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Kidney Transplantation: The Challenge of Human Leukocyte Antigen and Its Therapeutic Strategies

Tilahun Alelign[*1,2,3], **Momina M Ahmed**[4], **Kidist Bobosha**[3], **Yewondwossen Tadesse**[5], **Rawleigh Howe**[3] and **Beyene Petros**[1]

[1]College of Natural Sciences, Department of Microbial, Cellular and Molecular Biology, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia
[2]Department of Biology, Debre Berhan University, P.O. Box 445, Debre Berhan, Ethiopia
[3]Armauer Hansen Research Institute, Addis Ababa, Ethiopia
[4]St. Paul's Hospital Millennium Medical College and Addis Ababa University, Addis Ababa, Ethiopia
[5]School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

Kidney transplantation remains the treatment of choice for end-stage renal failure. When the immune system of the recipient recognizes the transplanted kidney as a foreign object, graft rejection occurs. As part of the host immune defense mechanism, human leukocyte antigen (HLA) is a major challenge for graft rejection in transplantation therapy. The impact of HLA mismatches between the donor and the potential recipient prolongs the time for renal transplantation therapy, tethered to dialysis, latter reduces graft survival, and increases mortality. The formation of pretransplant alloantibodies against HLA class I and II molecules can be sensitized through exposures to blood transfusions, prior transplants, and pregnancy. These preformed HLA antibodies are associated with rejection in kidney transplantation. On the other hand, the development of de novo antibodies may increase the risk for acute and chronic rejections. Allograft rejection results from a complex interplay involving both the innate and the adaptive immune systems. Thus, further insights into the mechanisms of tissue rejection and the risk of HLA sensitization is crucial in developing new therapies that may blunt the immune system against transplanted organs. Therefore, the purpose of this review is to highlight facts about HLA and its sensitization, various mechanisms of allograft rejection, the current immunosuppressive approaches, and the directions for future therapy.

The law of transplantation indicates that grafts between genetically identical individuals survive and grafts on genetically different individuals fail. Usually, transplant rejection of the kidney occurs when the immune response of the recipient recognizes the new kidney as being a harmful object. This remains a major immunological barrier to organ transplantation therapy. Thus, prior knowledge of the existing anti-HLA antibodies circulating among potential kidney recipients is important to set protective measures before transplantation.

HLA Sensitization: HLA sensitization refers to the presence of antibodies in the potential recipient against HLA molecules of the selected donor. Exposure to nonself HLA can cause the production of HLA-directed antibodies. Alloantibodies recognize antigenic epitopes displayed by the HLA molecule on the transplanted allograft and contribute to graft damage. There is a clear association between previous exposure to foreign HLA and the occurrence of a high degree of panel reactive antibody (PRA). The percentage of PRA estimates the likelihood of positive crossmatch to potential donors, and patients with greater quantities of preformed DSA have the highest likelihood of graft loss. Donor-specific anti-HLA antibodies (DSA) identified by single-antigen bead (SAB) array are questioned for their sensitivity and lack of event prediction after transplantation. Despite known technical limitations of SAB assay, it appears to be a highly useful tool for posttransplant monitoring of HLA antibodies and surveillance of antibodymediated rejection. The impact of sensitization in a potential recipient results in longer waiting time for transplantation, posttransfusion complications, exposure to more adverse effects of immunosuppressor drugs, and finally graft rejection. The common causes of HLA-sensitizing events include previous transplants, pregnancies, and blood transfusions that lead to the development of DSA. The risk of sensitization increases as there is exposure to more than one sensitizing factor.

Rejection is defined as an immune response that mediates injury and destruction of transplanted tissues. Kidney transplant rejection is a complex process, and the graft could be viewed as a one-way process in which host immune cells destroy a defenseless allograft. HLA molecules expressed on the surface of the donor cells induce an antigenic stimulus recognized by the recipient's immune system which triggers graft rejection. The immune response to an allograft rejection involves both the innate and the acquired immune systems. The innate immune system predominates in the early phase of response through recognizing host-derived molecules which results from tissue damage. Proinflammatory damage-associated molecular patterns, hypoxiainducible factors, adhesion molecules, dysfunction of the renal vascular endothelium, chemokines, cytokines, and Toll-like receptors are involved in the activation and recruitment of immune cells into injured kidneys. Immune cells of both the innate and the adaptive immune systems such as neutrophils, dendritic cells, macrophages, and lymphocytes contribute to the pathogenesis of renal injury. Initiated inflammatory events by chemokines and cell adhesion molecules play essential roles, not only for leukocyte migration into the graft but also for facilitating dendritic cells and Tcells trafficking between lymph nodes and transplants. The mechanisms of allograft rejection mainly depend on the adaptive immune system mediated by a complex interplay of cellular and humoral immunity.

Prevention of graft rejection remains a common problem in transplantation therapy. The major obstacles for a successful kidney transplantation are graft rejection, adverse effects of immunosuppressive drugs=, and lack of reservoir organs for transplantation In addition, sensitization to HLA represents a barrier to transplantation for patients who develop Table 1: Common immunosuppressive agents. Number Drugs Mechanism of action Effect Reference(s) 1 Mycophenolate sodium, tacrolimus, and azathioprine Inhibits signals transmitted by IL-2 binding to IL-2R (antiproliferating effect) Blocks T-cell activation, decreases both cell-mediated and humoral immunities2 Glucocorticosteroids: prednisone Anti-inflammatory Decreases circulating T-cells and inflammatory cytokines 3 Polyclonal antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) Leucocyte depletion/depleting antibodies. Eliminates CD4+ T-cell and B-cell interaction causing B-cell toxicity/apoptosis Modulation of alloantibody production 4 Mycophenolate mofetil Inhibits inosine monophosphate dehydrogenase (IMPDH), inhibits DNA synthesis and protein glycosylation, suppresses expression of CD25, 71, 154, 28 Decreases proliferation of B and T-cells 5 Anti-CD3 monoclonal antibody T-cell activation, opsonization, and depletion of antibodies 6 Tacrolimus, cyclosporine A Inhibits interleukin- (IL- 2 production by T-cell calcineurin antagonist, gene transcription, calcineurin inhibitors; causes decrease in gene expression Decreases both cell-mediated and humoral immunities 7 Anti-CD 20 monoclonal antibody (chimaeric)

Targets B-cells, depletes B-cell aggregates within allografts B-cell depletion 8 Anti-CD 25 monoclonal antibodies (IL-2R chain) Inhibits IL-2 function Plasmapheresis, mycophenolic acid Reduction of antibody titers 10 Intravenous immunoglobulin (IVIG) Reduces CD19, CD20, and CD40 expression by B-cells Blocks the binding of donor-reactive antibodies to target Fc receptors. Regulation of T and B lymphocytes 11 Rituximab B binds with CD20 antibody, inhibits B-cell proliferation, decreases the concentration of antibodies. Antibody-dependent cellular cytotoxicity, direct signaling, and antibody-mediated cytotoxicity Decreases the population of CD20 B-cells. 12 Plasmapheresis Removal of DSA in circulation (elimination of DSA) Reducing the antibody load 13 Immunoadsorption Treatment of multiple plasma volumes 14 OKT3 (murine) anti-CD3/ TCR monoclonal Antibodies TCR comodulates with CD3 15 Eculizumab (humanized monoclonal antibody) Binds to the C5 protein with high affinity, thereby inhibiting conversion of C5 to C5b. Preventing formation of the membrane attack complex (C5–9) 12 Journal of Immunology Research donor-specific anti-HLA antibodies (DSA) as a result of pregnancy, blood transfusions, or previous transplants. This results in prolonged waiting times for transplantation, and if transplanted, these patients are at higher risk of acute and chronic rejection. Thus, the detection of humoral sensitization before renal transplantation is important for the selection of the most suitable donor and to identify patients with high risk of rejection. When a patient is already sensitized, precise characterization of alloantibodies and exact HLA typing at the allele level are mandatory at the time of transplantation. Moreover, the knowledge of HLA sensitizations and identification of antiHLA antibodies among potential renal recipients are essential to control graft loss. The approaches to enhance graft survival are gaining acceptance in human tissues and organ transplantation. A better understanding of the cellular and molecular mechanisms that underline the immunological response to transplanted organ led to the discovery ofnew immunosuppressive agents.