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Multi-omics analysis revealed extracellular vesicle-mediated crosstalk between endotheliocyte and macrophage in ischemic acute kidney injury

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Objectives : Ischemia-reperfusion injury (IRI)-induced acute kidney injury (AKI) is accompanied by immune cell invasion and inflammation. However, the detailed mechanism of extracellular vesicle (EV)-carried proteins mediating intercellular crosstalk in the IRI microenvironment remains unclear.
Methods : The scRNA-seq was used to delineate intercellular communication between intrinsic and immune cells in kidney tissue of IRI. Mass spectrometry technique was used to detect the proteins in EVs derived from kidney tissue of IRI. Multi-omics analysis traced the cell type of proteins in EV and revealed their mediated intercellular crosstalk. Transmission electron microscopy, nanoparticle tracking analysis, and western blotting were used to characterize EV. Co-culture experiment, cell transfection technique, flow cytometry, RT-qPCR, western blot, and immunohistochemistry were used to evaluate cellular function.
Results : It showed that Fn1+ macrophage, endotheliocyte, and Cd81+ macrophage released the most EV protein molecules involving in IRI-kidney. The EV-mediated crosstalk is most significant between endotheliocyte and immune cell, especially Fn1+ macrophage. Endotheliocyte recruited and activated Fn1+ macrophage mainly through SPP1-CD44, Spp1- (Itgb1+itga4/5), and Spp1-(ItgaV+Itgb5). The recruited Fn1+macrophage amplified the inflammatory response by specific secretion of THBS-1 and MCP-1. In addition, it also found that SPP1 in EV also participated in the interaction between endotheliocyte and other immune cell and injured tubular cell.
Conclusions : These findings established the molecular bases by which kidney-EV mediated endotheliocyte-Fn1+ macrophage crosstalk in early IRI and provide new insights into immune inflammation induced by IRI.