BY GIUSEPPE REMUZZI, MD, AND JONATHAN S. BROMBERG, MD, PHD

LITERATURE Watch

Implications for transplantation

Mesenchymal Stromal Cells: What's In the Name? (and For What?)

CITATION **Akiyama K, Chen C, Wang DD, Xu X, Qu C, Yamaza T, et al. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/FAS-mediated T cell apoptosis. Cell Stem Cell 2012; 10: 544-555.**

CITATION **Bianco P, Cao X, Frenette PS, Mao JJ, Robey PG, Simmons PJ, et al. The meaning, the sense and the significance: Transplanting the science of mesenchymal stem cells into medicine. Nature Med 2013; 19: 35-42.**

CITATION **Griffin MD, Ryan AE, Alagesan S, Lohan P, Treacy O, Ritter T. Anti-donor immune responses elicited by allogeneic mesenchymal stem cells: What have we learned so far? Immunol Cell Biol 2013; 91: 40-51.**

SUMMARY AND ANALYSIS

Mesenchymal stromal cells (MSCs), also called mesenchymal stem cells, are fibroblast-like multipotent cells characterized by their ability to differentiate into tissues of mesodermal lineages, including adipocytes, chondrocytes and osteocytes. First described as stromal cells within the bone marrow, MSCs are now isolated from other sources including adipose tissue and umbilical cord blood. The diverse morphologies, promiscuous differentiation potential and absence of a specific phenotypic marker highlight the heterogeneity of these cells. The International Society of Cellular Therapy has suggested that a consensus panel of cell surface markers be developed to standardize their characterization across laboratories. This consensus is far from definitive and will continue to evolve. Indeed, different MSC populations derived from different tissues are becoming more apparent, presenting additional challenges to devising a universal definition. Bianco et al. reviewed the many doubts around MSCs and provide evidence that substantial ambiguities still plague the field regarding the nature, identity, function and mode of isolation of MSCs. These uncertainties will continue to have a major impact on translational approaches centered on the envisioned therapeutic use of MSCs.

The idea that MSCs exert functions other than as stem or progenitor cells is supported by evidence that MSCs down regulate immune effector functions. MSCs suppress T cell proliferation and dampen acquired effector T cell responses, while promoting the emergence of regulatory cells. There is growing evidence that the innate immune system also plays a key role in MSC-induced immunosuppression. These interactions are well illustrated by Akiyama et al., who ameliorated disease in murine models of systemic sclerosis and colitis by infusion of bone marrow–derived MSCs. The MSCs caused apoptosis of T cells by a Fas-FasL–mediated mechanism. Next, the apoptotic effector T cells were engulfed by macrophages, which were then induced to produce transforming growth factor β (TGF-β). Elevated TGF-β then led to the generation of potent regulatory T cells, which further suppressed immune function. These results show that evaluating the mechanism and effectiveness of MSCs must take into account multiple direct and indirect mechanisms of immune modulation.

The immunomodulatory effects of MSCs have led to many current clinical trials, but only a few of them have evaluated critical issues dealing with the safety of different cell sources, route and timing of administration, and cell dose. What must be added to these crucial outcome analyses are specific assays of immune function. The notion of potent immunosuppression and the immune-privileged nature of MSCs have also resulted to increasing numbers of studies with allogeneic MSCs along with patented allo-MSC products by biotechnology companies. These studies have not generally been accompanied by robust investigation of possible anti-donor alloimmune responses. Griffin et al. reviewed numerous experimental studies showing that allo-MSCs do indeed trigger donor-specific cellular and humoral immune responses. These findings bring up the question of whether allo-MSCs are as immunosuppressive as hoped, and whether anti-donor alloimmune responses limit their efficacy.

How can we solve the many open questions dealing with the therapeutic administration of MSCs? The time is probably not ripe for large clinical trials. We do not have enough knowledge of safety, pharmacokinetics and quantitative assays for *in vivo* immune responses. MSC development in organ transplantation should adopt an approach similar to that pursued to explore the pathophysiology of a rare condition in a few patients. Small studies with a few patients intensively studied will hopefully allow us to determine when and where MSCs should be administered and how they function to regulate host immunity. These considerations may be particularly imperative for new biological agents such as MSCs for which, despite encouraging initial results, uncertainty about safety and efficacy still exists. AJT

Dr. Remuzzi is Research Coordinator at the IRCCS Instituto di Richerde Farmacologiche "Mario Negri," and Director, Department of Immunology and Clinical Transplantation, Ospedale Papa Giovanni XXIII, Bergamo, Italy. Dr. Bromberg is professor of Surgery and Microbiology and Immunology, and is the chief of the Division of Transplantation, University of Maryland Medical Center, Baltimore. He is also section editor for "Literature Watch."

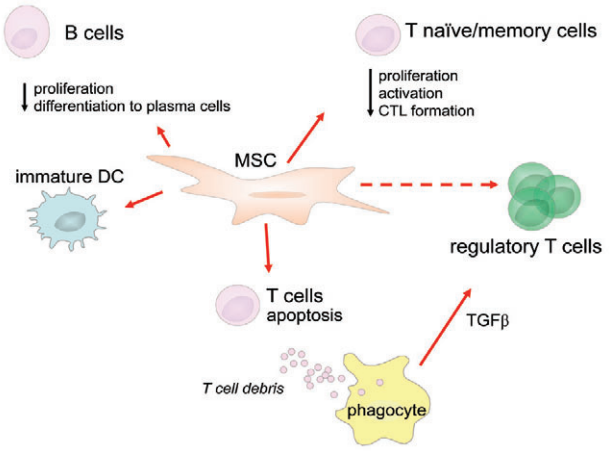

Figure 1. Multiple immunomodulatory mechanisms of MSCs. MSCs inhibit the proliferation/activation of T cells, including memory T cells, and promote the emergence of regulatory T cells via direct paracrine interactions, or via indirect effects through T cell apoptosis and macrophage activation. MSCs inhibit the maturation of dendritic cells (DCs) and modulate B cell function via an array of factors.