LS16-019 - Prolongation of kidney transplant survival through risk stratification of omics-wide incompatibilities using systems biology - a personalized medicine approach

Abstract

Half of all transplanted kidneys lose their function within 15 years. The most important cause is chronic rejection. However, previously known tissue antigens, which distinguish between self and nonself, do not explain all rejection events. Two individuals differ in several million genetic variants. This variation results in the altered or even missing expression of several thousand proteins in each individual. Our working hypothesis is that these genetic differences between donor and recipient are recognized as foreign by the recipient's immune system after transplantation and negatively affect organ survival. This concept has been described by us in a scientific article (R. Reindl-Schwaighofer. Transpl Int. 2018) published in 2018. To further test our hypothesis, we have genotyped more than 1,500 kidney donors and recipients and determined their individual genetic incompatibility. We were for the first time able to show the association between donor/recipient genetic incompatibility and transplant survival in a subgroup of first transplanted kidney recipients with an organ from a deceased donor. In addition, we could observe an increased rate of antibody signals against proteins with changes in their amino acid sequence due to genetic mutations carried by the donor. The results of this study were also published in a scientific article (R. Reindl-Schwaighofer. Lancet. 2019). Shortly thereafter a second high-impact publication describing the association of a single genetic difference in a non-HLA region was published in the New England Journal of Medicine by a group from Columbia. Together the two publications underpin the importance of this research area in kidney transplantation. In addition to describing the importance of genome-wide non-HLA genetic mismatch in kidney transplantation, we could successfully identify the influence of genetic variations in complement factor H on the complement system and show its association with graft survival. An evaluation of the genetic mismatch score developed in this WWTF project in a prospective multi-centre clinical trial is already under preparation.

Scientific disciplines:
Genomics (40%) | Bioinformatics (30%) | Systems biology (30%)

Keywords:
incompatibility, non-HLA, chronic antibody-mediated rejection

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Further links to the persons involved and to the project can be found under
https://www.wwtf.at/funding/programmes/ls/LS16-019/