

IMMUNOGENICITY AND TOLEROGENICITY IN TISSUE TRANSPLANTATION

Els Goulmy¹ and James Forman²

¹Department of Immunohaematology
University Hospital
2333 AA, Leiden
The Netherlands 39226

²Department of Microbiology
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75235-9048 U.S.A.

This discussion session was centered around three basic topics: I. Factors which modulate graft rejection including tolerance, II. Mechanisms of graft rejection, and III. Structure of target antigens in the allograft reaction. A number of selected contributors were invited to summarize and discuss their data in view of these topics.

The first topic was addressed by Els Goulmy who on behalf of Jon van Rood presented evidence for neonatal B cell tolerance in man. Studies in highly sensitized patients waiting for renal allografting with broadly reactive anti-HLA antibodies in their sera revealed that in 50% of the patients antibodies were not formed against the non inherited maternal antigens (NIMAs). These findings may have important implications not only for renal allograft selection but might also add significant information for selection between potential unrelated bone marrow donors. Whether the tolerance is due to chimerism is not known: yet if so, it only would partially explain the data. A human model dealing with acquired tolerance or factors which modulate graft rejection was presented by Malies Lagaaij (Leiden). Her data indicated that not all blood transfusions given prior to kidney transplantation resulted in better graft survival. Depending on sharing of HLA-DR or not between patient and transfusion donor determines whether the transfusion immunosuppresses or immunizes, respectively. In the latter situation; i.e., HLA-DR mismatched transfusions, cellular MLC and CML in vitro

activities as well as humoral responses increase and graft survival decreases. Whether class I matching between recipient and transfusion donor is playing a role is not clear, although the best results for graft survival are obtained in those cases where the sharing of HLA class I and II between recipient, blood transfusion donor and kidney donor is the greatest. The mechanism is unknown but might be a veto cell type of phenomenon. Next, an interesting animal model focusing on the induction of tolerance for self antigens was presented by Brigitta Stockinger (Basel). The self protein C5 is processed and presented with class II from normal mice and can activate C5 specific T cell clones obtained from C5 deficient mice. The C5 deficient mice are not tolerant to this protein as expected, but they are also not tolerant to the C5 precursor molecule pro-C5. Furthermore, T cell clones from deficient mice react with pro-C5 from C5 deficient macrophages. This lack of tolerance to pro-C5 may be due to either expression of low levels of this self antigen or low levels of class II molecules on cells responsible for tolerance induction in the thymus. A model for explaining tolerance to skin grafts was presented by Michael Rees (NIH). Mice grafted with Qa-1 congenic skin grafts do not reject this tissue unless the graft expresses a second helper antigen. Mice first grafted with Qa-1 disparate grafts lacking the helper antigen fail to reject this graft when re-grafted with a Qa-1 graft bearing the helper antigen. Adoptive transfer of spleen cells from Qa-1 tolerant mice together with anti-Qa-1 primed effector cells suppressed the ability of the effector cells to mediate graft rejection. The phenotype of these suppressor cells has not yet been established. Ken Murphy (St. Louis) produced transgenic mice which expressed IA on exocrine pancreatic cells. The IA on the pancreatic cells was shown to be capable of presenting peptide antigen to specific IA restricted hybridomas. These same cells when cultured with T cell clones were able to inactivate these T cells. Transfer of normal cells into these recipients resulted in tissue destruction of the exocrine pancreas. This model suggests peripheral tolerance of T cells potentially reactive against organ specific antigens not expressed in the thymus.

The second part of the session addressed the mechanism of graft rejection. Amy Rosenberg (NIH) focused on skin allografts, the effector cell populations involved in rejection of MHC class I or II disparate grafts, and the necessity of IA expression on the target cell for rejection of class II disparate grafts. The specificity of rejection

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was addressed using chimeras and allophenic mice. The results indicated that rejection was directed against cells bearing the target antigen and that bystander effects did not cause destruction to other cells in the graft. Hugh Auchincloss (Boston) showed in a xenogeneic model using monkey skin on mice that CD4⁺ and CD8⁺ cells were responsible for graft rejection. He also reported only a weak allogeneic T cell response mediated by mouse T cells against monkey stimulator cells unless mouse antigen presenting cells were present in in vitro cultures. His data suggests that for xenografts that target antigens only need be expressed on class II positive epidermal cells.

The third section addressed the structure of target antigens and how they may affect graft rejection. Jim Forman analyzed T cell recognition of an hybrid class I molecule (L^d/Q7) having H-2L^d α -1 and α -2 domains with the α -3 domain and carboxy-end derived from Q7 (Qa-2). Surprisingly, anti-H-2L^d bulk and cloned CTL failed to recognize this antigen. However, secondary CTL from in vivo primed animals could recognize this molecule. These latter CTL were not inhibited from mediating lysis by anti-Lyt-2 antibodies, whereas primary CTL were. This suggests that this hybrid molecule lacks the ability to interact with Lyt-2 and could explain why Qa-2 molecules do not act as restriction elements for antigen specific CTL. This data would further indicate a major role for the function of Lyt-2 for antigen specific CTL responses. Andrew Mellor (London) used Q9 (Qa-2) H-2D^b hybrid genes to produce transgenic mice. The mice expressed Q9/D^b or Q9 at relatively high levels on many tissues. The Q9 molecule was linked to the cell membrane through phosphatidylinositol while the Q9/D^b was not. Both served as transplantation antigens and were capable of inducing CTL activity against Qa-2 antigens. Edward Barksdale (Boston) examined the expression of class I and II transcripts and antigens in fetal tissue transplanted into allogeneic recipients. There was an inverse correlation between MHC expression and graft survival. He also reported that epidermal growth factor inhibited MHC mRNA while Mullerian inhibiting substance had an opposite effect. Thus, substances involved in the growth and differentiation of embryonic and fetal tissue appears to also regulate the expression of MHC transcription.