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Session Title : Update in ABO-incompatible kidney transplantation

Role of innate T cells in antibody-mediated rejection

Hideki Ohdan
Hiroshima University, Japan

Refractory B cell responses to T cell-independent (TI) carbohydrate antigens (Ags) are critical drivers of rejection reactions to ABO-incompatible allogeneic grafts and xenogeneic grafts from other species. Previously, we have detected B cells expressing receptors for blood group A carbohydrates in the CD5high B-1a subpopulation in mice, similar to that in blood group O or B in humans. We also have demonstrated that CD1d-restricted natural killer T (NKT) cells are required to produce anti-A antibodies (Abs), through collaboration with B-1a cells. After immunization of wild-type (WT) mice with human blood group A red blood cells (A-RBCs), interleukin (IL)-5 exclusively and transiently increased and the anti-A Abs were elevated in sera. However, these reactions were not observed in CD1d(-/-) mice, which lack NKT cells. Administration of anti-mouse CD1d blocking monoclonal Abs (mAb) prior to immunization abolished IL-5 production by NKT cells and anti-A Ab production in WT mice. Administration of anti-IL-5 neutralizing mAb also diminished anti-A Ab production in WT mice, suggesting that IL-5 secreted from NKT cells critically regulates anti-A Ab production by B-1a cells. In nonobese diabetic/severe combined immunodeficient (NOD/SCID/γc(null)) mice, into which peripheral blood mononuclear cells from type O human volunteers were engrafted, administration of anti-human CD1d mAb prior to A-RBC immunization completely inhibited anti-A Ab production. Thus, anti-CD1d treatment might constitute a novel approach that could help in evading Ab-mediated rejection in ABO-incompatible transplant recipients. To explore the biological significance of crosstalk between Toll-like receptors (TLRs) and B cell receptors (BCRs) in the TI B cell immunity, we here used MyD88-, TRIF-, and α-galactosyltransferase-deficient mice to study B cell phenotypes and functional properties during TI transplant-related glycan Ag exposure. BCR stimulation alone induced differentiation into CD5high B-1a cells, which were highly sensitive to a calcineurin inhibitor (CNI), while co-stimulation of TLRs and BCRs induced differentiation into CD5dim B-1b cells in MyD88-dependent and CNI-resistant manner. MyD88-dependent TLR stimulation in B-1b cells enhanced downstream factors in the BCR-calcineurin pathway, including a nuclear factor of activated T cells, cytoplasmic 1 (NFATc1). TLR inhibitor together with CNI abrogated refractory B-1b cell immune responses against the ABO-blood group Ags, while blocking both BCRs and TLR-MyD88 by using Bruton's tyrosine kinase inhibitor and histone deacetylase inhibitor abrogated refractory B-1b cell

immune responses against Gal-glycan Ags. Thus, this study provides a rationale for a novel therapeutic approach to overcome refractory transplant-related anti-glycan Ab production by blocking both BCR and TLR-MyD88 signals.