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Editorial - Emerging talents in alloimmunity and transplantation: 2022

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Editorial: Emerging talents in alloimmunity and transplantation: 2022

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Editorial on the Research Topic
Emerging talents in alloimmunity and transplantation: 2022

Introduction

In modern transplant and biomedicine, a proper understanding of both allo- and auto-immune processes is of key importance to minimize acute and chronic graft failure and consecutive rejection/pathology through both cellular and humoral effector mechanisms (Figure 1), e.g. cellular and humoral allo-sensitization, alloantigen-reactive T and B cells with the latter producing donor-specific anti-human leukocyte antigen (HLA) alloantibodies (DSA), and also the contribution of autoantibodies (1–7). This field includes many diverse disciplines, but similar underlying principles, such as the need for HLA-matching of donor organs/stem cells with the recipient, prevention and treatment of graft-versus-host disease (GvHD) (7), and the common need for effective immunosuppression (e.g. steroids or tacrolimus, TAC/FK506) (8), as standard immunosuppressive agent for life-long therapy.

Transplantation of donor-tissues and -organs and vascularized composite allografts is commonly summarized under the term solid organ transplantation (SOT), including e.g. hand, kidney, liver, heart, lung, and intestinal transplantation (8, 9). Of similar importance is hematopoietic stem cell transplantation (HSCT), to reconstitute the stem and progenitor cell compartment in the bone marrow, with both SOT and HSCT entailing GvHD as a potential complication (7, 10). In addition, there are numerous novel approaches of cell and gene therapies (CGTs), including advanced therapy medicinal products (ATMPs), in the US and Europe, respectively (10–14). Adjunct technology, such as machine perfusion of donor organs (e.g. hypo- vs. normothermic) and kidney/renal replacement therapies (RRTs) comprise another promising new field (15–18).

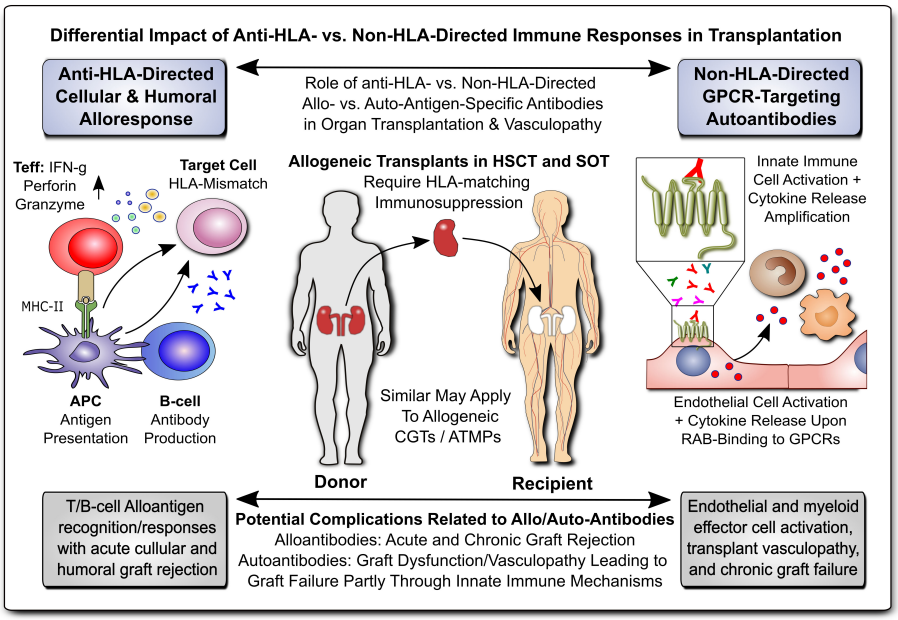

FIGURE 1
Differential Impact of Anti-HLA- & Non-HLA-Directed Allo- & Auto-Immune Responses in Transplantation. Allogeneic transplants in HSCT and SOT typically require HLA-matching and immunosuppression to prevent allograft rejection through anti-HLA-directed alloantigen-specific immune responses (e.g. T and B cell and alloantibody mediated), with a minor but significant contribution from non-HLA-directed auto-antigen-specific autoantibodies (e.g. GPCR-directed regulatory autoantibodies, RABs). APC, antigen-presenting cell; ATMP, advanced therapy medicinal product; CGT, cell and gene therapy; MHC, major histocompatibility complex; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation; Teff and Treg, effector and regulatory T cells; GPCR, G-protein coupled receptor; RAB, regulatory autoantibodies of non-HLA type that are e.g. GPCR-directed, as distinguished from anti-HLA-directed alloantibodies and donor-specific alloantibodies (DSA).

Prior viral infection can promote allograft rejection

Khorki et al. from Cincinnati Children's Hospital Medical Center in Ohio, USA, contributed the article "Prior viral infection primes cross-reactive CD8+ T cells that respond to mouse heart allograft". The authors studied the connection between transplant rejection and the presence of high levels of pre-existing memory T cells, in particular virus-specific memory T cells that can drive allograft rejection in allo-MHC animal models and clinical transplantation (1–3, 19–26). They established a mouse model that can track virus-specific, allo-specific, and cross-reactive T cells, revealing that prior infection induces substantial numbers of virus-specific T cells that cross-react to alloantigen, manifesting as early acute rejection of the heart allograft.

Cross-tissue inflammation in vascularized composite allotransplantation

Shah et al. in collaboration between groups from Yoram Vodovotz (Univ of Pittsburgh, USA) and Vijay Gorantla (Wake Forest Institute of Regenerative Medicine, USA) contributed the article "Peripheral nerve repair is associated with augmented cross-tissue inflammation following vascularized composite allotransplantation (VCA).". Indeed, VCA with concomitant nerve repair/coadaption (NR) and adjunct TAC immunosuppressive therapy is used to repair traumatic injuries but is often complicated by innate and adaptive immune activation/inflammation spanning multiple tissues (27). The effect of NR on the inflammatory cascade is currently unknown (28–30), although TAC has been reported to enhance NR (31–33). The authors here found that, while NR is considered necessary for graft function, it may result in dysregulated and mis-compartmentalized inflammation post VCA and thus suitable mitigation strategies are needed, pointing at their spatiotemporal bioinformatics pipeline.

Hypothermic machine perfusion alleviates IRI in intestinal transplantation in pigs

Hou et al. from the Research Institute of Transplant Medicine and Tianjin Key Laboratory for Organ Transplantation at the Tianjin First Central Hospital in China contributed the article: "Hypothermic machine perfusion alleviates ischemia-reperfusion injury (IRI) of intestinal transplantation (IT) in pigs.". IT is vulnerable to IRI, and due to the limitations of static cold storage (SCS), hypothermic machine perfusion (HMP) is rapidly increasing in popularity (34–40). Here, the authors established a stable intestinal HMP system and demonstrated that HMP could significantly alleviate intestinal IRI and improve the outcome after IT in pigs.

Microbiota transplantation for irritable bowel syndrome: review and meta-analysis

Wang et al. from the Department of General Surgery in Lanzhou China contributed the article "Fecal microbiota transplantation (FMT) for irritable bowel syndrome (IBS): a systematic review and meta-analysis of randomized controlled trials (RCTs).". The authors here assessed the safety and efficacy of FMT for patients with IBS in 19 RCTs within their PROSPERO study (CRD42022328377; https://www.crd.york.ac.uk/prospero/). They found that a single stool FMT was effective and safe for patients with IBS. At 3-36 months post initiation of treatment, FMT could significantly reduce the IBS-SSS score and improve the clinical response rate. However, the authors did not find a positive effect of capsule FMT on patients with IBS.

HDAC6-Inhibition in KTx to modulate adaptative/innate immunity: review article

Zhang et al. from the Institute of Organ Transplantation at Tongji Hospital/Medical College, and the Key Laboratory of Organ Transplantation, Wuhan, China, contributed the article "HDAC6 inhibition: A significant potential regulator and therapeutic option to translate into clinical practice in renal transplantation.". The enzyme histone deacetylase 6 (HDAC6) plays an essential role in many biological processes and exerts deacetylation-dependent and independent effects on a variety of molecular targets, including modulation of both innate and adaptive immune pathways (41). The authors here reason that HDAC6 inhibitors may be promising therapeutic candidates in kidney transplantation, e.g. to counteract ischemia reperfusion injury (IRI), to induce immune tolerance, to protect against oxidative stress, and to attenuate chronic interstitial fibrosis of the transplanted kidneys (42–45).

Immunomodulatory allogeneic and autologous cell therapy for COVID-19: review and meta-analysis

Couto et al. in a collaboration between Charité Berlin in Germany and The University of Sao Paulo in Brazil contributed the article "Systematic review and meta-analysis of cell therapy for COVID-19: global clinical trial landscape, published safety/efficacy outcomes, cell product manufacturing and clinical delivery.". This article provides the largest meta-analysis of 195 registered clinical trials to date. Demographic analysis found that the highest number of trials was conducted in the US, China, and Iran, with the highest number per capita in Israel, Spain, Iran, Australia, and Sweden. The leading cell type was multipotent mesenchymal stromal/stem cells (MSCs) (10, 12–14), which were remarkably heterogenous in their manufacturing and clinical delivery. A pooled analysis of 24 published clinical trials on MSC infusions in COVID-19 found a relative risk reduction for all-cause COVID-19 mortality of RR=0.63 (95% CI 0.46 to 0.85), in alignment with earlier smaller summaries that suggested some clinical benefit (13, 46–52).

Author contributions

GM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. WL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. OP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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