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Technical and Conceptual Advances in Histocompatibility and Immunogenetics Inform on Mechanisms of Transplant Rejection and Pave the Way to Development of Novel Therapies

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Advances over the past few decades in immunosuppression and patient management have improved the outcomes of solid organ transplantation (SOT) and hematopoietic stem-cell transplantation (HSCT). Despite this, achieving long-term graft survival continues to be hindered by rejection, mediated by humoral and cellular alloimmune responses against donor human leukocyte antigens (HLA). The collection of papers in this Histocompatibility and Immunogenetics Section highlight the emerging technical and conceptual breakthroughs that address mechanisms underlying anti-donor responses. These breakthroughs include novel techniques for HLA typing and urinary biomarker analysis to predict graft outcome, controlling the innate immune response in rejection by targeting macrophages and the complement system, and gaining a fuller understanding of heterologous immunity in allograft rejection. Ultimately, understanding the role of innate and adaptive immunity in allograft rejection will permit the development of effective therapies to reduce its occurrence in the clinic.

There is broad agreement that HLA mismatching leads to the generation of cellular and humoral alloimmunity to the graft after SOT and promotes graft vs. host disease (GVHD) in HSCT. HLA matching prior to transplantation is a means to select compatible donor-recipient pairs to reduce the risk of rejection or GVHD. The advent of next generation, high-throughput sequencing technologies for HLA typing will provide for the first time complete HLA gene sequences which can be used to interrogate the biologic and clinical relevance of introns, exons, promoter regions of HLA genes. In this issue, Drs. Lan and Zhang describe advances in NGS used for HLA typing in SOT and HSCT, as well as for immune monitoring. NGS allows for high resolution HLA matching in HSCT, bypassing the limitations presented by classical methods, such as incomplete donor typing and ambiguities. The authors emphasize that as NGS is more cost-effective and sensitive than other methods, it can generate more loci typing per run, allowing for better donor-recipient

Conflicts of interest

None

compatibility assessment. For this reason, NGS is also useful for donor selection in SOT, and antibody analysis in the case of highly sensitized patients. The authors remark that one limitation of NGS is its unsuitability for use in deceased-donor typing due to the longer turn-around time of 4–5 days. The authors also highlight the application of NGS to immune monitoring using the highly sensitive method to monitor graft health and detect donor-derived cell-free DNA as an early indicator of organ damage. Thus, NGS provides a new approach to diagnosing rejection, precluding the need for biopsies. They also describe how NGS can be applied to typing the T cell receptor repertoire and for detection of potentially harmful alloreactive T cells.

Understanding how heterologous immunity contributes to graft rejection and GVHD is important for developing new tools to identify patients at risk of rejection and new drugs to prevent rejection and graft loss. In this issue Dr. Frans Claas and colleagues expand on the pathogenic role of heterologous T memory cells that have dual specificity for viruses and alloantigens in the setting of SOT and HSCT. Drawing from both experimental and clinical studies, the authors make a case for virus-induced memory CD8 cells with alloreactivity, highlighting a role for heterologous immunity in rejection in SOT. These alloreactive CD8 cells also contribute to HSCT by interfering with mixed chimerism induction. Both naïve and memory T cells have alloreactive potential, with alloreactive CD4 T cells providing help to alloreactive CD8 cells. Furthermore, mismatches in either HLA class I or II can elicit alloreactive T cell responses, underlining the importance of matching for both classes. The authors note that while certain memory T cells have been shown to display alloreactive properties, some subtypes, such as regulatory T cells, aid in tolerogenesis. Therefore, the phenotype of a memory T cell determines if it has protective or pathological effects on the graft. Alloreactive T cells have also been shown to be recruited and activated by components of the complement pathway deposited on allogeneic endothelial cells (EC).

There is a growing appreciation that complement activation is involved in many facets of allograft rejection including post-transplant ischemia-reperfusion injury, generation and function of alloantibody and alloreactive T cells and chronic injury and fibrosis. Drs. Sheen and Heeger discuss the variable modes of complement activation and how the complement system contributes to chronic allograft failure. The authors provide insight into novel therapeutic strategies that were designed to target various components of the complement cascade to prolong graft survival. Studies centered on genetic or pharmacological blockade of the C3a/C5a signaling pathway demonstrated its ability to modulate T cell-dependent rejection. Clinical studies with eculizumab, a monoclonal antibody against C5, showed that the complement pathway is necessary for the development of antibody-mediated rejection (AMR) as it mediates the formation and function of alloantibodies. Additional agents directed against other components of the complement cascade, including C1-INH and PIC1, have also been shown to limit allograft rejection in experimental transplant models. The authors also note that complement activation promotes ischemia reperfusion injury (IRI) post-transplantation through signals transmitted by C3a/C5a and the complement-dependent inflammation accompanying IRI can cross-talk with adaptive immunity to generate alloreactive T and B cells. Thus, the complement cascade contributes to graft rejection through a variety of mechanisms and at multiple levels.

Salehi and Reed discuss the multi-faceted role of macrophage subsets in IRI, and in acute and chronic rejection. Though the graft injury has been shown to be mediated by macrophages, recent studies have found that certain macrophage subsets can have graft-protective effects depending on the nature of injury. M2 macrophages conferred protection from IRI and acute rejection, while persistent M2 activity exacerbated chronic injury. Furthermore, the authors describe a regulatory macrophage (Mreg) subset, with potential applications for cell-based therapy in the clinic. The authors conclude that the function and phenotype of macrophages is in turn influenced by factors including immunosuppressive drugs such as rapamycin, Bortezomib, and calcineurin inhibitors, with some activating, and others dampening macrophage function.

A penultimate goal in organ transplantation is to have non-invasive tests that can identify transplant recipients at risk of rejection. Drs. Ho, Rush and Nickerson provide an overview of the state-of-the art for non-invasive monitoring to identify patients at high risk of graft loss. The authors outline the key steps in biomarker development and performance evaluation of biomarkers. They also review promising urinary biomarkers predictive of late allograft outcomes including urinary-cell microRNA, Urine proteomics, and urinary chemokines. Of particular interest, they discuss two urinary chemokines CCL2 and CXCL9 that at 6 months post-transplant can be used to predict graft dysfunction at 24 months post-transplant. Finally, prospective studies are needed to demonstrate the utility of the urinary biomarker-guided strategy improves long-term graft outcomes.

The compelling conceptual advances and emerging techniques described in this section improve our understanding of the mechanisms involved in transplant rejection, provide new prognostic indicators of rejection and pave the way to the development of novel therapies to improve long-term transplant outcomes.

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