



Special Issue: Mesenchymal Stem Cells and Immunomodulation

## Brief Review

# Mesenchymal stem cells and immunomodulation

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Mesenchymal stem cells, more recently termed mesenchymal stromal cells (MSCs), were first identified from bone marrow<sup>1)</sup> where they function to support haematopoiesis. Due to their multipotent differentiation potential, immunomodulatory and tissue regenerative properties, as well as their capacity for large-scale expansion, there has been an explosion of research ultimately aimed at developing MSCs as a therapeutic cellular product for a diverse range of human diseases. Despite this intensive research effort, there is much we still do not understand about MSC biology, their biodistribution following transplantation and the mechanisms responsible for the profound efficacy reported in various experimental animal models.

Unravelling the mechanisms by which *ex vivo* expanded MSCs exert their therapeutic effects is complicated by MSC heterogeneity, arising from differences between tissue sources and donors, and the various methods employed across research centres for their isolation, propagation in culture and assays for functional evaluation, both *in vitro* and *in vivo*. The heterogeneity of MSC preparations makes it difficult to not only compare results between

studies, but to identify the molecular mechanism(s) responsible for attenuation of clinical and pathological disease. Notably, comparative analysis of MSCs derived from bone marrow (BM-MSCs) and adipose tissue (Ad-MSC), perhaps the two most well characterized sources of these stromal populations, have identified differences at the transcriptional level<sup>2, 3)</sup>, in their differentiation potential and immunophenotype<sup>4)</sup>, as well as immunomodulatory activity<sup>5, 6)</sup>. These findings highlight that even if they meet the proposed minimal criteria<sup>7)</sup>, tissue-specific MSCs cannot be considered functionally equivalent. Indeed, our own research revealed functional differences between tissue-specific MSCs relevant to their efficacy in a mouse model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE). While BM-MSCs displayed more potent immune-modulatory potential *in vitro* compared to Ad-MSCs and MSCs isolated from umbilical cord Wharton's jelly, they did not significantly decrease clinical signs of disease in EAE mice. Rather, Ad-MSCs expressed a broader repertoire of homing molecules that allowed their migration to lymphoid tissues and the central nervous system, leading to disease suppression<sup>8)</sup>.



Regardless of their source, MSCs are capable of interacting with cells of the innate and adaptive immune system and this immune-regulatory potential has formed the rationale for the application of MSCs in many disease settings. In view of this and with the aim of improving the consistency and reproducibility of results across studies, the MSC Committee of the International Society for Cell Therapy has released a proposal for immunological characterization of MSCs<sup>9</sup>. Amongst these shared guidelines is an evaluation of MSC immune plasticity, that is, assessing the priming of resting MSCs by exposure to pro-inflammatory mediators present in the *in vivo* inflammatory setting, such as interferon (IFN)- $\gamma$ . This inflammatory “licensing” of MSCs triggers their potent suppressive activity, in contrast to their resting state that has been shown to promote survival of immune cells<sup>10</sup>.

In the first review for this special issue on “Mesenchymal Stem Cells and Immunomodulation”, Dr Raghavan Chinnadurai, Department of Hematology and Oncology and Professor Jacques Gallipeau, Department of Pediatrics at Emory University describe how IFN- $\gamma$  primes the suppressive activity of MSCs and the importance of this licensing for their clinical utility.

The promise of MSC treatment demonstrated in experimental animal models has led to rapid clinical translation. A search on [clinicaltrials.gov](http://clinicaltrials.gov) for “mesenchymal stem cells” reveals over 400 clinical trials for a diverse range of conditions, including inflammatory and degenerative diseases affecting the brain, heart, connective tissues, respiratory tract, gastrointestinal tract and kidneys amongst others.

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is characterized by intestinal inflammation and the subject of a number of clinical trials utilizing MSCs. Dr Kulmira Nurgali's Enteric Neuroscience Group at Victoria University is currently investigating how MSCs could be used to attenuate IBD in experimental animal models of colitis. Their review summarizes the current evidence for MSC efficacy in clinical trials for IBD and the potential mechanisms by which MSCs may act to reduce intestinal inflammation. This provides an excellent example of how the immune regulatory properties of MSCs are being investigated for safety and efficacy in a clinical setting whilst the underlying mechanisms of action are still

being explored in the research laboratory.

Along with their broad trophic and anti-inflammatory properties, MSCs are readily amenable to genetic engineering and this has opened up an exciting field of research. Genetic modification provides a means by which the therapeutic efficacy of MSCs can be improved, through engineering expression of homing receptors to enhance their migration to inflammatory sites or for use as “Trojan horses” to deliver therapeutic molecules that target cancers or further suppress inflammation.

In the third review of this issue, Drs Elisabeth Aguilar, Marien Cobo and Francisco Martin from the Gene and Cell Therapy Group at Pfizer-University of Granada-Andalusian Government Centre for Genomics and Oncological Research outline the studies in which gene-modified MSCs have been applied for treatment of neurological diseases and summarize their work investigating MSCs engineered to express vasoactive intestinal peptide, a neuropeptide with known anti-inflammatory properties, for treatment of MS using the EAE animal model.

We hope that the readers of *Inflammation and Regeneration* will find these reviews, which provide an overview of the current state of MSC research, from understanding the basic mechanisms of their immune-modulatory activity, investigating their potential for treatment of inflammatory diseases in the laboratory and clinical setting, to their intersection of the stem cell and gene therapy fields, both informative and enjoyable.

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