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## Molecular mechanisms of ischemic AKI and potential therapies

HT Lee

*Columbia University, United States*

Although significant advances have been made in surgery and anesthesia, acute kidney injury (AKI) results in extremely high mortality and morbidity costing more than 10 billion dollars per year in the US (1). AKI frequently occurs in the critically ill and ~20% of patients experience an episode of AKI during their hospital stay (1). Surgical renal ischemia (e.g., kidney transplantation, partial nephrectomy) and renal hypo-perfusion (e.g., due to cardiogenic shock, aortic surgery or sepsis) are leading causes of clinical AKI (2). Unfortunately, there are no effective methods or drugs to treat or prevent AKI (5-7). Moreover, AKI is frequently associated with other life-threatening complications including multi-organ failure and sepsis and commonly progresses to chronic kidney disease (5, 6, 8). The clinically relevant animal models of renal injury (renal ischemia, hypo-perfusion or sepsis) have been invaluable in elucidating the pathophysiology behind AKI induced remote organ dysfunction as they allow for study designs and control of experimental conditions that are not feasible in the clinical setting.

Although incompletely understood, renal tubular cell necrosis, inflammation and apoptosis are major pathways that contribute to the pathogenesis of ischemic AKI (1, 6, 14). Necrosis and apoptosis primarily occur due to irreversible and intolerable cellular stress caused by ischemia reperfusion injury. We have demonstrated that several G-protein coupled cell surface receptors including A1 adenosine receptors, IL-11 receptors, Sphingosine 1-Phosphate receptors and as well as small heat shock proteins (HSP27) can attenuate renal IR induced necrosis as well as apoptosis in mice and rats (3, 4, 9). Renal IR also results in AKI severe inflammatory insults that occur during reperfusion from free radicals as well as infiltrating pro-inflammatory leukocytes. Inflammation however can occur even with mild cellular stress due to activation of hematopoietic (leukocytes) cells during and after renal ischemia and plays a particularly important role in kidney dysfunction. Sub-lethal injury due to inflammation is frequently amplified and the inflammatory cascade potentiates the cell death pathways of necrosis and apoptosis. Therefore, suppression of inflammation would be an important goal directed therapy in limiting kidney injury after surgery. We have demonstrated that inhalational anesthetics, A2a adenosine receptors as well as modulation of intracellular enzyme peptidylarginine deaminase 4 can attenuate the inflammatory response after renal IR and protect against ischemic AKI (5, 7, 8, 10, 12, 13).

Clinically, it has been difficult to define the causality and pathophysiology behind the interactions between AKI and multi-organ dysfunction. It has become increasingly clear in animal models that AKI secondary to renal ischemia is not an isolated event and that it results in remote organ dysfunction to the heart, lungs, liver, intestines and brain through a pro-inflammatory mechanism that involves neutrophil migration, cytokine expression and increased oxidative stress (9, 10). We demonstrated that ischemic AKI causes rapid dysregulation of Paneth cells located in small intestinal crypts leading to profound upregulation and release of IL-17A resulting in intestinal, hepatic and other organ dysfunction after renal IR. We also demonstrated that genetic deletion of Paneth cells or neutralization of IL-17A was able to block this cascade and protect against ischemic AKI and associated remote intestinal and hepatic injury (11).

Understanding of the mechanisms behind the extra-renal effects of AKI is vital as it may identify therapeutic targets to decrease mortality after AKI. In this session, we will discuss the recent progress in understanding the pathophysiology of AKI, potential therapies for AKI targeting the 3 major pathways of cellular injury that contributes to AKI including necrosis, apoptosis and inflammation. Finally, we will discuss the significance of AKI-induced extra-renal organ dysfunction and potential therapies by modulating small intestinal Paneth cells.

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