FP7 BIOMARGIN: URINARY PROTEIN BIOMARKERS OF RENAL GRAFT INJURIES IN KIDNEY ALLOGRAFT RECIPIENTS

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Background
In renal allograft recipients, histological examination of graft biopsies is the gold standard to confirm graft injuries, but biopsies are invasive and histological grading is not very robust. There is thus a need for robust, non-invasive methods to predict and diagnose acute and chronic graft lesions. The goal of the presented research is to discover urine biomarkers with good diagnostic performance for graft injuries.

Methods/Materials
In the discovery step, 245 urine samples with matched kidney allograft biopsies were analyzed from patients with different renal graft conditions (normal biopsy controls (NL), antibody-mediated rejection (ABMR), Interstitial Fibrosis/Tubular Atrophy (IFTA) and T-cell mediated acute rejection (TCMR)) using LC-MS²-based proteomics. Using in-house developed software, all missing peptide intensities in all samples were looked up in the MS1 data layer and verified using a decoy search. Five different hypotheses were tested using multivariate analysis. The FDR-corrected p-value was set <0.001 and the fold change (before log transformation) at least at 2. The generated model was first internally cross-validated. In a next validation step, 200 additional, independent samples were analyzed using the same proteomic pipeline.

Results
For every tested hypothesis, the statistically significant proteins were filtered by a Gene Ontology Analysis and a final model was generated based on a list of statistically & biologically relevant proteins that can classify patients based on the local and central biopsy reading. Unsupervised statistical models were used to check for outliers, due to errors in biopsy readings, to improve the models. Especially for the hypothesis no ABMR vs ABMR we have promising results (see figure). All models will be validated in an independent data set of 200 patients.

Conclusion

The generated models can help clinicians to improve patient treatment and long term graft survival.