2. Cellular and molecular mechanisms of allograft rejection

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Excluding hyperacute rejection, two main patterns of rejection have been identified: (a) acute rejection and (b) chronic rejection, designated for ‘cellular’ and ‘humoral’ mechanisms of the immune response, respectively. Obviously, however, both arms of the immune response contribute in both major rejection patterns. Thus ‘rejection’ is not one and the same, but a given clinical situation may result from various pathophysiological mechanisms.

Cellular and molecular cascades of the in situ inflammatory response

The major events occurring inside the allograft upon induction of rejection have been summarized on several occasions (1). An allograft (like all other organs in the body) is continuously flushed by white cells (Figure 1). If immunosuppression is inadequate, the donor-directed recipient lymphocytes recognize the alien transplantation antigens, presented by the so-called antigen-presenting cells (APC), and immunization occurs. At least the vascular endothelial cells and the so-called ‘dendritic’ macrophages can function as APC. In addition also shedded antigens cause sensitization in the host lymphoid system.

At least two types of lymphocytes (CD4 and CD8) collaborate in the induction process. Triggered ‘blast’ cells express a variety of receptors, including the receptor for interleukin-2 (IL-2), and produce a variety of factors, lymphokines, including IL-2, IL-3 (M-CSF), IL-4 (BSF-1), IL-5 (TRF), IL-6, and gamma-interferon. The lymphokines drive antigen-responding T cells to ‘autocrine’ proliferation and to the production of specific effector cells, B cells to produce antibodies, and activate non-specific effector mechanisms, including donor non-directed lymphoid cells, the large granular lymphocytes (LGL) or ‘NK effector cells’, mononuclear phagocytes and platelets.

The steps summarized below should not be considered as a switch-on — switch-off system, but rather as a cascade where all components are generated in an escalating manner (Figure 1).

One of the first events in a rejecting allograft is an increase in leukocyte influx and outflux and proliferation of inflammatory cells in situ. Concomitantly,
Fig. 1. Major cellular and molecular pathways in allograft rejection. The antigen-presenting cells (APC) have transplantation antigens on their surface and provide a 'second signal', interleukin (IL)-1 alpha and beta to resting T cells possessing receptors (T3, T4) to this antigen. Both dendritic cells and endothelial cells can function as APC. Obviously, at least two types of T cells, CD4+ and CD8+, collaborate in the induction of transplantation immunity. As a result of antigen presentation, the antigen-reactive T cells display the IL-2 receptor (IL-2R) and secrete a variety of lymphokines including IL-2, −3, −4, −5 and interferon (IFN)-gamma. The net effect of these lymphokines is to induce T and B cell proliferation, including the generation of antibody-secreting