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Discovering Molecular Signatures in ATMR: Single-cell RNA-sequencing Analysis of Human Blood and Tissue Spatial Transcriptomics

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Objectives : Acute T cell-mediated rejection (ATMR) is one of the most important causes of kidney graft injury and loss, yet in-depth transcriptomic analyses of relevant tissues and circulating immune cells are limited. To address this gap in knowledge, we performed single-cell RNA-sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs), coupled with spatial transcriptomics analysis of graft biopsy specimens, to obtain unprecedented insight into the molecular pathogenesis of ATMR.
Methods : In this study, we conducted single-cell RNA sequencing (scRNA-seq) on PBMCs and GeoMx digital spatial profiling (DSP) on kidney allograft biopsy samples. scRNA-seq study included four patients with biopsy-proven ATMR and two without. For spatial analysis, we compared tissue from two patients diagnosed with ATMR to their zero-time protocol biopsies, and six regions of interest (ROIs) per biopsy section were selected, focusing on the evident T-cell infiltration area in the interstitium and glomeruli.
Results : Integrating two methodologies, we pinpointed $CD8^+$ effector memory T cell expression profiles and key upregulated genes, including LTB, GZMK, PSME2, UBE2L6, and STAT1. Among them, STAT1 was confirmed as the central gene through network and pathway analysis, suggesting its pivotal role in the pathogenesis of rejection. Moreover, immunohistochemistry and immunofluorescence on kidney allograft tissue validated the co-expression of STAT1 with CD8, indicating an active inflammatory response.
Conclusions : Our comprehensive study using spatial transcriptomics and scRNA-seq demonstrated a distinct CD8+ STAT1+ T cell subset with clonal expansion and a memory phenotype, implying that certain transcriptomic changes in ATMR tissues can also be observed in systemic circulation. This correlation suggests that the localized immune response in the kidney during the development of ATMR also influences the systemic immune response, which enables us to find out the potential surrogate markers in the blood for ATMR detection.

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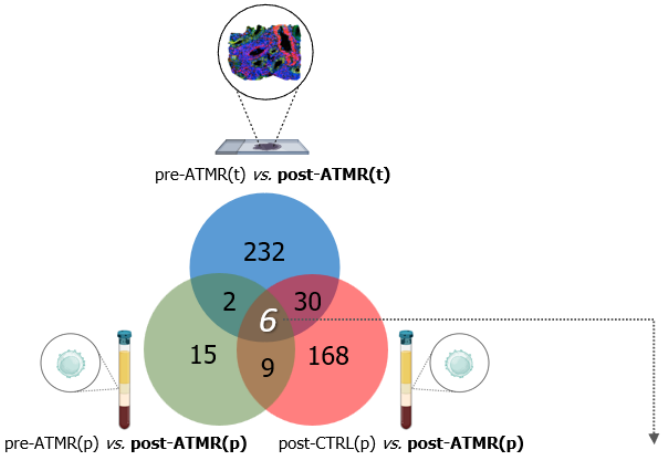

	pre-ATMR(p) *vs.* **post-ATMR(p)**		post-ATRL(p) *vs.* **post-ATMR(p)**		pre-ATMR(t) *vs.* **post-ATMR(t)**	
Gene Name	Avg_log2FC	P value	Avg_log2FC	P value	Log2	P value
LTB	0.719866	8.86E-21	0.7056263	1.27E-17	2.490126847	0.003389082
STAT1	0.513027	6.16E-18	0.617755	9.98E-18	3.016796304	0.01070265
GBP5	0.361742	1.24E-09	0.3181942	3.04E-05	2.475547913	0.037119843
PSME2	0.340883	1.67E-11	0.4650574	1.51E-17	2.09226451	0.000431585
GZMK	0.335638	0.003209	0.6533712	3.48E-10	2.096567011	0.033995338
UBE2L6	0.307778	7.15E-09	0.4056673	4.95E-11	2.141781386	0.001960715

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