Adhesion molecules

Key players in Mesenchymal stem cell-mediated immunosuppression

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Adhesion molecules are known to be important components of an active T-cell mediated immune response. Signals generated at a site of inflammation cause circulating T cells to respond by rolling, arrest and then transmigration through the endothelium, all of which are mediated by adhesion molecules. Consequently, strategies have been developed to treat immune disorders with specific antibodies that block the interaction of adhesion molecules. However, the therapeutic effects of such remedies are not always achieved. Our recent investigations have revealed that intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) work together with chemokines to induce immunosuppression mediated by Mesenchymal stem cells (MSCs), thus demonstrating the dual role of adhesion molecules in immune responses. Since MSCs represent an important component of the stromal cells in an inflammatory microenvironment, our findings provide novel information for understanding the regulation of immune responses and for designing new strategies to treat immune disorders.

In a typical T-cell mediated immune response, T cells are first activated by antigen-presenting cells in lymph nodes and then migrate through the endothelium at the site of inflammation where they help eliminate foreign pathogens. Adhesion molecules are critical mediators of this process. When T cells respond to chemokines, adhesion molecules trigger their rolling, activation, stable arrest and transmigration. Under conditions of shear flow, the rolling of T cells on the endothelial surface is conducted through the interaction of the T-cell surface adhesion molecules, L-selectin,2 α4 integrins3 and lymphocyte function-associated antigen-1 (LFA-1),4 with their respective endothelial ligands, glycosylation-dependent cell adhesion molecule-1 (GLYCAM1), vascular cell adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule 1 (ICAM-1). Moreover, endothelial cells express E-selectin and P-selectin, which are also involved in leukocyte rolling.5 After the transient rolling along the endothelium, stimulation of leukocytes by
chemokines and other chemoattractants leads to conformational changes and clustering of their surface adhesion molecules, especially integrins. Such changes result in increased adhesive ligand-receptor binding affinity, which promotes the firm arrest of leukocytes on endothelium. The key interaction in this process is the binding of leukocyte integrins to immunoglobulin-like adhesion molecules, such as ICAM-1 and VCAM-1 on endothelial cells. The final step, with the participation of platelet endothelial cell adhesion molecule (PECAM), is leukocyte transmigration through the endothelium to the site of injury. Recent insights into leukocyte adhesion have demonstrated that cell-cell adhesion is a complex and finely-tuned process.

**Anti-Adhesion Therapies**

The fact that adhesion molecules positively participate in immune responses has led to efforts to develop anti-adhesion strategies for the treatment of inflammatory disorders such as asthma, psoriasis, Crohn disease, multiple sclerosis, inflammatory bowel disease and cancer. Most therapies target the interaction of integrins and immunoglobulin-like adhesion molecules with their targets. Several drugs in preclinical and clinical trials show future promise, such as natalizumab, a humanized monoclonal antibody targeting very late antigen-4 (VLA-4) for the treatment of Crohn disease and relapsing-remitting multiple sclerosis. In addition to having some adverse effects, such as increased viral infection, immunotherapies that target adhesion molecules have been found to be ineffective for other inflammation-related diseases, including myocardial infarction and hemorrhagic shock, although the targeted adhesion molecules are key players in the pathogenesis of these diseases. In animal studies, anti-ICAM-1 did not significantly affect experimental melanin-induced uveitis or experimental autoimmune encephalomyelitis (EAE) in rats. Likewise, anti-VCAM-1 did not protect against ischemic damage either in rats or in mice. Several factors may account for these apparently contradictory results. Firstly, the overlapping effects of different adhesion molecules may make a single treatment insufficient to block the disease. Secondly, it is difficult to precisely target the molecules that are critical for a disease with a complicated pathogenesis. Our recent studies have revealed that under some special circumstances, adhesion molecules can lead to immunosuppression, making it necessary to re-evaluate the function of adhesion molecules in an immune response.

**Adhesion Molecules ICAM-1 and VCAM-1 and Play a Key Role in Mesenchymal Stem Cell-Mediated Immunosuppression**

Mesenchymal stem cells (MSCs) are a population of tissue stromal/stem cells that have been successfully isolated from bone marrow, adipose tissue, placenta, umbilical cord, skin, liver and intestine. Investigations by various laboratories have shown that these cells have enormous potential for the treatment of a number of immune disorders, owing to their exquisite ability to suppress immune responses. In animal models, preclinical and clinical trials, MSC-based cell therapy has become a promising strategy for the prevention and treatment of graft-versus-host disease, liver fibrosis, sepsis, multiple sclerosis and rheumatoid arthritis. To achieve better clinical application of these cells, we have examined the cellular and molecular mechanisms through which MSCs suppress immune responses. We found that these cells are not innately immunosuppressive, rather they become immunosuppressive upon interaction with the inflammatory environment. The specific immunosuppressive effector varies among species: the effector molecule in mouse MSCs is nitric oxide (NO), while indoleamine 2,3 dioxygenase (IDO) serves the same purpose in human and non-human primate MSCs.

NO is a highly-labile small molecule and many biochemical compounds affect its perfusion rate. Mathematical models have predicted that NO can act on the T cells and inhibit their proliferative block via the target molecule NO. Moreover, NO or IDO by MSCs and the resulting metabolites are immunosuppressive only in close proximity with T cells. Normally, MSCs express very low levels of chemokines and adhesion molecules. In the presence of an active immune response, however, the inflammatory cytokines, interferon γ (IFNγ), tumor necrosis factorα (TNFα) and interleukin-1 (IL-1) stimulate the upregulation of several T-cell-specific chemokines by MSCs, especially ligands of CXCR3 and CCR5 and immunoglobulin-like adhesion molecules ICAM-1 and VCAM-1. Chemokines and adhesion molecules attract and anchor T cells to MSCs, where high concentrations of immunosuppressive effector molecules can act on the T cells and inhibit their proliferation. Blockade of chemokine receptors CXCR3 and CCR5 or ICAM-1/VCAM-1, significantly reversed such MSC-mediated immunosuppression in vitro and in vivo, suggesting that chemokines and adhesion molecules indeed cooperate with the effector molecules (NO or IDO) to exert the immunosuppressive effect by inflammatory cytokine-stimulated MSCs.
Therefore, MSCs and possibly other stromal cells recruit leukocytes in a similar fashion as endothelium, but they have set a trap with a high concentration of NO or IDO-catalyzed metabolites. Once the leukocytes are in proximity with and adhere to MSCs, these immunosuppressive molecules lead the T cells to undergo apoptosis, cell cycle arrest or become regulatory T cells (Fig. 1).25,26,30 Further elucidation of the dual role of adhesion molecules in an immune response will improve our understanding of immunoregulation and help to develop better adhesion molecule-targeting therapies.

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