



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

Stuart P. Atkinson

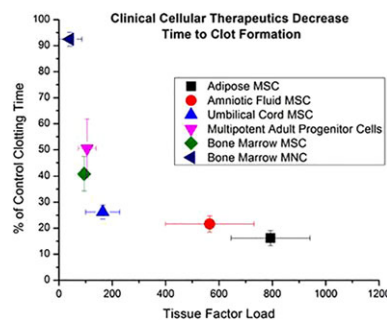
Centro de Investigación
Príncipe Felipe, Valencia,
Spain

Intravenous infusion represents an often-used delivery route for stem cell therapeutics; however, unwanted interactions between blood and the cell population employed can induce significant levels of clotting. Increased clotting has the potential to reduce the regenerative output of stem cell therapies, but more importantly, this process may also increase the risk of deleterious side effects. Both *in vitro* [1] and *in vivo* [2] assessments of interactions between human mesenchymal stem cells (MSCs) and blood have demonstrated that the expression of tissue factor (TF), a proclotting component, accelerates clot formation and reduces therapeutic efficacy, although we lack a fuller understanding of the clotting potential of other therapeutically relevant stem cell populations. Our first Featured Article from George et al. [3] now establishes that a wide range of stem cell types differentially promote clot formation via varying levels of TF expression, thereby advocating for the implementation of clotting activator analysis in safety assessments for stem cell therapies. In a Related Article, Gleeson et al. [4] demonstrate how the proclotting characteristics of MSCs can impede treatment of myocardial infarction (MI), but also describe how an anticoagulating strategy can nullify these deleterious effects and promote regenerative function.

The application of MSCs also extends to the treatment of multiple sclerosis (MS), a neurodegenerative disease of the central nervous system characterized by inflammatory demyelination and the development of severe neurological disability. The anti-inflammatory, immunomodulatory, and antioxidant activities of MSCs combined with their favorable safety profile have brought hope of an effective stem cell therapy for MS patients; however, we lack a full understanding of how MS and the associated proinflammatory environment affect MSC function. Unfortunately, very recent studies have provided evidence that MSCs derived from MS patients suffer from an early aging-like phenotype [5] with diminished paracrine neuroprotective abilities [6]. Our second Featured Article from Redondo et al. [7] describes how an increased susceptibility to nitrosative stress in combination with the reduced expression, activity, and secretion of antioxidants can contribute to the functional deficits observed in MSCs derived from MS patients. In a Related Article, Strong et al. [8] report that obesity imposes proinflammatory characteristics on adipose-derived stem cells (ASCs), impairs their ability to modulate the immune system, and negatively affects their therapeutic effect in MS patients.

FEATURED ARTICLES

Time to Consider Clotting in Clinical Cellular Therapeutics?



Given the potential for stem cell therapies to induce clotting, thereby reducing therapeutic effectiveness and increasing the risk of unwanted side effects, researchers from the laboratory of Charles S. Cox, Jr. (University of Texas Health Science Center, Houston, TX) sought to explore the clotting potential of a wide range of therapeutically relevant cell types. In their *STEM CELLS Translational Medicine* article [3], George et al. established that therapeutic cells derived from bone marrow, adipose, amniotic fluid, umbilical cord, and multipotent adult progenitor cell donors all display widely varying levels of proclotting activity that correlated with TF

expression. Of note, adipose- and amniotic fluid-derived MSCs expressed the highest TF levels, leading to the most accelerated clot formation of all cells tested. However, the authors discovered that treatment with an anti-TF antibody reduced clotting for some cell types, although analysis of amniotic fluid- and bone marrow-derived MSCs suggested the involvement of an additional clotting mechanism for these cell types. Overall, the authors advise the consideration of TF levels as a safety measure for the approximately 800 active clinical trials employing cell/stem cell therapies in the United States.

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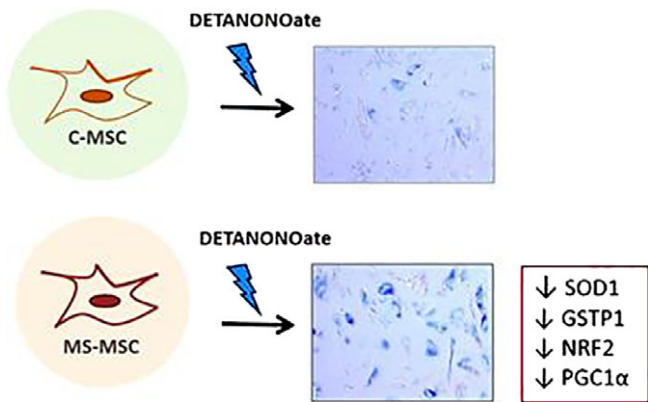
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Dysregulation of Antioxidant Responses: A Potential Problem for Autologous MSC-Based Therapy in Multiple Sclerosis Patients

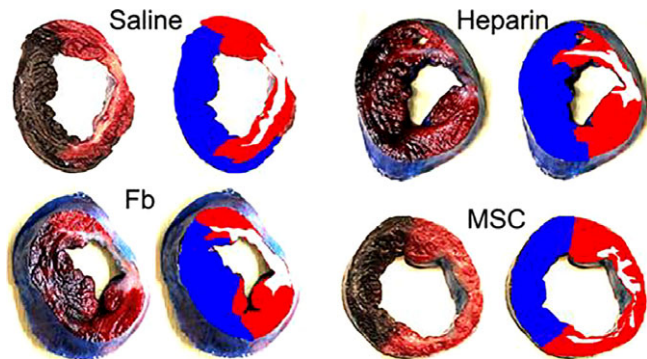
Previous studies from the laboratory of Claire M. Rice (Southmead Hospital, Bristol, UK) revealed that MSCs derived from MS patients suffered from an early aging-like phenotype, displaying reduced expansion and neuroprotective activity and premature senescence in vitro, indicating a potential problem for their in vivo therapeutic application. In a new *STEM CELLS Translational Medicine* article, Redondo et al. [5] now establish that MSCs derived from MS patients display an elevated sensitivity to nitrosative stress (as determined by exposure to DETANONOate, a nitric oxide donor) and the diminished expression, activity, and secretion of antioxidants such as superoxide dismutase 1 (SOD1) and glutathione S-transferase P (GSTP1). The authors linked the reduced expression of antioxidants to a decrease in expression of master regulators of antioxidant responses (NRF2 and PGC1 α) and negatively correlated this downregulation with the duration of the progressive phase of MS. The authors advocate for the reversal of these functional deficits before therapeutic applications of MSCs from MS patients and, interestingly, suggest that MSC dysfunction could play a role in the pathophysiology of progressive MS and/or its comorbidities.



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RELATED ARTICLES

Identifying and Solving a Clotting Problem in MSC Treatment of Myocardial Infarction



Researchers from the laboratory of Noel Caplice (University College Cork, Cork, Ireland) knew that the intracoronary delivery of MSCs represented an exciting means to treat MI in an expanded number of patients by promoting the preservation of cardiac structure and function; however, they also recognized safety concerns regarding MSCs and blood clotting. In their *STEM CELLS* study, Gleeson et al. [4] discovered that expression of TF by MSCs generated clots in vitro and decreased coronary flow reserve in a porcine MI model, possibly through the potentiation of microvascular thrombosis, leading to aberrant remodeling of the heart. However, the administration of heparin alongside MSCs inhibited clot formation and led to improved heart function and attenuated

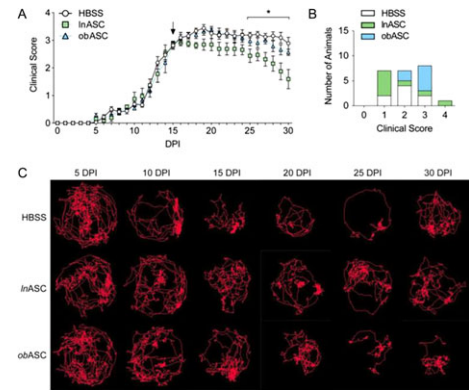
scar formation. The adjointed figure displays heart section images post-MI treated with saline, heparin, heparin-assisted MSC, or fibroblasts; red and white labeling indicates the area at risk and the infarct territory, respectively. Overall, the authors highlight the potential clotting risk of MSC-based therapies, but also describe a means to successfully negate deleterious MSC-derived effects and promote regenerative capabilities in the infarcted heart.

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Obesity May Hinder Adipose-Derived Stem Cell Therapy in Multiple Sclerosis Patients

ASCs represent another stem cell type suited to the treatment of MS, and researchers from the laboratory of Bruce A. Bunnell (Tulane University School of Medicine, New Orleans, LA) sought to discover if ASCs derived from obese female patients (obASCs) displayed any functional deficits when compared with those derived from lean patients (InASCs). In their *STEM CELLS* study, Strong et al. [8] therapeutically assessed both ASC types in a murine experimental autoimmune encephalomyelitis model of MS. Although InASCs reduced disease severity in all cases, obASCs failed to alleviate clinical symptoms and inhibit inflammation in the central nervous system, possessed a more proinflammatory profile, and displayed a diminished immunomodulatory capacity, overall indicating their unsuitability in treating diseases such as MS. The adjoining figure demonstrates the clinical scores (A and B) and representative images of track visualizations (C) for control (Hanks' balanced saline solution [HBSS]) and InASC- and obASC-treated mice. These data demonstrated for the first time that obesity influences ASC biology, and indicated that donor demographics might represent a crucial factor in the identification of stem cells suitable for MS treatment.

DOI: 10.1002/stem.2272



REFERENCES

- 1 Christy BA, Herzig MC, Montgomery RK et al. Procoagulant activity of human mesenchymal stem cells. *J Trauma Acute Care Surg* 2017;83(suppl 1):S164–S169.
- 2 Moll G, Rasmusson-Duprez I, von Bahr L et al. Are therapeutic human mesenchymal stromal cells compatible with human blood? *STEM CELLS* 2012;30:1565–1574.
- 3 George MJ, Prabhakara K, Toledano-Furman NE et al. Clinical cellular therapeutics accelerate clot formation. *STEM CELLS TRANSLATIONAL MEDICINE* 2018;7:731–739.
- 4 Gleeson BM, Martin K, Ali MT et al. Bone marrow-derived mesenchymal stem

- cells have innate procoagulant activity and cause microvascular obstruction following intracoronary delivery: amelioration by anti-thrombin therapy. *STEM CELLS* 2015;33:2726–2737.
- 5 Redondo J, Sarkar P, Kemp K et al. Reduced cellularity of bone marrow in multiple sclerosis with decreased MSC expansion potential and premature ageing in vitro. *Mult Scler* 2018;24:919–931.
- 6 Sarkar P, Redondo J, Kemp K et al. Reduced neuroprotective potential of the mesenchymal stromal cell secretome with ex vivo expansion, age and progressive

- multiple sclerosis. *Cytotherapy* 2018;20:21–28.
- 7 Redondo J, Sarkar P, Kemp K et al. Dysregulation of mesenchymal stromal cell antioxidant responses in progressive multiple sclerosis. *STEM CELLS TRANSLATIONAL MEDICINE* 2018;7:748–758.
- 8 Strong AL, Bowles AC, Wise RM et al. Human adipose stromal/stem cells from obese donors show reduced efficacy in halting disease progression in the experimental autoimmune encephalomyelitis model of multiple sclerosis. *STEM CELLS* 2016;34:614–626.