Donor leukocytes in transplanted organs — not such a bad thing after all?  
Part 2: Inducers of the rejection response

As described in the November 2015 Serology Bulletin, donor white blood cells (leukocytes) within a transplanted organ are also transferred to the recipient along with the organ. These “passenger” leukocytes are now known to be some of the most immunogenic cells in an allograft, and thus are potent inducers of the rejection response.

The mechanism: Unless the donor and recipient are HLA-identical (i.e., identical twins), there is some degree of major histocompatibility complex (MHC) mismatch in every donor-recipient pair. When recipient T-lymphocytes recognize the foreign MHC antigens on donor cells, they become activated1,2; these activated T-lymphocytes then move to the grafted organ, where they initiate the rejection reaction that leads to the destruction of the parenchyma and blood vessels of the graft. Because dendritic cells (Figure 1) within the leukocyte population are particularly rich in MHC class II antigens, they trigger a potent rejection response by maximally activating recipient T-lymphocytes (Figure 2).1,2

Clinical course: In the short-term, the rejection episodes triggered in large part by passenger leukocytes within transplanted organs are of clinical concern, but are usually well-controlled by increased immunosuppression.1 One might assume that the occurrence of multiple rejection episodes would eventually have a detrimental effect on long-term graft survival, but interestingly, studies in animal models have shown that this is not the case. In a mouse model of skin transplants3, and a pig model of kidney transplants4, reducing the number of passenger leukocytes in the graft did not delay rejection of the grafts. Thus, donor leukocytes within transplanted organs are a problem in the short-term because they trigger rejection episodes, but are not a problem from the point of view of long-term allograft survival.

Leukocyte reduction/removal: Although the animal studies just mentioned suggest that removing passenger leukocytes (or substantially reducing their numbers) from transplanted organs may not improve long-term graft survival, the potential benefit of reduced numbers of rejection episodes led to studies of passenger leukocyte reduction in humans. The method commonly used is perfusion of the organ, prior to transplant, with a monoclonal antibody recognizing CD45, a cell-surface antigen found only on leukocytes and not on other cells of the body.5 A study in kidney transplant recipients6 corroborated the findings from animal studies by showing that the proportion of recipients experiencing a rejection episode was 3.5-fold lower in recipients of allografts perfused with anti-CD45 (18%) compared to recipients of allografts perfused with albumin (63%); however, long-term (18-month) allograft survival was similar in the two groups (79% vs 77%, respectively). A later study, also in kidney transplant recipients,7 extended these findings by providing insight into how this anti-CD45 perfusion system works; the anti-CD45 monoclonal antibody binds to the leukocytes within the transplanted organ during the perfusion step pre-transplant, and after transplantation, these antibody-coated leukocytes activate complement and are destroyed (Figure 3).

Summary: Donor leukocytes, particularly dendritic cells, within transplanted organs are potent inducers of the rejection response, but do not have a negative impact on long-term graft survival. Treatment of organs pre-transplant with anti-CD45 monoclonal antibody reduces the number of passenger leukocytes that survive within the organ post-transplant, thus reducing the number of rejection episodes. Further studies are needed to determine if anti-CD45 treatment is the most effective method for reducing donor leukocyte transfer with organs, and to better define the clinical situations where such treatment would be most beneficial.

Figure 1: Electron micrograph of a dendritic cell

Figure 2: Induction of graft rejection by passenger leukocytes

Figure 3: Mechanism of complement-dependent cytotoxicity

Resources