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Mechanism of Allo-Immune Response

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Allogeneic transplantation is performed between individuals of same species. The success is impeded by allo-response-induced graft rejection. T cells that recognize allogeneic antigens (named histocompatibility antigens), mismatched between the donor and recipient, are activated via direct and/or indirect antigen-presentation pathway, and initiate allo-responses. The activated T cells, particularly CD8 T cells, damages the antigen-bearing cells and tissues through the effector function, resulting in the graft rejection. Histocompatibility antigens are derived from polymorphic proteins. They were originally defined via the identification of the chromosome loci responsible for rejection of transplanted tumors and tissues in laboratory mice. The loci were designated H, representing histocompatibility, and include H2 locus which contains genes encoding the molecules related to peptide presentation: H2-K, D, and L for class I, and H2-A and E for class II molecules in mouse. The molecules mapped to HLA locus, which encodes HLA-A, B, and C class I, and HLA-DP, DQ, and DR class II molecules. The H2 and HLA loci genes are classified to major histocompatibility antigens or complex (MHC), and the rest histocompatibility (H) antigens are to minor H antigens. Mismatch on the MHC locus between donor and recipient induces strong allo-responses. The strong immunity against allo-MHCs is ascribed to the function of MHCs as antigen-presenting molecules and the high frequency of the reactive T cells in naïve pool, more than 10-fold higher frequencies compared to those of T cells reactive to a nominal foreign viral antigen. Minor H antigen loci are spread across whole chromosomes. Minor H antigens are reduced to a short processed peptide bound to specific MH class I and II molecules, and thereby, induce CD8 and CD4 T cell responses, respectively. Simple amino acid change in the MHC-presenting peptides can establish self vs non-self discrimination, and evokes T cell allo-response. With the advance in genome sequencing and identification of MHC-bound peptides, information on the minor H antigens and the MHC-restriction is growing. T cells reactive to minor H antigens are similar to nominal foreign viral peptide, in terms of the frequencies in naïve pool, and the TCR diversity. But not all minor H antigens are equal and show immune hierarchy among different minor H antigens. For instance, a dominant minor antigen, named H60 in B6 anti-BALB.B (H2-matched but background gene-mismatched allogeneic transplantation setting), can take more than 10 to 25 % of CD8 T cells in peripheral blood of the immunized individuals. However, the immune hierarchy can change,

depending on the tissue and cell transplantation. Tissue distribution of minor H antigens affects the dominance. Also, the tissue distribution influences degrees of negative selection of the reactive T cells, which occurs in the thymus of the recipient after hematopoietic cell transplantation. Extents of CD8 T cell responses to minor H antigens depend on the presence or absence of concomitant CD4 T cell activation (called CD4 help). The CD4 help determines generation of memory and non-responsiveness of the CD8 T cell. The CD4 helper-deficient CD8 T cells becomes exhausted, unable to clear the specific antigen-bearing allogeneic cells. The lessons learned from mouse models can be extrapolated to human allo-transplantation.