ACTIVATED NATURAL KILLER CELLS AND ACTIVITY OF ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANTATION: BIOMARGIN CASE-CONTROL STUDY

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While early outcome after kidney transplantation is excellent, late graft failure has not improved sufficiently yet. Acute T-cell mediated rejection (TCMR) has largely been overcome nowadays by powerful immunosuppressive agents. However, antibody-mediated rejection (ABMR) is now recognized as a foremost cause of kidney graft failure, though the best therapeutic target(s) for ABMR still remains largely elusive.

We therefore aimed to further elucidate the principal immune cell subtype in ABMR among the repertoire of graft-infiltrating immune cells, using unbiased innovative microarray transcriptomic analyses in the BIOMARGIN case-control study (n=95) and three external validation datasets of kidney transplant biopsies (n=985). Given the co-occurrence of ABMR and TCMR in a single biopsy, a stringent bioinformatics analytical pipeline was built to discover mRNA markers that were specific for ABMR in BIOMARGIN. Expression analysis demonstrated enrichment of several immune-related pathways in ABMR, in particular NK-cell pathways. Next, we used recently developed deconvolution algorithm to estimate the relative fraction of major leukocytes (22 subtypes) in each biopsy based on RNA transcripts expression. This analysis underscored the prominent role of NK cells and their activation in ABMR in BIOMARGIN dataset, which largely validated in external cohorts. Notably, estimated infiltration of activated NK cells was specifically reflected histological lesions of ABMR disease activity (e.g. microvascular inflammation), but not the risk of ABMR or chronic ABMR (presence of DSA or transplant glomerulopathy, respectively). To correct the estimated leukocyte subtypes proportion to the global inflammation in a biopsy, we adjusted the deconvolution data for the expression of pan-leukocyte marker CD45. Association of CD45-adjusted leukocyte subsets infiltration with biopsies phenotype in BIOMARGIN data showed that activated NK cells are highly specific for ABMR versus no rejection (ROC AUC=0.92), but also discriminates best ABMR from TCMR (ROC AUC =0.77). Finally, immunostaining visualized the presence of activated NK cells in ABMR kidney biopsies. These data implicate the therapeutic potential of targeting NK cells or their activation status to improve the graft outcome after kidney transplantation.