Perspective

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Innate Immune Cells in Kidney Transplantation

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Perspective

End-Stage Renal Disease (ESRD) is best treated with a kidney transplant. Although advancements in immunosuppressive medications and procedures have greatly reduced the frequency and importance of acute rejection, the development of chronic cellular or humoral rejection still has a major impact on the fate of kidney transplants. In this context, adaptive alloimmune response has always been viewed as the primary, if not the only, actor, and the role of innate immunity has been largely ignored for a long time. However, a rising body of data suggests that innate immune responses play an important role in priming the rejection machinery and controlling the activation of alloantigen-specific adaptive immunity over the previous two decades.

Cellular components such as phagocytic cells (neutrophils, macrophages), dendritic cells, Natural Killer (NK) and other innate lymphoid cells, and blood proteins, including members of the complement system and other mediators of inflammation, are the primary ingredients of innate immunity.

Several variables can cause innate immune responses to b activated in clinical kidney transplantation. Brain death itsel can promote the systemic production and release of pro inflammatory cytokines such as monocyte chemotactic peptide- and interleukin-6, leading to the activation of innate immun pathways such as monocyte recruitment and activation i several organs including the kidneys in Donation after Brai Death (DBD). Furthermore, warm and cold ischemia during kidney extraction and preservation, followed by reperfusion at the time of transplantation, is known to activate innate immune responses via a variety of molecular pathways, including oxidative stress and resident cell death. Excitingly, there is now convincing evidence that adaptive immune response activation can cause tissue damage via cellular and molecular components of innate immunity in kidney transplant rejection.

Different cell types engaged in the innate immune response can play an essential role in kidney transplantation and are impacted by the recipient's immunological suppression. Recognition of allogeneic non-self-activates recipients T lymphocytes, which can cause direct cytotoxicity on graft cells or affect other immune system cells such as B lymphocytes or macrophages. Dendritic cells may also play a significant role as antigen-presenting cells in this situation, and their activation might impact innate immune responses in many ways, such as by activating natural killer cells.

Through multiplex immunofluorescent labeling, several researchers identified inflammatory cells in renal allograft biopsies from individuals with chronic-active antibody-mediated rejection. CD8+ cytotoxic T cells (granzyme B+ and CD57+) and M2 macrophages (CD68+ and CD163+) dominated the glomerular compartment. T cells (CD4+ or CD8+ T cells) and macrophages were also found in the tubular interstitial compartment, however only a small number of CD8+ T cells expressed granzyme and/or CD57. There were also CD3+FoxP3+ cells in the tubular compartment, and their higher quantity was strongly linked with poor renal transplant survival.

Cross-Talk between Complement and Innate Immune Cells in Kidney Transplantation

The activation of the complement system as well as the coagulation cascade characterizes innate immune responses in kidney transplantation. These essential components of innate immunity are inextricably linked. The complement system is an important modulator of the innate immune response, and as such influences other endogenous systems. The complement cascade can be activated by three major complement activation pathways (classical, alternative, and lectin pathway) that converge into a common sequence leading to the formation of C_3- and C_5-convertases as well as the production of the anaphylatoxins C_3a and C_5a as well as the C_5b-$_9$ membrane attack complex. The complement system is tightly controlled to prevent over-activation, which can cause systemic inflammation, coagulation/fibrinolysis dysregulation, and tissue damage, all of which contribute to allograft injury.

Complement activation in kidney transplantation can be caused by donor-brain death and is linked to poor renal allograft outcomes. Some studies looked at the involvement of the alternative route in a Fisher rat model of brain death. Anti-factor B pre-treatment of rats demonstrated unique complement-regulatory and

anti-inflammatory effects, expanding the burgeoning area of complement therapies. Complement activation may contribute to the development of renal failure via tubular $C_5b\text{-}_9$ generation. It evaluated at the alternative route of complement factor properdin and the terminal $sC_5b\text{-}_9$ complex in the urine of 707 renal transplant recipients, which had previously been studied. It was discovered that, independent of proteinuria, the urinary presence of properdin and the terminal $sC_5b\text{-}_9$ complex had a significant impact on the rate of graft failure and graft survival after kidney transplantation, implying that they could be useful biomarkers of immunological injury and kidney allograft deterioration.

Innate Immune Cells and Therapy

Dendritic cells, monocytes, macrophages, neutrophils, and natural killer cells are innate immune cells that play a major part in most immunological processes following kidney transplantation, and their activity can be greatly altered by immunosuppressive treatments. The ultimate objective for each physician is to define the therapeutic range of certain medicines in order to achieve better graft outcomes with fewer adverse events such as graft rejection or the incidence of infections. Some studies looked at how the duration of time spent within the therapeutic range of a tacrolimus-based immunosuppressive regimen could affect long-term clinical results in live kidney transplantation.

Because there is a significant correlation between staying within the tacrolimus therapeutic range in the first year and improved long-term results in live kidney transplants, this is a highly interesting strategy for future tacrolimus exposure monitoring. Therapy regimen differences can have an impact on cell phenotypic and biological consequences. A monocentric prospective cohort study of kidney transplant patients with de novo DSA was conducted to assess transcriptomic and phenotypic changes in T and B lymphocytes, as well as serum cytokines, after therapy with high dosage intravenous immunoglobulin. High dosage intravenous immunoglobulin produced modest changes in B and T cell phenotype, but results need to be validated in a larger population before high dose intravenous immunoglobulin may be used clinically following kidney transplantation.

Some researchers examined the impact of presently used immunosuppressive drugs on innate immune cells, their direct effects, and the effects on induced adaptive immunological response in the context of kidney transplantation in their review. Their review suggests that new medication options targeting innate immune cells might be investigated in order to extend allograft function while minimizing immunosuppression.