Asian Transplantation Week 2023

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Session Title : Single cell biology in transplantation

Single cell transcriptomics in kidney transplantation

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Title: Single-cell transcriptomics in kidney transplantation Abstract: Kidney transplantation (KT) has made significant strides in one-year survival rates for patients and allografts. However, long-term outcomes have seen limited improvement, particularly beyond five years. This disparity between short- and long-term allograft survival remains poorly understood. Late graft loss is often attributed to chronic allograft dysfunction (CAD), a progressive and irreversible condition diagnosed late in its course. The intricate cellular mechanisms driving CAD in human kidney grafts, including the roles of different cell types, remain unclear, hindering the discovery of therapeutic targets. Over the past 15 years, we conducted a prospective study funded by the NIH, employing protocol biopsies to investigate the distinctive molecular pathways associated with CAD progression in more than 300 kidney transplant recipients over seven years post-transplant. Our analyses revealed that CAD progression was marked by increased inflammation-related genes and decreased metabolic function genes, particularly in proximal tubule cells. Cell enrichment analysis indicated down-regulated genes in distal and proximal tubule cells and up-regulated genes in monocytes and natural killer cells, although further studies are needed for cell type-specific validation. To address the complexity of kidney heterogeneity and immune responses in grafts, we employed single-cell transcriptomics. Single-cell approaches in human kidney allografts remain underexplored, with limited reports available. Comparing grafts to native kidneys has inherent limitations, as it fails to account for immune responses, immunosuppression effects, and cellular adaptations. Furthermore, rare cell types like podocytes may be lost in these analyses. **The lecture includes 3 sections: In Part 1,** we used single nuclei RNA-sequencing to unveil the cellular landscape and transcriptome of normal kidney allografts, offering insights into the impact of the host environment, immunosuppression, and injury on transcriptional profiles. Notably, immune cells were elevated in normal allografts, hinting at subclinical inflammation and repair processes. Part 2 delved into the single-cell landscape of failing kidney grafts with CAD. Our analysis uncovered two fibrosis states with distinct cellular subclusters and immune profiles. Proximal tubular cells transitioned into an injured mixed tubular phenotype, driving fibrosis through ECM deposition and inflammatory cell recruitment. Activated B, T, and plasma cells were increased in the high ECM state, while macrophage subtypes were increased in the low ECM

state. Intercellular communication between parenchymal cells and donor-derived macrophages played a key role in injury propagation, highlighting novel targets for intervention. Part 3 explored operational tolerance (OT) in kidney transplantation, where grafts remain stable without immunosuppression. Single-cell analysis of immune landscapes revealed differences between OT, standard-of-care immunosuppression, and healthy individuals. Enhanced proportions of regulatory B and T cells were associated with OT, suggesting a role in graft acceptance. Ligand-receptor analysis highlighted interactions that enhance regulatory T-cell function. Further investigation into a larger cohort is warranted to confirm these findings. *In summary, our single-cell analyses provide a comprehensive understanding of kidney transplantation, shedding light on normal allografts, CAD progression, and potential pathways to achieve operational tolerance. These insights pave the way for targeted interventions and improved long-term outcomes in kidney transplantation.*