Podocyte injury triggers the formation of intercellular bridges

Nina Cintron Pregosin,¹ and Sandeep K. Mallipattu²

¹Stony Brook University; and ²Stony Brook Medicine

Abstract ID 26483 Poster Board 523

Background: Podocytes are terminally differentiated visceral epithelial cells that are necessary for maintenance of the glomerular filtration barrier. Podocyte loss is characteristic of multiple kidney diseases, including focal segmental glomerulosclerosis (FSGS) and rapidly progressive glomerulonephritis (RPGN) which have a high risk of progression to end-stage kidney disease, requiring dialysis. In these diseases, podocyte loss triggers the activation and proliferation of neighboring parietal epithelial cells (PECs) which reside along the Bowman’s capsule. Aberrant PEC proliferation leads to crescent or pseudo-crescent formation in the Bowman’s space and eventual glomerular injury.

Recent evidence suggests that in the setting of injury podocytes might be capable of physically interacting with neighboring cells by forming cytoplasmic bridges from one cell to another. Similar intercellular bridges were identified in a variety of cell types including neuronal cells, epithelial cells, and immune cells, and have been established to serve as a direct mechanism of cell-cell communication. However, the role of these bridges between podocytes and PECs has not been previously characterized. The goal of this study is to investigate how podocyte-PEC bridges form, what they do, and whether they are pathological or physiological. The long-term impact of this project is to investigate intercellular bridges as potential therapeutic targets for ameliorating podocyte loss.

Methods: We investigated the formation of intercellular bridges in three models of podocyte injury: podocyte-specific loss of Kruppel-like factor 4 (Klf4ΔPod) nephrotoxic serum nephritis (NTS) and diabetic nephropathy. Immunohistochemistry, immunofluorescence staining, and electron microscopy were used to identify intercellular matrix extensions in glomeruli. Single nucleus (sn)RNA-seq was performed on each injury model.

Results: Periodic-acid schiff staining and electron microscopy revealed de novo bridges glomeruli of Klf4ΔPod mice and in mice treated with NTS. Intercellular bridge formation appeared to be correlated with the severity of injury, as few intercellular bridges were observed in mice with diabetic nephropathy. We also observed colocalization of endogenous podocyte markers (synaptopodin, nestin) and markers for activated PECs (CD44), suggesting that intercellular bridges form between podocytes and activated PECs. Enrichment analysis of differentially expressed genes between wild type and Klf4ΔPod mice and NTS treatment showed common upregulated pathways including focal adhesion (ACTN1, COL4a4, COL4a5, BIRC3), axon guidance (ROCK2, MYL12A, MYL21B), and actin cytoskeleton regulation (FGFR2, MYH9, MSN) in the podocyte and PEC clusters.

Conclusions: This is one of the first studies to demonstrate that intercellular bridges extend between injured podocytes and activated PECs.

Support/Funding Information: NIH/NIDDK, Veteran Affairs, Dr. W. Burghardt Turner Fellowship