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EDITORIAL

Mesenchymal stem cells in autoimmune diseases: hype or hope?

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See related research by Schurgers *et al.*, http://arthritis-research.com/content/12/1/R31

Abstract

Intervention with mesenchymal stem cells (MSCs) represents a promising therapeutic tool in treatment-refractory autoimmune diseases. A new report by Schurgers and colleagues in a previous issue of *Arthritis Research & Therapy* sheds novel mechanistic insight into the pathways employed by MSCs to suppress T-cell proliferation *in vitro*, but, at the same time, indicates that MSCs do not influence T-cell reactivity and the disease course in an *in vivo* arthritis model. Such discrepancies between the *in vitro* and *in vivo* effects of potent cellular immune modulators should spark further research and should be interpreted as a sign of caution for the *in vitro* design of MSC-derived interventions in the setting of human autoimmune diseases.

Immunomodulation by mesenchymal stem cells *in vitro* and *in vivo*

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can be cultured from various adult and fetal tissues and that are capable of differentiating into multiple mesenchymal lineages including bone, cartilage, tendon, marrow stroma and adipose tissue [1]. Because of their unique regenerative potential, MSCs are considered a promising therapeutic modality for tissue regeneration and repair. Moreover, MSCs are thought to be critically involved in the formation of survival niches for memory T cells and B cells in the bone marrow, thereby regulating the size, stability and plasticity of immunological memory.

Awareness has additionally been raised by the finding that MSCs display immunomodulatory properties *in vitro*, as evidenced by their ability to inhibit T-cell proliferation. This inhibition affects the proliferation of T cells induced by alloantigens, mitogens and CD3-ligation. Moreover, MSCs have also been shown to inhibit the proliferation of B cells, and possibly the activity of natural killer cells. The molecular interactions responsible for these inhibitory effects observed *in vitro* are the subject of intense investigations and include the action of prostaglandin E_2, nitric oxide, indoleamine 2,3-dioxygenase and programmed death ligand-1 [2].

Because of their potent inhibitory effects *in vitro*, MSCs have been used in several preclinical disease models, most often aiming to inhibit alloreactive immunity such as is observed in graft-versus-host disease (GVHD), and in transplantation models. Several studies have now shown that infusions of MSCs can be effective in controlling GVHD or in promoting engraftment and survival of allogeneic bone marrow cells. Opposing observations have also been reported, however, as injection of allogeneic MSCs has been shown to trigger allo-specific immune responses *in vivo* resulting in graft rejection [3]. Therefore it is conceivable that the modulatory effects observed in *in vivo* transplantation models are not all mediated by immune suppression, but possibly also through other mechanisms. The latter are presently not known, but could include production of MSC-derived cytokines capable of expanding alloreactive natural killer cells. Such natural killer cells can efficiently kill donor/host-derived professional antigen-presenting cells and thereby inhibit the induction of allo-specific T-cell responses [4,5].

The observation that MSCs themselves can induce alloreactive T-cell responses indicates a discrepancy between *in vivo* findings and the immunosuppressive *in vitro* findings as also observed by Schurgers and colleagues. Although this is poorly understood, MSC-based interventions are already pioneered in the clinical setting and the first promising results have been reported in the context of human GVHD [6] and Crohn's disease [7].

Mesenchymal stem cells in autoimmune rheumatic diseases

Despite these promising results from transplantation settings, effects in preclinical autoimmune disease models

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are less coherent. Some studies report amelioration of arthritic symptoms in preclinical arthritis models, whereas other studies – such as that by Schurgers and colleagues – could not report beneficial effects or even describe a worsening of the disease course [1,8]. The latter could in part be related to the use of allogeneic MSCs, as it has been reported that the use of allogeneic cells – presumably through additional cytokine release as a consequence of the underlying allo response – leads to the exacerbation of arthritis [9]. Furthermore, direct comparison of these studies is hampered by the use of different MSC culture conditions *in vitro*, different tissues from which the MSCs are derived, and a variety of different administration schedules currently used *in vivo*. Moreover, studies on the phenotype of MSCs in bone marrow indicate that MSCs are a heterogeneous population comprised of subpopulations that differentially express a number of receptors to interact with immune-competent effector cells. The ability of MSCs to modulate immune responses therefore probably depends, in part, on the composition of the starting population.

Despite our incomplete understanding of the mechanisms underlying these divergent results, and inspired by positive reports on the use of bone marrow-derived MSCs in the outcome of GVHD and transplantation engraftment without the observation of severe side effects associated with the infusion of MSC, the first studies in human autoimmune disease are already appearing [10,11]. Not unexpectedly, however, the clinical effects are not coherent.

Concluding remarks

The mechanisms underlying the possible *in vivo* immunomodulatory effects of MSCs remain a critical and unresolved question. By comparing side by side the effects of MSCs *in vitro* and *in vivo*, the study by Schurgers and colleagues brings fresh encouragement to the endeavors to elucidate the immunomodulatory effects of MSCs in rheumatic diseases [1]. Given the apparent difficulties in recapitulating the *in vitro* effects *in vivo*, however, researchers should be cautioned and should remain critical concerning the use of MSCs for the treatment of human autoimmune disease. It is likely that the endeavors will eventually pay off, but more experience with the use of MSCs in the setting of GVHD can help guide their use for rheumatic diseases, thereby certifying or revoking their therapeutic use for the control of autoimmunity.

Abbreviations

GVHD, graft-versus-host disease; MSC, mesenchymal stem cell.

Competing interests

The authors have no competing interests.

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