HLA in Transplantation: Challenges and Perspectives

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Solid organ transplantation of hearts, lungs, pancreas, livers, and kidneys is an unprecedented success story in medicine history. For patients with end-stage organ failure, it is sometimes the only life-saving treatment option. The story began 70 years ago in Boston when Joseph Murray performed the first successful organ transplantation of a kidney between the genetically identical Herrick twins Ronald (donor) and Richard (recipient). Retrospectively, Murray was smart as he provided the first technical proof of concept for kidney transplantation in humans without any risk of rejection [1]. Even then it has been known for decades already due to the findings of Sir Peter Medawar that the recipient's immune system is fighting against any genetically different donor organ based on HLA disparities usually resulting in a fundamental rejection of the allograft. Despite the minimal scientific contribution of the first kidney transplantation, it unequivocally resulted in an immediate and profound enthusiasm among researchers and surgeons to continue this concept.

According to the Global Observatory on Donation and Transplantation (GODT, www.transplant-observatory.org), more than 150,000 transplants are nowadays performed worldwide per year. Organs are usually allocated considering urgency and waiting time but also histocompatibility and HLA immunization. HLA disparities against which antibodies have been detected within a recipient may be defined as unacceptable resulting in a positive virtual allocation crossmatch and exclusion of that recipient from the allocation process. Consequently, HLA disparities without detectable antibodies are acceptable for transplantation under modern immunosuppressive medications. This life-long immunosuppression aims to reduce the risk for de novo HLA immunization and premature allograft loss. Today's 1-year allograft survival rates for deceased kidney organs for example are as high as 94% and reduce to 76% within the following 4 years posttransplant [2].

Despite these distinguished achievements in organ transplantation over the last decades the highly interdisciplinary transplant community of surgeons, internists and transplant immunologists will have to meet new challenges for the future. Within this special issue of Transfusion Medicine and Hemotherapy, we present a glimpse of new challenges from different perspectives.

The fundamentals of the immune response against alloantigens certainly also apply to the setting of transplantation. It is well known that in the long term following transplantation the indirect allorecognition pathway may lead to the activation of B lymphocytes and formation of HLA antibodies. Doxiadis et al. [3] summarize in their review our past and current knowledge of the immunogenic basis of the HLA molecule, i.e., epitopes. In the beginning, HLA antigens have been revealed by the reaction of antibodies isolated from the serum of pregnant women. The reaction patterns of thousands of sera have been compiled by an ambitious collaboration of HLA pioneers worldwide which gave rise to the HLA nomenclature. Even then a differential immunogenicity of HLA has already been proposed. Today, it is our challenge to translate the more than 38,000 currently known HLA disparities (mainly detected by

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molecular means) back to clinically relevant immunogenic epitopes.

In the setting of transplantation, HLA plays a crucial role in two ways. First, donor HLA is the target of the immune response. Second, recipient HLA works as presenter of peptides from alloantigens. This ambivalence and interplay between donor and recipient HLA in allorecognition is nicely presented by Peereboom et al. [4] in an original paper on HLA-DPB peptides presented in the context of HLA-A*02: 01 leading to T-lymphocyte activation.

Since Paul Terasaki's seminal work on the predictive value of the crossmatch prior to transplantation, cytotoxic donor-specific HLA antibodies are deemed the immunological barrier to successful kidney transplantation [5]. However, with the advent of imlifidase as a very potent IgG-cleaving enzyme a few years ago, this dogma is no longer absolute. Schrezenmeier et al. [6] present in their original work the first kidney transplant across a positive crossmatch using imlifidase performed in Germany. This proof of concept demonstrates nicely the risks but also the potential benefits of this newly developed desensitization procedure and its value for highly immunized patients desperately waiting for a suitable kidney donor offer.

Highly HLA-sensitized patients are an increasing problem in all organ allocation systems worldwide. There are two major reasons contributing to this phenomenon. First, more advanced healthcare increasingly provides patients with repeated chances to re-enter the waiting list after the failure of the first, second, and third transplant. Second, with improved sensitivity of HLA antibody diagnostics over the last 2 decades the proportion of highly immunized patients on the waiting list increased. To meet the demand, Eurotransplant developed the Acceptable Mismatch (AM) program to prioritize the allocation to highly immunized patients. In a monocentric study, Strehler et al. [7] present a very detailed analysis of the benefits of the AM program for highly sensitized patients.

Conflict of Interest Statement

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Author Contributions

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