Editorial

Aspects of Corneal Transplant Immunology

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J Ophthalmic Vis Res 2017; 12(3): 249-250

Eduard Zirm performed the first successful allogeneic corneal transplant in 1905,[1] making this corneal graft a pioneering event in early organ transplantation.[2] Despite this long history, our knowledge of corneal immune function and graft rejection pathophysiology and its prevention are lagging in comparison to solid organ transplantation. This is, to some extent, due to a misunderstanding of the concept of corneal immune privilege, which is considered an unbreakable rule.[3]

New findings that connect the corneal sensory plexus to immune system have increased our understanding of immunological reactions like rejection. One such study highlighted the regulatory functions of the peripheral nervous system in immunological reactions.[4] It has been shown that dendritic cell (DC) density correlates with decreasing corneal nerves.[5] Substance P, an important nerve mediator, regulates immune reactions by affecting migration, proliferation, and activation of inflammatory cells.[6] Paunicka et al showed a key role of substance P in allogenic graft rejection.[7] They reported that cornea trephination in one eye of mice resulted in a 100% rejection rate of a corneal graft in the opposite eye due to a failure in regulatory T cell function. They found that corneal incisions increased the levels of substance P by nearly threefold in the opposite eye and induced suppression of regulatory T cells. This effect can be prevented by blockage of substance P. Moreover, bilateral changes in the corneal nerves in unilateral corneal disease may be one reason for the higher risk of contralateral graft rejection in a recipient with a previous episode of rejection in the other eye.[8]

Characterizing rejection at the cellular level and knowing the distribution and the role of effector cells is pivotal. For a long time, we thought that the central cornea did not contain any immune cells. However, Liu et al tracked the DCs from donor corneas that were positive for major histocompatibility complex (MHC) class II in the draining lymph nodes of corneal transplant hosts.[9] They also found immature MHC class II-negative DCs in donor corneas before transplantation. In another study, bone marrow-derived cells were detected in addition to immature DCs in the central cornea. If we consider previous studies that report the reduction of corneal allograft rejection by treatment with bone marrow-derived DCs and tolerogenic DCs, it suggests a new horizon for prolonging corneal graft survival, especially in high-risk keratoplasty.[10-12]

Another key issue in the mechanism of rejection is the important role of angiogenesis and lymphangiogenesis and the ways to manage these processes. High-risk keratoplasty is defined as a recipient cornea with two or more quadrants of corneal vascularization or a history of graft rejection.[13] This shows the importance of corneal vascularization in corneal graft rejection. In fact, one of the main factors that helps maintain the immune privilege of the cornea is it being avascular and alymphatic. Corneal barriers to angiogenesis and lymphangiogenesis [vascular endothelial growth factor receptor (VEGF), thrombospondin-1, pigment epithelium-derived factor, etc.] can be bypassed through corneal injury, inflammation, and corneal transplantation.[14] Di Zazzo et al showed the angiogenic effect of allogeneic T cells by VEGF-A signaling.[15] Although lymphatic vessels mediate the afferent arm of immune responses in a corneal graft, its importance in high-risk keratoplasty is sometimes ignored simply because of our inability to detect these vessels by clinical examination as opposed to visible blood vessels.[16] Hopefully, anti-VEGF therapy can suppress lymphatic vessels like blood vessels.[17] It has been reported that this modality can prolong graft survival in high-risk corneal transplants in an animal model.[18] The efficacy of anti-VEGF in high-risk keratoplasty is subject to ongoing research.

There is a huge need for strong evidence-based studies to evaluate risk factors and possible effective interventions to treat rejection. It appears that studies based on national corneal transplantation registries can provide invaluable information about these issues. A recent study was published about the effect of gender matching between the donor and recipient based on more than 18,000 corneal transplantations in the UK.[19] They

showed that donor-recipient mismatches significantly decrease the 5-year survival rate. Transplantation of a male donor to a female recipient has the highest risk of rejection among possible patterns of gender matching. This effect is more prominent in patients with Fuchs' endothelial dystrophy and less prominent in high-risk patients or those with pre-existing inflammation. Based on the results of this study, the authors suggested gender matching as much as possible and considered this as a simple and almost zero-cost recommendation to improve graft survival. There are increasing numbers of studies and findings regarding corneal immunological mechanisms and reactions, especially rejection, that could open a new horizon for more successful keratoplasty in the near future.

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Access this article online	
Quick Response Code:	**Website:** www.jovr.org
	DOI: 10.4103/jovr.jovr_115_17

How to cite this article: Zarei-Ghanavati M, Liu C. Aspects of corneal transplant immunology. J Ophthalmic Vis Res 2017;12:249-50.