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Crosstalk between Connexin 32 and mitochondrial apoptosis signaling pathway plays a pivotal role in renal ischemia reperfusion: Induced acute kidney injury

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Aims: Perioperative acute kidney injury (AKI) resulted by renal ischemia reperfusion (IR) is not conducive to the surgical patients' recovery. Our previous study demonstrated that reactive oxygen species (ROS) transmitted by gap junction (GJ) composed of connexin32 (Cx32) contributed to AKI. However, its underlying mechanisms were largely unknown. Thus, the present study focuses on the deeper reasons for AKI aggravation, relative with ROS transmitted by Cx32.

Results: In vivo studies, renal IR caused severe impairment in renal tissues and a mass of ROS generation, which were coincident with activation of NF-κB/p53/PUMA-mediated mitochondrial apoptosis pathways. Cx32 deficience alleviated renal IR-induced AKI, and simultaneously attenuated ROS generation and distribution in renal tissues, which further inhibited NF-κB/p53/PUMA-mediated mitochondrial apoptosis pathways. Similarly, in vitro studies, hypoxia reoxygenation (HR)-induced cellular injury and cell apoptosis in both human kidney tubular epithelial cells (HK-2) and rat kidney tubular epithelial cells (NRK52E) were significantly attenuated by Cx32 inhibitors or Cx32 gene knock-down. More importantly, Cx32 inhibition not only decreased ROS generation and distribution in human or rat kidney tubular epithelial cells, but also inhibited its downstream NF-κB/p53/PUMA-mediated mitochondrial apoptosis pathways activation.

Innovation & Conclusion: This is the first time to elaborate the deep mechanisms of IR-induced renal injuries integrally. Cx32 plays a critical role in IR-induced AKI. GJ composed of Cx32 manipulates ROS generation and distribution between neighboring cells, which alters activation of NF-κB/p53/PUMA-mediated mitochondrial apoptosis pathways. Both inhibiting Cx32 function and scavenging ROS effectively reduce mitochondrial apoptosis and subsequently attenuate AKI, providing effective strategies for kidney protection.

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