Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 6 Issue 6 June 2023

Editorial

Corneal Transplantation: Immunobiology and Immune-Mediated Allograft Rejection

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Received: February 27, 2023

Published: May 01, 2023

Cornea is an immune privileged site and an immune privileged tissue which provides protection from the Immune-Mediated destruction. Human Corneal Transplantation (Keratoplasty) is considered to have superior short and long term outcomes and minimal requirement for immunosuppression compared to Solid Organ Transplants because of the inherent immune privilege and tolerogenic mechanisms associated with the anterior segment of the eye.

As per Pleyer and Schlickeiser, 2009, the ocular immune privilege is not absolute and it is revocable against any unfavorable complications like inflammation. They mentioned that Chronic Inflammation results in corneal Neo-angiogenesis and Lymph-angiogenesis leading to a post-transplant high risk graft failure. Inflammation may cause up regulation of HLA expression in all corneal layers. According to Williams., *et al*. 1989 inflammation recruits bone marrow derived APCs into the Cornea.

Corneal transplant can be performed by Penetration Keratoplasty, Deep Keratoplasty, Endothelial Keratoplasty. According to Pleyer., *et al*. 2009, the high risk factor for corneal transplant are, Inflammation, Neo-vascularization, Lymph-angiogenesis, Pre-sensitization or Previous Rejection, large or eccentric graft, Infection, Viral Replication (Herpes Simplex Virus).

Corneal Immunobiology is different from other organ. Modest expression of the HLA class I antigen are expressed particularly in the corneal Epithelium. HLA Class I antigen expression in the Stroma and Endothelium is less. As per Whitsett & Stulting .,*et al* 1984, HLA Class II antigens have been found scattered in the corneal Epithelium particularly in the limbus region and in the corneal Strom. HLA Class II expression is confined to the Langerhans cells in the peripheral Epithelium. HLA Class II antigen expression in interstitial dendritic cells in the peripheral Stroma is modest. Epithelial cells express ABO blood group Antigens.

During Corneal Transplant, enhanced expression of HLA class I and Class II antigens is detected which is induced by the surgical process. The corneal endothelium slightly express HLA antigen and is best capable of generating cytotoxic lymphocytes. According to Treseler., *et al*. 1986 Only Corneal Endothelium and Stroma can generate T lymphocyte (CTL) response. The relative absence of mature APC, these cells are necessary to initiate the corneal allograft response.

According to Hamrah., *et al*. 2002, Cells with Antigen Presentation capability are absent in normal Cornea. A population of CD45+ Cells resident in the central Cornea of mice has been described. As per Griffith., *et al*. 1995, 1996, The constitutive expression of Fas ligand (CD95L) in Cornea promotes apoptosis in the cell bearing Fas, such as lymphocytes. (Griffith et al. 1995, 1996). Streilein, 1996, D'orazio & Neiderkorn 1998, showed that Immunosuppressive Cytokines in aqueous humor (TGF β, MSH) and vasoactive intestinal peptide (VIP) are present in normal aqueous fluid.

According to Pleyer., *et al*. 2009, corneal allograft rejection can occur in each of the three main layers, Epithelium, Stroma, and Endothelium either independently or simultaneously. Among which

the Endothelium is the most critical cell layer and most critical target of allograft rejection which cause rapid and irreversible decrease density in corneal endothelial cell density. The normal cornea is devoid of MHC Class II + APC, thus lacks passenger leucocytes. Minor H is the primary antigen to be presented to T cells. Both Direct and Indirect pathways of allo-recognition are seen. In normal risk Keratoplasty, CD4+T cells are activated via indirect pathway whereas CD8+ T cells are activated via Direct allo-recognition pathway. Hamrah., *et al*. 2003 showed that Corneal dendritic cell express MHC Class II antigens after stimulation. Donor derived APCs can migrate centrifugally out of the grafts and gain access to the host bed and to the ipsilateral lymph nodes. (Liu., *et al*. 2002). Neiderkorn 1995 described that Presence of donor derived LCs increase Rejection rate. Th1 cells activated via direct pathway could be detected as early as 72 hrs. after transplantation.

CD28 with CD80/86 or CTLA-4 with CD80/86 is thought to inhibit a T cell response. CD40-CD154 (CD40L) is another important Co-stimulatory pathway of rejection. Anti CD28 monoclonal antibodies, CTLA-4Ig, CD154mAB profoundly reduce Allograft Rejection in both high risk and normal risk Keratoplasty.

According to Larkin., *et al*. 1997, the presence of NK cells and Neutrophils in the graft issue. CD4+/CD8+ T cells are found in the aqueous humor. Besides, the functional molecules like Adhesion Molecules (VCAM 1, E Selectin, ICAM 1), Cytokines (IFN γ, TNF α, IL4, IL13, IL2), Chemokines (RANTES, MCP 1, MIP 1b, MIP 2 are present in normal cornea), controls the amplitude and duration of the allograft response. Cytokines IL1β, TNF β, IL5, IL6, IL10, IL2 are absent or expression is very low. TGF β type 1 and 2, IL1 receptor antagonist (IL1ra) constitutively expressed in normal cornea and remain normal after transplantation but 5-10 fold increase upon Transplant Rejection.

Major., *et al*, explored high risk patients; there are 3 main factors that abolish immune privilege, Vascularization of corneal tissue, Ocular Inflammation, Sensitization events like previous graft rejection. Corneal graft rejection is mostly Cell-Mediated. APC of donor express high levels of MHC class II and Co-Stimulatory Molecules and activated.

Collaborative corneal transplant studies data have shown no benefit of HLA matching but also revealed that ABO blood group matching may improve corneal graft survival. Studies using modern methods for HLA typing have demonstrated that HLA typing may enhance corneal graft survival in high risk patients. There is studies state that alloantibodies can cause serious injuries to corneal button. As per Hargrave., *et al*, 2003, Endothelial cells are most important in maintaining corneal transparency but are also the most vulnerable to complement dependent and independent lysis by cytotoxic antibodies. Keratocytes localized in the corneal Stroma and Epithelial cells are also prone to antibody mediated destruction. Allo-specific Antibodies are not always the cause of corneal graft decompensating but can cause serious graft damage in a complement dependent or independent manner.

According to the observations of Major., *et al*, 2021, DSA assessment requires being a mandatory process both pre transplant as well as de novo formation post-transplant for several reasons. One of the major reasons is, among the four types of corneal graft rejection (Cell Mediated, Antibody Mediated, Acute, Chronic) may require different therapeutic approaches and that should be distinguished. DSA monitoring has become a mainstay of AMR risk stratification in Solid Organ Transplant recipients, but it is not routinely performed after Keratoplasty. Establishing a link between pre transplant sensitization or development of de novo antibodies, and individualized decision making in this patient population requires large, prospective randomized clinical trials with the use of modern DSA detection methods.

As per Crawford., *et al*, 2013 Corticosteroids have been used in Ophthalmology since 1950s and remain the cornerstone of IS therapy for graft rejection prevention and treatment. In 1980 systemic Cyclosporine A (Cs A) was introduced in high risk corneal transplant recipients. Four types of Corneal Rejection may or may not be overlapped. Stratification of Immunological Risk of Transplant Rejection and Personalized Treatment are warranted for a long term excellent outcome of Corneal Transplantation.