WWTF Project LS20-081

Genomics-based immunological risk stratification in kidney transplantation

Abstract

In our previous WWTF funded research we showed that non-HLA genetic mismatch in kidney transplant donor and recipient pairs have a major impact on graft survival (Lancet 2019). This data extended the concept of HLA epitope mismatch to genome-wide incompatibilities. The applied genotyping approach allowed for the simultaneous evaluation of over 50,000 genetic variants that result in amino acid mismatches and reflected genetic variation on the population level. Not all identified variants were immunogenic and resulted in antibody formation. Following up on this data we propose a refined risk prediction tool based on: a) whole exome sequencing in already existing 350 transplant pairs from our prospective transplant biobank to cover individual level genetic variation that can not be identified using genotyping and b) a refined bioinformatics pipeline to identify immunogenic variants by integrating antibody accessibility (protein structure) and indirect allorecognition by recipient T-cells (MHC-restriction). As a proof of principle, the detection of antigen-specific indirectly alloreactive T-cells will be tested by using HLA class II / allopeptide tetramers to provide novel insight into the immunogenicity of HLA and non-HLA incompatibilities on a mechanistic level. Overall, the project will increase our understanding of immunological non-self and ultimately make immunological risk stratification clinically feasible allowing for a precision medicine approach in transplantation.

Scientific disciplines:
302084 - Transplantation medicine (40%) | 301301 - Human genetics (30%) | 301902 - Immunology (30%)

Keywords:
kidney transplantation, alloimmunity, genomics

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Further links about the involved persons and regarding the project you can find at
https://archiv.wwtf.at/programmes/life_sciences/LS20-081