EDITORIAL

Editorial for the March 2018 Focus Issue 'Omics in Transplantation'

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It has been well appreciated in solid organ, composite tissue and cell transplantation that HLA mismatches between donor and recipient are key contributors to the alloimmune response. However, in recent years, it became evident that HLA incompatibility cannot be the only driver of alloimmunity. Even recipients of fully HLA-matched organs exhibit antidonor immune reactivity which in the long run leads to graft inflammation, fibrosis and ultimately premature graft failure. These observations led to research activities to uncover the contribution of non-HLA incompatibilities on transplant pathology and failure.

This focus issue of Transplant International is therefore devoted to summarizing the current evidence of non-HLA alloimmunity and the impact of genetic diversity in transplantation by applying novel cutting-edge omics technologies.

Reindl–Schwaighofer and colleagues focused on the consequence of genome-wide genetic diversity for antigraft antibody responses [1]. Several polymorphic gene products have been identified as minor histocompatibility antigens which lead to the production of donor-specific alloantibodies (DSA) via semi- and indirect allorecognition. The evolution in genotyping now allows to identify genetic variants in the donor and recipients on a genome-wide basis. Recently, first adequately powered genome-wide studies show that non-HLA mismatches may equally contribute to premature graft loss as HLA incompatibilities do. The challenging task to come is the identification of the immunodominant epitopes in the non-HLA proteins. Customizable peptide arrays will allow for the identification of these individual epitopes and then a similar process as the identification of anti-HLA specific antibodies over the last decade will be necessary to further refine these alloimmune mechanisms.

Dorr and colleagues from Minnesota present the contribution of genetics to acute rejection after kidney transplantation [2]. While it is evident that genome-wide association studies with acute rejection in transplantation are limited by the imbalance between the number of potential predictors, that is roughly 10 million SNPs and the few outcomes, some progress have been made recently. Although no candidate genes in either the donor or the recipient have been identified to increase the risk of rejection, pharmacogenomics studies over the last years have shown that genetic variants of the cytochrome P450 enzyme family contribute to metabolism of maintenance immunosuppression. For example, almost all Caucasians have low capacity for tacrolimus metabolism compared to African Americans. The clinical utility and importance of this observation led to the publication of guidelines for genotype-guided tacrolimus dosing by the Clinical Pharmacogenomic Implementation Consortium (CPIC). Pharmacogenomics has the potential to improve individual management and outcomes specifically in populations with highly unpredictable metabolism such as in patients of African ancestry.

A consortium from Ireland and Scotland presents omics-based strategies to explore complications such as cancer and post-transplant diabetes (PTDM) in renal allograft recipients [3]. Although key clinical risk factors have been identified for PTDM, the imperfect explained variability of outcomes suggests additional, yet uncovered contributors. Studies applying a candidate gene approach identified similarly to patients with type 2 diabetes mellitus in the general population TCF7L2, CDKAL1 and KCNQ1 to be associated with the development of PTDM. In addition, omics-based technologies allow for an unbiased discovery of further potential molecular predictors. The first emerging genome-wide studies found 26 candidates of which eight could be independently validated but none survived adjustment for multiplicity.

Post-transplant cancer is a serious clinical complication and with the improvement of graft survival over the last decade will be an even bigger issue in the future. If the individual risk could be estimated specific screening measures could be taken to detect such malignancy in time and allow for treatment in time. Most of the omics studies were conducted in skin cancer and

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some candidate genes have been identified but in accordance with PTDM studies, none of the candidates reached a significant threshold after adjustment for multiplicity. Nevertheless, larger consortia such as The International Genetics & Translational Research in Transplantation Network (iGeneTRAiN) will allow pooling of samples to better address the imbalance between predictors and outcomes.

Maybe even more important than the identification of genetic risk factors for skin cancer is the uncovering of genetic risk factor for allograft loss in heart transplantation. While progress has been made in the last years, the median survival is still below ten years and every other patient experiences an acute rejection within the first years. In analogy to what has been observed in kidney transplantation, even HLA-identical donor hearts are rejected in the long term suggesting non-HLA alloimmune as contributing factor. In fact, large-scale analyses showed that about 18% of allograft failures can be attributed to HLA mismatches but roughly 38% of the failures are caused by immunological reactions against non-HLA epitopes suggesting an obvious incomplete understanding of the genetic underpinnings of rejection. In this issue, Keating et al. discuss how advances in genome-wide tools will be used to unveil sources of alloimmunity and outline many key genomic findings [4].

We truly believe these innovative approaches presented in this focus issue will enlarge the understanding of transplant alloimmunity and provide the basis of enhanced individual matching and even potentially targeted therapy.

REFERENCES

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