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Concurrent Session 1

The interaction between mesenchymal stem cells and the immune system

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Mesenchymal stem cells (MSCs) possess a strong immunosuppressive effect *in vitro* and *in vivo* in both animals and humans. However, the mechanisms that govern these immune modulatory functions of MSCs remain largely elusive. Previous studies with bulk populations of MSCs indicate that soluble factors such as PGE2 and TGFbeta are important, while others support a role for cell-cell contact. We examined immunosuppressive effects of cloned MSCs derived from mouse bone marrow and showed that the majority of these clones were able to differentiate into adipocytes and osteoblast-like cells. Importantly, we have shown them to potently inhibit TCR-triggered proliferation and cytokine production of freshly-isolated T cells. *In vivo*, injection of MSCs prevented the rejection of allogeneic skin transplants, reduced graft versus host disease and suppressed antigen-specific DTH responses in mice. The immunosuppressive effect of MSCs requires the interaction with activated T cells, but independent of IDO, PGE2 and TGFβ. We also investigated the effect of MSCs on lymphocyte survival. We found that MSCs inhibit apoptosis of splenocytes and thymocytes as well as purified T and B cells in absence of inflammatory cytokines. The protective effect of MSCs was absent when lymphocytes were not in contact with MSCs, indicating that the anti-apoptotic effect is exerted through direct interaction between MSCs and lymphocytes. Interestingly, this anti-apoptotic effect could be inhibited by neutralization of IL-6. Consequently, we found that the expression of IL-6 by MSCs was augmented by contact with lymphocytes. Taking together, our data show that MSCs can significantly affect the immune system and the end results are dependent on the availability of inflammatory cytokines.

Keywords: mesenchymal stem cells, immune responses, immunosuppression, cell survival

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Dr Shi received his PhD in Immunology in 1992 from University of Alberta, Canada, working with Douglas Green. His postdoctoral training was at the University of Toronto with Gordon Mills. His first academic appointment was at the Holland Laboratory of American Red Cross and George Washington University in 1995.

Since 1988, Dr Shi has been studying apoptosis, especially in T cells. His research on activation-induced cell death (AICD), role of c-myc in apoptosis, opioid and stress-induce lymphocyte apoptosis, mTOR inhibitor and cancer therapy, CD4+ T cells and asthma, granzyme B and Th2 AICD, and MHCIb $CD8^+$ T cells and autoimmunity were published in *Nature*, *Science*, *Nat Med, Immunity and J Exp Med*. His current research focuses on apoptosis in T cell subsets and the molecular mechanisms of mesenchymal stem cell mediated immunosuppression. Dr Shi was an Associate Editor of the *J Immunol* and is currently an Editor of *Cell Res*.