulation of hnRNPK. *Stem Cells*. 2019;37:270-283.
6. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*. 2002;297:353-356.
7. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol*. 2017;35:441-468.
8. Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. *J Cell Biol*. 2018;217:459-472.
9. Benilova I, Karran E, De Strooper B. The toxic Aβ oligomer and Alzheimer's disease: An emperor in need of clothes. *Nat Neurosci*. 2012;15:349-357.
10. Losurdo M, Pedrazzoli M, D'Agostino C, et al. Intranasal delivery of mesenchymal stem cell-derived extracellular vesicles exerts immunomodulatory and neuroprotective effects in a 3xTg model of Alzheimer's disease. *Stem Cells Translational Medicine*. 2020;9:00-00.
11. Kärkkäinen V, Pomeshchik Y, Savchenko E, et al. Nrf2 regulates neurogenesis and protects neural progenitor cells against Aβ toxicity. *Stem Cells*. 2014;32:1904-1916.
12. Zhu E, Zhang J, Li Y, Yuan H, Zhou J, Wang B. Long non-coding RNA Plnc1 controls adipocyte differentiation by regulating peroxisome proliferator-activated receptor γ. *FASEB J*. 2019;33:2396-2408.

13. Li M, Xie Z, Wang P, et al. The long non-coding RNA GAS5 negatively regulates the adipogenic differentiation of MSCs by modulating the miR-18a/CTGF axis as a ceRNA. *Cell Death Dis*. 2018;9:554.
14. Sun L, Goff LA, Trapnell C, et al. Long non-coding RNAs regulate adipogenesis. *Proc Natl Acad Sci U S A*. 2013;110:3387-3392.
15. Cui G-H, Wu J, Mou F-F, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. *FASEB J*. 2018;32:654-668.
16. Wang S-S, Jia J, Wang Z. Mesenchymal stem cell-derived extracellular vesicles suppresses iNOS expression and ameliorates neural impairment in Alzheimer's disease mice. *J Alzheimers Dis*. 2018;61:1005-1013.
17. Xie Z, Li J, Wang P, et al. Differential expression profiles of long non-coding RNA and mRNA of osteogenically differentiated mesenchymal stem cells in ankylosing spondylitis. *J Rheumatol*. 2016;43:1523-1531.
18. Bomsztyk K, Denisenko O, Ostrowski J. hnRNP K: One protein multiple processes. *Bioessays*. 2004;26:629-638.
19. Li Z, Chao TC, Chang KY, et al. The long non-coding RNA THRIL regulates TNFα expression through its interaction with hnRNPL. *Proc Natl Acad Sci U S A*. 2014;111:1002-1007.
20. Li J, Johnson D, Calkins M, Wright L, Svendsen C, Johnson J. Stabilization of Nrf2 by tBHQ confers protection against oxidative stress-induced cell death in human neural stem cells. *Toxicol Sci*. 2005;83:313-328.
21. Kanninen K, Malm TM, Jyrkkänen H-K, et al. Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. *Mol Cell Neurosci*. 2008;39:302-313.