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Unveiling the Molecular Signature of Acute T Cell-Mediated Rejection in Human Renal Transplantation: A Comparative Analysis of Pre- and Post-Transplant PBMCs and Transplant Tissues Using Single-Cell RNA Sequencing and Spatial Transcriptomics

Minji Kang[1], Jeongin Song[2], Yunyoung Jang[2], Julia Young Baik[1], Hyun Je Kim[1], Yong Chul Kim[2], Seung Hee Yang[3], Chung-Gyu Park[1]

[1]Department of Biomedical Siences, Seoul National University graduate school, Republic of Korea
[2]Department of Department of Internal Medicine, Seoul National University Hospital, Republic of Korea
[3]Department of Kidney Research Institute, Seoul National University Medical Research Center, Republic of Korea

For decades, kidney transplants have been instrumental in saving the lives of numerous patients afflicted with chronic kidney failure. The advent of immunosuppressants, particularly those targeting T cells such as cyclosporin and tacrolimus, significantly contributed to the widespread adoption of kidney transplantation. Despite the availability of T cell-specific immunosuppressants, approximately 20% of kidney transplant recipients still experience Acute T Cell-Mediated Rejection (ATMR), a phenomenon whose underlying molecular biological mechanism remains poorly understood.

To address this knowledge gap, we undertook a comprehensive study involving single-cell transcriptome analysis and spatial transcriptome analysis. This investigation involved the examination of both peripheral blood and tissue samples from patients who experienced ATMR after renal transplantation (n=2) as well as patients who did not encounter such rejection (n=2).

Herein, we demonstrate significant insights into the molecular characteristics of T cell-mediated rejection in kidney transplantation. Comparing two-week protocol biopsy tissue to zero-time biopsy tissue, we identified 270 up-regulated differentially expressed genes (DEGs) in the interstitium considered as a target site of TCMR. Additionally, we discovered a hyper-expanded cell type in PBMCs, presumed to contain numerous alloreactive T cells, and further explored DEGs within this cell type between the groups. By integrating the results from both single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, we observed specific up-regulation of LTB, GZMK, STAT1, PSME2, UBE2L6, and GBP5 genes in the group of TCMR patients potentially important in

TCMR. Notably, network analysis revealed the connection of STAT1 with the other identified genes, suggesting its potential role in the rejection process. These findings highlight the importance of these genes in understanding and distinguishing the molecular characteristics of T cell-mediated rejection in kidney transplantation. The identified genes may serve as crucial targets for further research and potentially contribute to the development of improved therapeutic strategies for TCMR in kidney transplant patients.