STEM CELLS

Immunosuppression by mesenchymal stem cells

Mesenchymal stem cells (MSCs) are fibroblast-like cells that can develop into several types of tissue. MSCs have been shown to have immunosuppressive functions in various settings, including autoimmune diseases and transplantation, but the mechanisms by which MSCs suppress immune responses have not been clearly defined. Now, a study from Yufang Shi's laboratory shows that specific cytokines activate MSCs for immunosuppression, and this is mediated by the concerted action of chemokines and nitric oxide.

First the authors looked at the effect of MSCs on T-cell activation. Co-culture of MSCs with freshly isolated splenocytes in the presence of CD3-specific antibody to stimulate T cells resulted in the suppression of T-cell responses. Using blocking antibodies, and by directly testing the effect of adding various pro-inflammatory cytokines, the authors showed that interferon-γ (IFNγ), together with either tumour-necrosis factor (TNF), interleukin-1α (IL-1α) or IL-1β, was required to induce the suppressive activity of the MSCs.

Next the authors looked at the mechanism of suppression by MSCs. Blocking inducible nitric-oxide synthase (iNOS) activity using a selective inhibitor was sufficient to restore T-cell proliferation in mixed co-cultures of MSCs and splenocytes, showing that nitric oxide has a role in mediating suppression. Exposure of MSCs to the pro-inflammatory cytokines increased their expression of iNOS and production of nitric oxide. Furthermore, the same pro-inflammatory cytokines that were identified as inducing the immunosuppressive function of MSCs were shown to allow the MSCs to attract T cells; as nitric oxide can only act in close proximity to the cells that produce it, this is likely to ensure that cells are drawn close enough to the MSCs for nitric oxide to be effective.

Further experiments showed that cytokine-activated MSCs express CXC-chemokine ligand 9 (CXCL9)–CXCL11, and that blockade of CXC-chemokine receptor 3 (the receptor for CXCL9–CXCL11) prevented the chemotaxis of T cells towards MSCs and prevented the suppression of T-cell activation.

Finally, using a mouse model of graft-versus-host disease (GVHD) and MSCs from mice deficient in iNOS or the IFNγ receptor 1 chain, the authors showed that cytokine-induced nitric-oxide production by MSCs is crucial for the suppression of GVHD in this model.

This study describes a mechanism by which the immunosuppressive function of MSCs is regulated — a better understanding of immunosuppression by MSCs should lead to more efficient use of these cells in therapeutic settings.

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