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Discovery of cellular and molecular pathways involved in the development of anti HLA antibody through single cell RNA sequencing in highly sensitized mouse model

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Objectives: Presence of allo-antibody to HLA, so called "sensitization" is an important obstacle for successful kidney transplantation. It is well known that B cell lineage including antibody producing plasma cells have a major role for the induction of sensitization. However, the specific molecular pathway involved in "sensitization" has not been fully investigated yet. In this regard, we proposed to observe the specific pathway involved in the sensitization to HLA using allosensitized mouse model using HLA.A2 transgenic mice.

Methods: Wild-type C57BL/6 mice were sensitized with two times of skin allografts from C57BL/6-Tg (HLA-A2.1)1Enge/J mice. We performed single-cell RNA sequencing analysis using splenocytes isolated from allogenic mice (C57BL/6-Tg (HLA-A2.1)1Enge/J to C57BL/6) and syngenic control (C57BL/6 to C57BL/6) and compared the gene expression in single cell level to characterize the HLA sensitization.

Results: We generated 10,705 and 17,411 single-cell transcriptomes from allogenic and syngenic control mouse, respectively. Five major cell types (B-cells, T-cells, NK cells, macrophages, and neutrophils) and their transcriptome data were annotated according to the representative differentially expressed genes (DEGs) of each cell cluster. The percentage of B-cells and T-cells were significantly increased in allogenic mouse, while that of NK cells, macrophages, and neutrophils were decreased. Hsp90aa1 and genes encoding histocompatibility antigen such as H2-Eb1, H2-Ab1, H2-Aa, H2-Oa, H2-DMa, H2-Ob, H2-Q4 were upregulated in B-cells. In addition, GO and KEGG enrichment analyses indicated that the upregulated genes in B-cells were mainly enriched in antigen processing and presentation pathways.

Conclusions: This study identified the comprehensive profiles of complex immune response after transplantation using single-cell RNA sequencing analysis. The results indicated that overexpressed genes in B-cells after allosensitization were mainly involved in antigen processing and presentation pathways. It may offer detailed understanding of pathogenesis of HLA sensitization after transplantation and may have implications for the identification of potential therapeutic targets for desensitization.