

Abstract Category: Immunomodulation

HUMAN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS MODULATE IN VIVO T-CELL ALLOREACTIVITY AND INFLAMMATION FOLLOWING MURINE HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Given their ease in *ex vivo* expansion, favorable infusion safety profile, and immunomodulatory properties, human bone marrow-derived mesenchymal stem cells (hMSCs) have been catapulted into clinical use as novel therapeutic cellular agents for preventing and treating acute graft-versus-host disease (GVHD). However, MSC-mediated effects on T-cell activation and function have primarily been demonstrated within *in vitro* culture conditions. Mouse models have been instrumental in defining the pathophysiology of acute GVHD. Therefore, we sought to define hMSC effects on *in vivo* immunomodulation using an established murine model of allogeneic bone marrow transplantation (allo-BMT). First, to determine if hMSCs could modulate mouse T-cell alloreactivity, hMSCs were used in a mixed lymphocyte reaction (MLR) of mouse dendritic and T cells. Human MSCs inhibited mouse T-cell proliferation in a reproducible, concentration-dependent fashion. We next sought to determine if hMSCs could also influence *in vivo* T-cell alloreactivity in the context of allo-BMT using C57BL/6 (B6; H-2^b) and B6D2F1 (H-2^{bx_d}) mice as HSCT donors and recipients, respectively (B6→B6D2F1). Syngeneic transplant recipients (B6D2F1→B6D2F1) were also used as controls. Human MSCs were tail-vein injected one (D1) and four (D4) days following allo-BMT (D0) and weight loss and GVHD clinical scores were measured across experimental groups (n=6 mice per group). Early administration of hMSC infusions associated with improvement in D10 clinical GVHD scores in allogeneic transplant recipient mice versus untreated allogeneic controls. In addition, infusion of hMSCs resulted in significant reductions in splenic T cell expansion and in numbers of TNF α and IFN γ -producing CD4⁺ and CD8⁺ cells at D10 compared to untreated allogeneic controls. Furthermore, circulating serum levels of TNF α measured in hMSC-treated allo-BMT recipients were reduced to near syngeneic control levels at D10 versus high-level induction of circulating TNF α measured in untreated allogeneic controls. Finally, early attenuation in splenocyte T-cell proliferation and circulating TNF α correlated with improved survival in allo-BMT mice receiving hMSC infusions. Summarily, these preliminary results show that improved survival with hMSC infusion in allogeneic transplant recipient mice associates with early attenuation in clinical GVHD and reduction in T-cell proliferation and levels of circulating TNF α . Mechanistic study to further define *in vivo* hMSC-mediated immunomodulation may ultimately translate into improving the use of regenerative stromal cell therapies during clinical allogeneic hematopoietic stem cell transplantation.