Received: 6 January 2020 | Accepted: 8 January 2020

DOI: 10.1002/sctm.20-0003

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

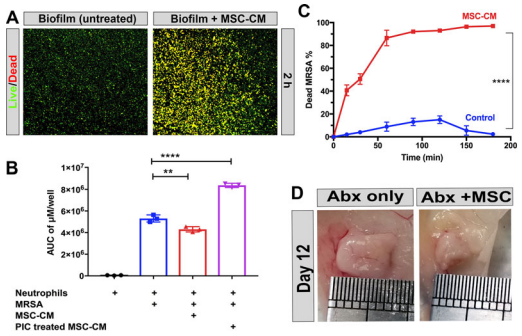
Centro de Investigación Príncipe Felipe, Valencia, Spain

A wide range of experimental and clinical studies have underlined the immunomodulatory, anti-inflammatory, and wound healing capabilities of mesenchymal stem cells (MSCs), leading to their application in a range of reparative and regenerative approaches. However, these multifunctional cells also possess another less appreciated ability, with multiple in vitro studies providing evidence for the potent and direct bactericidal activity of MSCs.[1] Given the unfortunate rise of antibiotic-resistant bacteria and the devastating effects observed following infections in debilitated patients, many have sought to explore cotreatment with MSCs as a means to potentiate conventional antibiotic therapy.[1] Previous research efforts have demonstrated that MSCs directly influence the immunological properties of macrophages and neutrophils via secreted factors,[2,3] while they also produce antimicrobial peptides that directly kill bacteria either by disrupting the integrity of the microbial membrane[4] or by recruiting immune cells following the induced release of proinflammatory cytokines. Overall, the full delineation of the molecular mechanisms that underlie the antimicrobial activity of MSCs in vitro and in vivo may allow for the development of exciting new means to prevent devastating infections by antibiotic-resistant bacteria. In our first Featured Article from *STEM CELLS Translational Medicine*, Chow et al explore the mechanisms by which MSCs augment the antimicrobial activity of various classes of conventional antibiotics, including the generation of enhanced activity against drug-resistant strains of *Staphylococcus aureus* (*S. aureus*).[5] In a Related Article published in *STEM CELLS*, Qian et al demonstrated that adipose-derived MSCs can attenuate *S. aureus*-induced lung injury and improve survival of infected mice by reducing the bacterial load and alleviating inflammatory responses through paracrine-acting secreted factors.[6]

Asthma, a chronic inflammatory disease characterized by CD4+ T helper 2 lymphocyte-controlled immune responses against allergens that result in lung remodeling, deregulated inflammation, airway hyperresponsiveness, and airflow obstruction, affects a significant and ever-rising number of people worldwide. The common house dust mite (HDM) represents the most common allergen implicated in human asthma, affecting approximately 85% of asthmatic patients globally.[7] Conventional therapeutics efficiently relieve asthmatic symptoms in most patients; however, said approaches fail to reverse established lung remodeling and bring little relief to those cohorts of patients with more severe pathologies.[8,9] As MSCs display pro-regenerative, immunomodulatory, and anti-inflammatory capabilities, they may serve as a potentially exciting treatment option for patients with severe asthma; however, important questions remain concerning the dosing regimens required to optimize therapeutic effects and the exact mechanisms involved in the anti-asthmatic response following MSC administration. In our second Featured Article from *STEM CELLS Translational Medicine*, Castro et al. report that while multiple doses of MSCs can reduce lung inflammation and remodeling and improve lung mechanics in a mouse model of allergic asthma, this approach also results in immunosuppressive side-effects.[10] In a Related Article published in *STEM CELLS*, Braza et al demonstrated that lung macrophages phagocytose MSCs following administration to a mouse model of asthma, with macrophages then becoming polarized into an immunosuppressive phenotype to induce the anti-inflammatory effects observed.[11]

FEATURED ARTICLES

Exploring the Antibacterial Activity of Human Mesenchymal Stem Cells



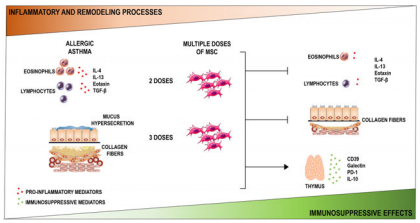
Bacterial biofilm formation represents an important challenge to the treatment of chronic infections, as these microbial aggregates favor bacterial persistence and immune response evasion[12] while also inhibiting the effect of antibiotics.[13] Researchers led by Steven Dow (Colorado State University, Ft. Collins, CO, USA) previously studied chronic *S. aureus* biofilm infection in a mouse implant infection model to demonstrate how the antibacterial activity of systemically

delivered MSCs prompted the resolution of wound infections when combined with antibiotic therapy.[14] Now, the authors return with a new *STEM CELLS Translational Medicine* article in which they report on their exploration of the mechanisms by which human MSCs can control/eradicate severe bacterial infections.[5] Chow et al established that MSCs exhibited elevated levels of bactericidal activity in vitro and that MSC-secreted factors (present in conditioned media) inhibited biofilm formation and even disrupted the growth of established biofilms. The authors also discovered that antibiotic therapy synergized with MSC-secreted factors to promote the killing of drug-resistant bacteria (such as methicillin-resistant *S. aureus* [MRSA]) and that MSCs interacted with the host innate immune responses to trigger neutrophil extracellular trap formation and increase bacterial phagocytosis. Indeed, the combination of MSC administration with antibiotic therapy (Abx in adjoined figure) effectively reduced bacterial numbers and improved wound healing in mice with established *S. aureus* biofilm infections. The authors hope that their findings will provide the impetus for the implementation of MSC administration alongside antibiotic therapy as an efficient means to treat highly drug-resistant infections present in relatively inaccessible sites.

https://doi.org/10.1002/sctm.19-0092

Exploring Adipose-Derived Stem Cell Therapy for the Treatment of Asthma

Previous studies reported that a single administration of MSCs in a mouse model of HDM-induced allergic asthma fostered a reduction in selected inflammatory parameters but, unfortunately, failed to improve lung function or inhibit lung remodeling.[15,16] In an attempt to improve the efficacy of MSC-based asthma therapies, researchers from the laboratory of Patricia Rieken Macedo Rocco (Federal University of Rio de Janeiro, Brazil) explored the impact of multiple-dose MSC administrations on experimental allergic asthma. Reporting in a recent *STEM CELLS Translational Medicine* article, Castro et al evaluated the therapeutic outcomes of two or three intravenous doses of human adipose tissue-derived MSCs provided 24 hours after the intranasal delivery of HDM in C57BL/6 mice.[10] Interestingly, multiple doses of MSCs significantly reduced lung inflammation and remodeling while improving lung mechanics; however, this approach also prompted an immunosuppressive effect. Indeed, the authors discovered that multiple MSC doses reduced total leukocyte counts in bone marrow, spleen, and mediastinal lymph nodes while modulating T-cell subpopulations and enhancing expression levels of immunosuppression-associated mediators in the thymus. The authors hope that future MSC-based clinical trials in patients with severe asthma will consider their fascinating findings, and they next aim to evaluate the short- and long-term outcomes linked to multiple MSC administrations in models of allergic asthma.

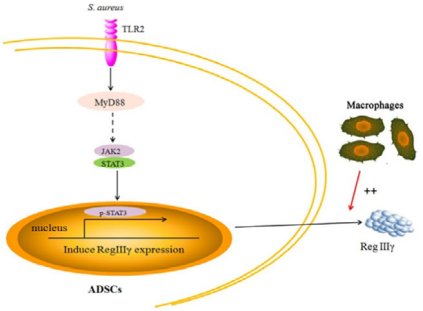


https://doi.org/10.1002/sctm.19-0120

RELATED ARTICLES

Deciphering How Adipose-Derived Stem Cells Protects Against Bacterial-Induced Lung Injury

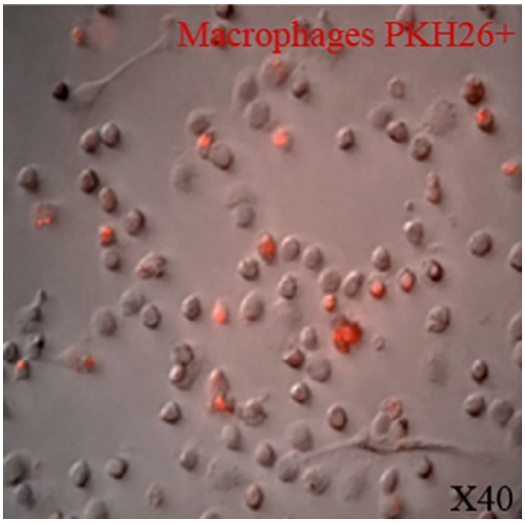
Severe bacterial infections represent a leading cause of acute lung injury (ALI) and recent research efforts have suggested that adipose-derived MSCs may represent a potentially exciting treatment option that takes advantage of the secretion of paracrine-acting factors.[17] As described in their recent *STEM CELLS* article, researchers from the laboratory of Feng Xu (Zhejiang University, Hangzhou, China) evaluated the therapeutic effect of MSCs on *S. aureus*-induced ALI in mice, finding that intratracheal injections of cells attenuated the severity of lung inflammation, reduced bacterial load, and improved the survival of infected mice.[6] Mechanistically, Qian et al established that the activation of the Toll-like receptor 2 (TLR2), myeloid differentiation primary response 88 (MyD88), and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) intracellular signaling cascades prompted the secretion of the regenerating islet-derived IIIγ (RegIIIγ) from MSCs, which mediated the direct antimicrobial effects. RegIIIγ belongs to the C-type lectin superfamily, and studies have indicated roles for RegIIIγ in antibacterial and anti-inflammatory processes, as well as in promoting cell proliferation and differentiation.[18] Finally, the authors determined that a paracrine secretion pathway engaged by macrophages further amplified the above-mentioned signaling pathways to promote the observed therapeutic responses. Overall, this fascinating study provides more evidence that treatment with MSCs may benefit patients with severe bacterial infections due to their inherent antimicrobial capacities.



https://doi.org/10.1002/stem.2337

MSC Therapy Induces the Formation of Anti-Inflammatory Macrophages in Mouse Asthma Model

Mechanistic insights into how MSCs dampen the chronic inflammation associated with allergic asthma have suggested that administered cells very rarely integrate within the lungs[19] and that any therapeutic effect derives from paracrine-acting effectors[20] and interactions with macrophages.[21] To further explore the therapeutic mechanisms underlying MSC-based asthma treatment approaches, researchers led by Stéphanie Dirou and Patricia Lemarchand (Université de Nantes, France) evaluated responses in an acute mouse model of HDM-induced allergic asthma following a single intravenous injection of MSCs and described their findings in a recent *STEM CELLS* article.[11] Braza et al reported that this approach normalized and stabilized lung function by inhibiting the contractile response of bronchi and resolving inflammation. To better appreciate the in vivo fate of MSCs, the authors fluorescently labeled cells with the PKH26 red fluorescent marker before MSC administration and then digested lungs to obtain and analyse a single-cell suspension. This approach confirmed the general lack of MSC engraftment in the lungs, but also uncovered a huge overlap of fluorescently-labeled cells with markers of anti-inflammatory immunosuppressive M2 macrophages. This suggested to the authors that macrophages phagocytose the vast majority of the administered MSCs and so mediate the in vivo anti-inflammatory efficacy of MSCs through the formation of a tolerogenic microenvironment that may counterbalance T-cell mediated airway inflammation in asthma.



https://doi.org/10.1002/stem.2344

REFERENCES

1. Marrazzo P, Crupi AN, Alviano F, Teodori L, Bonsi L. Exploring the roles of MSCs in infections: focus on bacterial diseases. *J Mol Med (Berl)*. 2019;97:437-450.
2. Vasandan AB, Jahnavi S, Shashank C, Prasad P, Kumar A, Prasanna SJ. Human mesenchymal stem cells program macrophage plasticity by altering their metabolic status via a PGE2-dependent mechanism. *Sci Rep*. 2016;6:38308.
3. Maqbool M, Vidyadaran S, George E, Ramasamy R. Human mesenchymal stem cells protect neutrophils from serum-deprived cell death. *Cell Biol Int*. 2011;35:1247-1251.
4. Mahlapuu M, Håkansson J, Ringstad L, Björn C. Antimicrobial peptides: an emerging category of therapeutic agents. *Front Cell Infect Microbiol*. 2016;6:194.
5. Chow L, Johnson V, Impastato R, Coy J, Strumpf A, Dow S. Antibacterial activity of human mesenchymal stem cells mediated directly by constitutively secreted factors and indirectly by activation of innate immune effector cells. *Stem Cells Translational Medicine*. 2019;9:235-249.
6. Qian J, Hu Y, Zhao L, et al. Protective role of adipose-derived stem cells in *Staphylococcus aureus*-induced lung injury is mediated by RegIIIγ secretion. *Stem Cells*. 2016;34:1947-1956.
7. Gregory LG, Lloyd CM. Orchestrating house dust mite-associated allergy in the lung. *Trends Immunol*. 2011;32:402-411.
8. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention. NHLB-WHO Workshop Report*. Bethesda: National Heart, Lung and Blood Institute Publication; 2002:2.
9. Barnes PJ. New therapies for asthma: is there any progress? *Trends Pharmacol Sci*. 2010;31:335-343.
10. Castro LL, Kitoko JZ, Xisto DG, et al. Multiple doses of adipose tissue-derived mesenchymal stromal cells induce immunosuppression in experimental asthma. *Stem Cells Translational Medicine*. 2019;9:250-260.
11. Braza F, Dirou S, Forest V, et al. Mesenchymal stem cells induce suppressive macrophages through phagocytosis in a mouse model of asthma. *Stem Cells*. 2016;34:1836-1845.
12. Bjarnsholt T. The role of bacterial biofilms in chronic infections. *APMIS Suppl*. 2013;136:1-51.
13. Hanke M, Kielian T. Deciphering mechanisms of staphylococcal biofilm evasion of host immunity. *Front Cell Infect Microbiol*. 2012;2:62.
14. Johnson V, Webb T, Norman A, et al. Activated mesenchymal stem cells interact with antibiotics and host innate immune responses to control chronic bacterial infections. *Sci Rep*. 2017;7:9575.
15. Kitoko JZ, de Castro LL, Nascimento AP, et al. Therapeutic administration of bone marrow-derived mesenchymal stromal cells reduces airway inflammation without up-regulating Tregs in experimental asthma. *Clin Exp Allergy*. 2018;48:205-216.
16. Mariñas-Pardo L, Mirones I, Amor-Carro Ó, et al. Mesenchymal stem cells regulate airway contractile tissue remodeling in murine experimental asthma. *Allergy*. 2014;69:730-740.
17. Zhang S, Danchuk SD, Imhof KMP, et al. Comparison of the therapeutic effects of human and mouse adipose-derived stem cells in a murine model of lipopolysaccharide-induced acute lung injury. *Stem Cell Res Ther*. 2013;4:13.
18. Lehotzky RE, Partch CL, Mukherjee S, et al. Molecular basis for peptidoglycan recognition by a bactericidal lectin. *Proc Natl Acad Sci USA*. 2010;107:7722-7727.
19. Nemeth K, Keane-Myers A, Brown JM, et al. Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma. *Proc Natl Acad Sci USA*. 2010;107:5652-5657.
20. Lee JW, Fang X, Krasnodembskaya A, Howard JP, Matthay MA. Concise review: mesenchymal stem cells for acute lung injury: role of paracrine soluble factors. *Stem Cells*. 2011;29:913-919.
21. Mathias LJ, Khong SM, Spyroglou L, et al. Alveolar macrophages are critical for the inhibition of allergic asthma by mesenchymal stromal cells. *J Immunol*. 2013;191:5914-5924.