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Immunological mechanisms of the morphological changes in rejection of the transplanted rgans

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Rejection of an allograft is characterized by an intense and localized inflammatory response that occurs within the graft. This response consists of a complex array of cellular and humoral inflammatory components triggered by the nonspecific activation of macrophages and endothelial cells during the period of warm and cold ischemia and the reperfusion, and specific interaction of T cells with alloantigenes. The inflammatory response, nonspecific as well as specific, is regulated by the action of soluble mediators. These mediators play a critical role in the pathogenesis of rejection, shaping manifestation of both acute and chronic allograft rejection. Inflammatory mediators participate in rejection in several distinct capacities. First, the product of inflammation regulates the intragraft immune response by promoting inflammatory cell accumulation and T cell activation. Second, the component of the inflammatory response may act directly on T cells to modulate their function. Finally, the inflammatory response is an important effector pathway for graft dysfunction and injury, especially in vascularized organ grafts. The inflammatory response that occurs in acute rejection is most analogous to classical delayed type hypersensitivity (DTH) reaction. The trigger for DTH responses is interaction of T cells, usually CD4+ phenotype, with antigen, or in the cases of rejections, with alloantigen. These reactions are characterized by edema and altered vascular permeability, along with prominent infiltration by both antigenspecific and nonspecific T cells, B cells, and macrophages. Proinflammatory cytokines such as IL-1β, Gamma-interferon (γ-IFN) and TNF-β seem to be particularly important in this response. The earliest events that promote trafficking and accumulation of inflammatory cells within the allograft are regulated through a series of activation and adhesion processes. The first step involves rolling of leukocytes along the vessel walls, resulting from a loose and transient adhesion of the leukocyte to the endothelium that is mediated by the selectin family of adhesion molecules, L-selectin, expressed on leukocytes, will specifically associate with P-selectin and E-selectin that are expressed on stimulated endothelium. Next, firm adhesion of leukocytes to endothelial cells is promoted through binding integrins on inflammatory cells (LFA-1) to their ligands (VCAM-1, ICAM-1 etc) on the endothelial cells. A three-step model has been proposed to explain entry of the cellular infiltrate into the graft. Chemokines, a large family of chemoattractant cytokines (more than 30 chemokines and about 10 chemokine receptors have been identified to date) is released from the cells in inflamed tissue and firmly binds to glycosaminoglycans on the vascular endothelium. Via a process termed „haptotaxis“ leukocytes are attracted along the solid matrix of the vessel wall. The same chemokines responsible for haptotaxis along the vessel wall are involved in chemotaxis of the cells through the tissue to the site of injury. Once confronted with foreign alloantigen in the graft, previously activated T cells are capable of releasing proinflammatory cytokines (Th CD4+ cells) or directly killing the foreign cells (Tc CD8+ cells). If preexisting antibodies to ABO blood groups, HLA, or other polymorph antigens expressed on the graft are present in the recipient, they can immediately bind to the graft and activated complement or cytolitic „K“ cells. Platelets and fibrin are deposited, granulocyte and monocytes infiltrate and fibrinoid necrosis of the vessel wall ensues. Hyperacute rejection is now very rare, eliminated by routine crossmatch prescreening. Cellular infiltrates, triggered by the HLA differences and recruitment of T lymphocytes and monocytes characterize both the acute and subacute type of rejection. Eosinophils, granulocytes, macrophages and NK cells may variably also be present. Chronic rejection occurs very slowly. Extracellular matrix is destroyed by inflammatory proteases, and debris is phagocytosed by macrophages and granulocytes. Cytokines produced by macrophages and lymphocytes, including platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), induce smooth muscle proliferation, narrowing blood vessels, producing ultimately arteriosclerosis of all vessels in the graft and loss of function.

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