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## **Identification of key genes and biological pathways associated with ischemia-reperfusion injury in the human kidney using RNA-seq**

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**Objectives:** Ischemia-reperfusion injury (IRI) is a very complex pathologic process. We aim to identify the key dysregulated genes and canonical pathways in IRI in human kidney tissues using RNA-sequencing (RNA-seq).

**Methods:** Five male patients scheduled for total nephrectomy due to renal cell carcinoma or transitional cell carcinoma were enrolled. The average age of patients was 64.8 years. Kidney functions before surgery were intact (mean creatinine: 0.89 mg/dL, mean estimated glomerular filtration rate: 88.1 mL/min, mean hemoglobin: 14.2 g/dl). Kidney tissues were obtained by gun biopsy pre-hypoxia, after 15 minutes of hypoxia, and after 10 minutes of reperfusion. To identify biological mechanisms affected by IRI at the transcriptomic level, we analyzed steady-state gene expression using RNA-seq. The significantly differentially expressed genes (DEGs) between the groups (pre-ischemia *vs.* ischemia, ischemia *vs.* reperfusion, pre-ischemia *vs.* reperfusion) were identified (adjusted *p-value* < 0.1). DEGs were analyzed to discover the significantly enriched biological pathways during ischemia and reperfusion (*p-value* < 0.05).

**Results:** We identified significantly enriched canonical pathways that may be related to the IRI. DEGs affected by ischemia (pre-ischemia *vs.* ischemia) were related to a well-known hypoxic response such as phosphatidylcholine metabolism, and aryl hydrocarbon receptor, heat shock proteins (HSPs) and JAK/STAT signaling pathway. DEGs affected by reperfusion (ischemia *vs.* reperfusion) were enriched in pathways associated with sphingolipids metabolism, and oxidative stress responses. However, DEGs affected by both ischemia and reperfusion (pre-ischemia *vs.* reperfusion) were significantly enriched in inflammatory response including MAPK signaling pathway and pathway related to signaling and production of cytokines such as IL-1, IL-8, IL-15, and IL-17.

**Conclusions:** We showed that different biological pathways are involved in IRI depending on the damage processes (ischemia only, reperfusion only, or both) in the human kidney. Therefore, we suggest that process-specific pathologic approaches might be needed to effectively prevent severe damage after ischemia-reperfusion.