Abstract

Background: Ischemia-reperfusion injury (IRI) stands as a major trigger for primary graft dysfunction (PGD) in lung transplantation (LTx). Especially in LTx from donation after cardiac death (DCD), effective control of IRI following warm ischemia (WIRI) is crucial to prevent PGD. This study aimed to identify the key factors affecting WIRI in LTx from DCD.

Methods: Previously reported RNA-sequencing dataset of lung WIRI was reanalyzed to identify nuclear receptor subfamily 4 group A member 1 (NR4A1) as the immediate early gene for WIRI. Dynamics of NR4A1 expression were verified using a mouse hilar clamp model. To investigate the role of NR4A1 in WIRI, a mouse model of LTx from DCD was established using *Nr4a1* knockout (*Nr4a1*$^{-/-}$) mice.

Results: NR4A1 was located around vascular cells, and its protein levels in the lungs increased rapidly and transiently during WIRI. LT × from *Nr4a1*$^{-/-}$ donors significantly improved pulmonary graft function compared to wild-type donors ($P < 0.001$). Histological analysis showed decreased microvascular endothelial cell death ($P = 0.007$), neutrophil infiltration ($P < 0.001$), and albumin leakage ($P < 0.001$). Evans blue permeability assay demonstrated maintained pulmonary microvascular barrier integrity in grafts from *Nr4a1*$^{-/-}$ donors, correlating with diminished pulmonary edema ($P < 0.001$). However, NR4A1 did not significantly affect the inflammatory response during WIRI, and IRI was not suppressed when a wild-type donor lung was transplanted into the *Nr4a1*$^{-/-}$ recipient.

Conclusions: Donor NR4A1 plays a specialized role in the positive regulation of endothelial cell injury and microvascular hyperpermeability. These findings demonstrate the potential of targeting NR4A1 interventions to alleviate PGD and improve outcomes in LTx from DCD.