ACTIVATED NATURAL KILLER CELLS PREDICT GRAFT OUTCOME IN KIDNEY TRANSPLANTATION

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Different immune cells have been implicated in the complex pathophysiology of graft failures after kidney transplantation. However, the most promising therapeutic target(s) among immune cells (or their subtypes) in graft outcome and survival has not been yet clearly demonstrated and validated in kidney transplantation. Hence, in current study we aimed to identify which immune cell subtype possesses the highest predictive value for graft failure by analyzing microarray mRNA expression data of kidney transplant biopsies.

We first applied a lately constructed computational deconvolution algorithm to estimate the relative fraction of twenty-two different subsets of immune cells based on the RNA transcripts expression of 547 genes in publicly available GSE21374 dataset. The logistic regression analysis (ROC AUC) of these twenty-two different immune cells subsets estimation showed that among them activated NK cells have the highest discriminative power in predicting graft failure at both 1 and 2 years post-biopsy in category of all biopsies (AUC=0.74). Restricting this analysis to biopsies with rejection (the type of rejection was not provided in GSE21374 dataset), the association between activated NK cell infiltration and graft failure strengthened further to AUC=0.79.

Also, unweighted Cox proportional hazard analysis further confirmed that the single cells most robustly associating with graft failure were activated NK cells, specifically in biopsies with acute rejection. In biopsies without rejection, this association was just significant (p=0.046). We then evaluated individual NK cell transcripts expression in the GSE21374 dataset, according to the association with graft failure. These analyses, both using the differentially expressed genes (DEGs) from the deconvolution algorithm as with the literature-based NK-cell related transcripts set (cytotoxins, activating and inhibitory receptors, and maturation markers), again highlighted the prominent feature of activated NK cell genes in predicting one-year post-biopsy kidney failure. These data underscore targeting NK cells activation as promising efficacious therapeutic strategy to prevent or attenuate graft failure, resulting in improved graft outcome and survival in kidney transplantation.