Received: 29 January 2020 | Accepted: 29 January 2020

DOI: 10.1002/sctm.20-0044

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 amniotic membrane of the placenta represents an exciting source of stem and stem-like cells, including human amnion epithelial cells (hAECs)—an easy-to-collect and abundant cell population possessing an embryonic stem cell-like differentiation capacity, potent immunomodulatory and anti-inflammatory properties[1] but, importantly, lacking tumorigenic potential.[2] Furthermore, hAECs are immune-privileged, thereby exhibiting a low risk of host rejection upon transplantation. These advantageous characteristics have prompted the exploration of hAECs in therapies for conditions ranging from stroke[3] to lung diseases such as bronchopulmonary dysplasia (BPD), a common complication in premature infants.[4] Other related stem cells readily isolatable from the placenta include stem cells derived from the amniotic membrane and amniotic fluid, as well as mesenchymal stem cells (MSCs) derived from the placenta. As with MSC populations isolated from other tissues, placenta MSCs display multipotential differentiation capacity and potent immunomodulatory abilities and have been employed to promote angiogenesis in non-diabetic rodent models of hind limb ischemia at 2 to 3 weeks post-treatment[5]; however, questions remain as to the exact therapeutic mechanisms at play. In our first Featured Article published in *STEM CELLS Translational Medicine* this month, Malhotra et al. report on the long-term safety outcomes in premature infants with severe BPD treated with hAECs.[6] In a Related Article recently published in *STEM CELLS*, He et al. demonstrated that human placenta MSCs exert potent angiogenic activity through an immunomodulatory mechanism involving T cell-dependent reprogramming of macrophage differentiation toward an M2 phenotype in mouse hind limb ischemia models.[7]

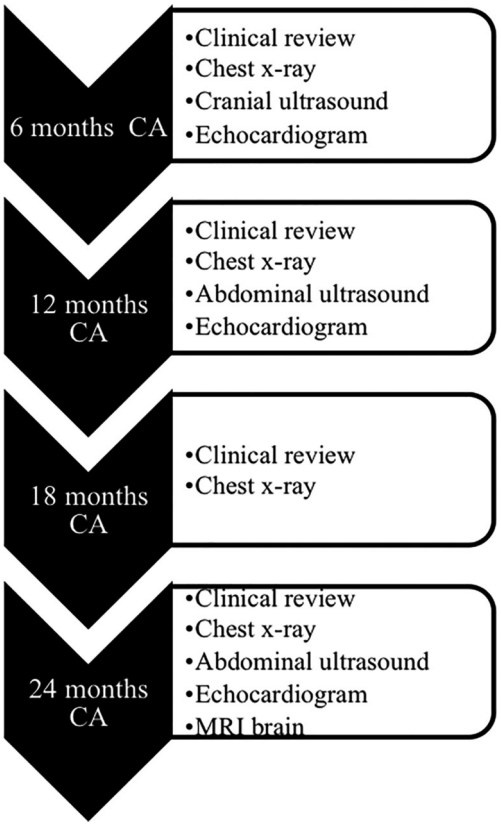
The osteogenic potential of human MSCs has led to their application in bone repair/regeneration strategies, and a huge number of studies have explored a range of growth factors and scaffolds that can promote their optimal therapeutic function. Biocompatible scaffolds must possess a structure and composition that promotes MSC survival, osteoinductivity, and osteoconductivity when employed for bone regrowth; however, they must also exhibit predictable mechanical and degradation properties during the healing process. Porous hydroxylapatite/collagen hybrid biomaterials have been found suitable for bone grafting and regeneration,[8,9] and studies have begun to explore how the complex interactions of such advanced biomaterials with MSCs promote bone regrowth over short time periods[10]; however, we currently lack data reflecting the times required in vivo by the bone to regrow or repair. Age represents another critical aspect impacting the differentiation capacity of MSCs; while evaluations often employ MSCs derived from young donors, MSCs from older donors tend to exhibit skewed differentiation propensities. Can a deeper understanding of MSC aging aid the development of treatment strategies for age-related bone diseases such as osteoporosis? In our second Featured Article published in *STEM CELLS Translational Medicine* this month, Mazzoni et al. describe how the combination of a hybrid hydroxylapatite/collagen scaffold and human adipose-derived MSCs fosters the continuous expression of osteogenic, osteoclastic, and chondrogenic genes that combine to favor bone regrowth in vivo.[11] In a Related Article recently published in *STEM CELLS*, Chen et al. reported on their studies regarding the age-dependent osteogenic and adipogenic differentiation of MSCs that highlighted the histone-modifying enzyme enhancer of zeste homolog 2 (EZH2) as a potential therapeutic approach to osteoporosis and obesity.[12]

FEATURED ARTICLES

Long-Term Safety Results for Amnion Cell Therapy in Infants with Bronchopulmonary Dysplasia

BPD, a common complication in premature infants, causes an increased risk of long-term respiratory issues, with severe forms of the disease prompting developmental delay and the onset of other neuromorbidities.[4] In a previous study, researchers led by Atul Malhotra (Monash University, Clayton, VIC, Australia) evaluated the safety and tolerability of allogeneic hAECs in six premature infants with established severe BPD and described the immediate and short-term outcomes.[13] Now, the team returns with a *STEM CELLS Translational Medicine* article, in which they report on the longer-term safety outcomes of these infants.[6] Premature infants previously received hAECs intravenously, with the long-term follow-up data revealing that all but one infant survived to the evaluation endpoint and that these five infants were weaned off oxygen at a median time of 24 months. Magnetic resonance imaging of the brain established the presence of mild to moderate white matter loss, and the neurodisabilities diagnosed

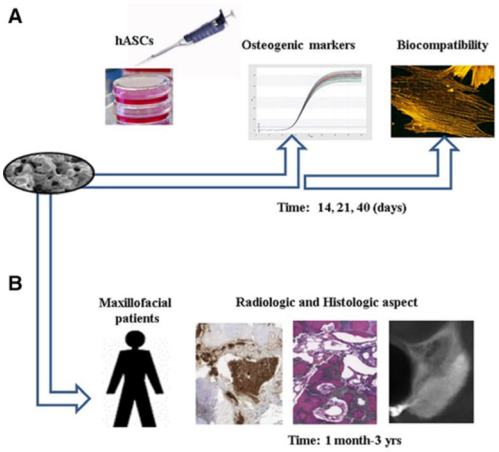
included hemiplegic cerebral palsy, global developmental delay, and severe hearing loss. However, the authors failed to observe evidence of tumor formation following hAEC administration or any long-term adverse events that could be attributed to hAEC administration. Overall, these findings establish the safety of low-dose allogeneic hAEC administration in vulnerable premature infants. Ongoing studies will aim to elucidate the optimum dosage and timing of hAEC administration toward optimizing treatment outcomes for BPD patients.



https://doi.org/10.1002/sctm.19-0251

Hybrid Scaffold-Induced Differentiation of Human MSCs Favors Bone Regrowth Patients

The osteoinduction of MSCs cultured on advanced scaffolding materials represents a potentially exciting means to effectively treat bone fractures or injuries that can significantly impact patients' quality of life. The long-term clinical results of cheekbone augmentation employing hydroxylapatite/collagen hybrid biomaterials demonstrated an excellent biocompatibility profile,[14] and a recent study from the laboratories of Mauro Tognon and Fernanda Martini (University of Ferrara, Italy) recently sought to evaluate the potential of human adipose-derived MSCs cultured on this biomaterial. Reporting in *STEM CELLS Translational Medicine*, Mazzoni et al. evaluated the biocompatibility and osteoinductivity of the hybrid scaffold with MSCs cultured for more than 40 days and investigated the clinical potential in patients undergoing surgical procedures in the cheekbone area with a follow-up three years.[11] The in vitro analyses established the osteoconductive nature of the hybrid scaffold through the observed upregulation of osteogenesis-, chondrogenic-, and osteoclast-related gene expression at all time points assessed, as well as via the detection of matrix mineralization, alkaline phosphatase activity, and through protein-based analysis. Encouragingly, clinical evaluations following the in vivo application of MSCs cultured with the hybrid scaffold provided evidence of biocompatibility and bone regrowth, with histological analysis of biopsy specimens revealing prominent ossification. In summary, the authors suggest that the induced and continuous expression of osteogenic, osteoclastic, and chondrogenic genes in MSCs in response to the hybrid scaffold permits the enhanced bone regrowth activity observed in patients.



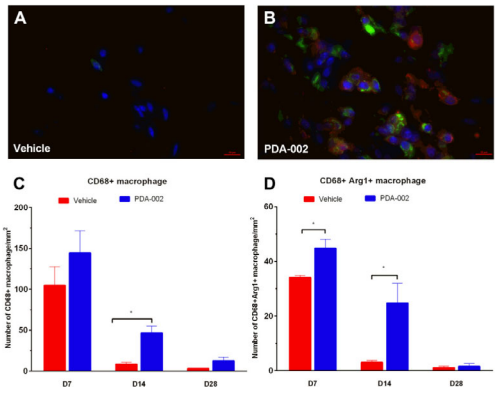
https://doi.org/10.1002/sctm.19-0170

RELATED ARTICLES

Reprogrammed Macrophages Aid Placenta Mesenchymal Stem Cell-Mediated Angiogenesis

Researchers led by Shuyang He (Celgene Cellular Therapeutics, Warren, NJ) previously established the immunomodulatory capabilities of placenta MSCs[15,16] and discovered that these cells promoted angiogenesis in non-diabetic rodent models of hind limb ischemia at two to three weeks post-treatment, even though the MSCs persisted for less than one week.[5] In their subsequent *STEM CELLS* article, He et al. investigated how human placenta MSCs (PDA-002) robustly induced angiogenesis using mice hind limb ischemia models and highlighted an immunomodulatory mechanism involving T-cell-dependent reprogramming of macrophage differentiation toward an M2-like phenotype. In brief, the administration of human placenta MSCs improved blood flow and promoted collateral vessel formation in the injured limb while also prompting the appearance of M2-like macrophages in ischemic

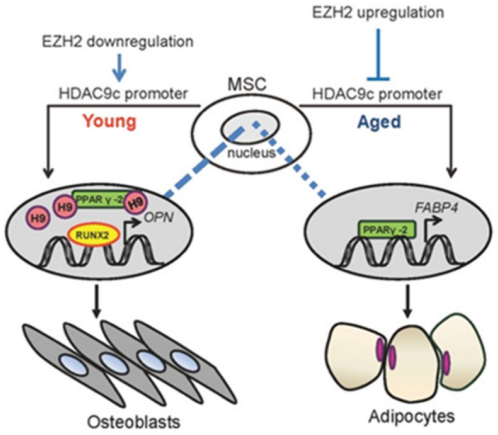
tissue and an increase in T-helper 2 cells in draining lymph nodes. Fascinatingly, human placenta MSC administration in nude mice failed to induce M2 macrophage polarization *or* angiogenesis; however, both responses returned following T-cell reconstitution. Overall, the authors established that human placenta MSC therapy enhanced angiogenesis via the T-cell-dependent polarization of macrophages toward a proregenerative/anti-inflammatory phenotype, a finding that they hope will help to guide the future design of clinical trials and define important parameters, such as dosing, administration route, and potential biomarkers that report MSC activity and clinical efficacy.



https://doi.org/10.1002/stem.2598

The Age-Dependent Expression of Epigenetic Modifiers in MSCs Highlights Therapeutic Targets for Osteoporosis and Obesity

Previous findings from the laboratory of Long-Yuan Li (National Chung Hsing University, Taichung, Taiwan) described how EZH2, the catalytic component of the polycomb-repressive complex 2, mediated the epigenetic silencing of histone deacetylase 9c (HDAC9c) and how HDAC9c expression accelerated osteogenesis and attenuated adipogenesis in MSCs through the inactivation of peroxisome proliferator-activated receptor-gamma 2 (PPARγ-2) activity.[17] Given the rise in age-related osteoporosis and obesity and the possible link to dysregulated MSC differentiation,[18] the authors sought to explore the relevance of the EZH2-HDAC9c axis in the alteration to osteogenic and adipogenic differentiation potential of both human and mouse MSCs during normal aging. Writing in *STEM CELLS*, Chen et al.[12] discovered that while young MSCs expressed low levels of HDAC9c, leading to the osteogenesis of MSCs due to the sequestration of PPARγ-2, older MSCs displayed increased EZH2 expression and reduced HDAC9c expression, leading to the loss of osteogenic differentiation and an increase in MSC adipogenesis. In summary, this study linked the dysregulation of an epigenetic control mechanism in MSCs to age-associated osteoporosis and obesity, thereby highlighting the targeting of the EZH2-HDAC9c axis as a potential therapeutic approach to conditions that affect over ten million individuals worldwide and suppose a serious economic burden.



https://doi.org/10.1002/stem.2400

REFERENCES

1. Miki T. Stem cell characteristics and the therapeutic potential of amniotic epithelial cells. *Am J Reprod Immunol*. 2018;80:e13003.
2. Miki T, Lehmann T, Cai H, Stolz DB, Strom SC. Stem cell characteristics of amniotic epithelial cells. *Stem Cells*. 2005;23:1549-1559.
3. Evans MA, Lim R, Kim HA, et al. Acute or delayed systemic administration of human amnion epithelial cells improves outcomes in experimental stroke. *Stroke*. 2018;49:700-709.
4. Cheong JLY, Doyle LW. An update on pulmonary and neurodevelopmental outcomes of bronchopulmonary dysplasia. *Semin Perinatol*. 2018;42:478-484.
5. Francki A, Labazzo K, He S, et al. Angiogenic properties of human placenta-derived adherent cells and efficacy in hindlimb ischemia. *J Vasc Surg*. 2016;64:746-756.e1.
6. Malhotra A, Lim R, Mockler JC, Wallace EM. Two-year outcomes of infants enrolled in the first-in-human study of amnion cells for bronchopulmonary dysplasia. *Stem Cells Transl Med*. 2019;9:00-00.
7. He S, Gleason J, Fik-Rymarkiewicz E, et al. Human placenta-derived mesenchymal stromal-like cells enhance angiogenesis via T cell-dependent reprogramming of macrophage differentiation. *Stem Cells*. 2017;35:1603-1613.
8. Venkatesan J, Kim SK. Nano-hydroxyapatite composite biomaterials for bone tissue engineering—a review. *J Biomed Nanotechnol*. 2014;10:3124-3140.
9. Duan W, Haque M, Kearney MT, Lopez MJ. Collagen and hydroxyapatite scaffolds activate distinct osteogenesis signaling pathways in adult adipose-derived multipotent stromal cells. *Tissue Eng Part C Methods*. 2017;23:592-603.
10. Mazzoni E, D'Agostino A, Manfrini M, et al. Human adipose stem cells induced to osteogenic differentiation by an innovative collagen/hydroxylapatite hybrid scaffold. *FASEB J*. 2017;31:4555-4565.
11. Mazzoni E, D'Agostino A, Iaquinta MR, et al. Hydroxylapatite-collagen hybrid scaffold induces human adipose-derived mesenchymal stem cells to osteogenic differentiation in vitro and bone regrowth in patients. *Stem Cells Transl Med*. 2019;9:00-00.
12. Chen YH, Chung CC, Liu YC, et al. Enhancer of zeste homolog 2 and histone deacetylase 9c regulate age-dependent mesenchymal stem cell differentiation into osteoblasts and adipocytes. *Stem Cells*. 2016;34:2183-2193.

13. Lim R, Malhotra A, Tan J, et al. First-in-human administration of allogeneic amnion cells in premature infants with bronchopulmonary dysplasia: a safety study. *Stem Cells Transl Med*. 2018; 7:628-635.
14. D'Agostino A, Trevisiol L, Favero V, et al. Hydroxyapatite/collagen composite is a reliable material for malar augmentation. *J Oral Maxillofac Surg*. 2016;74:1238.e1-1238.e15.
15. He S, Khan J, Gleason J, et al. Placenta-derived adherent cells attenuate hyperalgesia and neuroinflammatory response associated with perineural inflammation in rats. *Brain Behav Immun*. 2013;27: 185-192.
16. Liu W, Morschauser A, Zhang X, et al. Human placenta-derived adherent cells induce tolerogenic immune responses. *Clin Transl Immunol*. 2014;3:e14.
17. Chen Y-H, Yeh F-L, Yeh S-P, et al. Myocyte enhancer factor-2 interacting transcriptional repressor (MITR) is a switch that promotes osteogenesis and inhibits adipogenesis of mesenchymal stem cells by inactivating peroxisome proliferator-activated receptor γ-2. *J Biol Chem*. 2011;286:10671-10680.
18. Meunier P, Aaron J, Edouard C, et al. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. *Clin Orthop Relat Res*. 1971;80:147-154.