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"The severe shortage of allogeneic donors currently limits the number of transplants performed. This supply-demand disparity could be corrected by the ability to use organs from other species (xenografts), but the immune barriers to xenografts make it unlikely that non-specific immunosuppression could prevent rejection without unacceptable toxicity. Induction of specific tolerance would overcome the need for non-specific immunosuppressive therapy. We have developed a humanized mouse model that allows the reconstitution of immunodeficient mice with human T and B cells and APCs. These human cells demonstrate robust immune function, including xenograft rejection, proliferative T cell responses and class-switched antibody responses to protein antigens. We have also shown that normal, polyclonal human T cells can develop in porcine thymic xenografts that replace the human thymus graft in this humanized mouse model. These human T cells are specifically tolerant to the porcine thymus donor, suggesting an approach to achieving xenograft tolerance in humans. The xenogeneic thymus transplant approach has allowed porcine kidney xenograft survival in non- human primates. However, data obtained in the humanized mouse model suggest that there may be defects in human T cell function in pig thymus xenografted mice resulting from a failure of the T cells that are positively selected on porcine thymic epithelium to interact optimally with HLA molecules on human APCs in the periphery. We have obtained evidence in the pig-mouse combination that implantation of recipient thymic epithelial cells with the porcine thymus xenograft can overcome such defects. We now aim to develop strategies to bypass the consequences of MHC incompatibility between porcine thymic epithelium and peripheral human APCs in the pig-human system. The effect of co-implantating human thymic epithelial cells (huTEC) in the porcine thymic grafts will be explored, using fetal, juvenile and adult huTEC. A second approach will be to provide porcine APCs in the periphery by inducing mixed xenogeneic chimerism in xenogeneic thymus-grafted humanized mice. We will examine the effects of these manipulations on peripheral T cell responses, homeostatic expansion and phenotypic conversion, survival, and Treg function and phenotype. Additionally, we aim to evaluate the mechanisms of tolerance to pig and human donor antigens of T cells generated in porcine thymus grafts. The role of deletion of T cells with TCR recognizing pig donor antigens will be explored using human TCR transgenesis into human hematopoietic stem cells. The role of regulatory T cells and the effect of huTEC implantation on regulatory cell function will be explored. The results of these studies will advance this promising approach to xenograft tolerance induction toward clinical application."
