THE MECHANISM OF VASCULAR PERMEABILITY IN RENAL ISCHEMIC REPERFUSION INJURY: POTENTIAL ROLE OF ANGIOPOIETIN-1 AND HYALURONAN.

Adis Tasanarong, Sookkasem Khositseth, Supachai Thitiarchakul

Nephrology Unit, Department of Medicine, Faculty of Medicine, Thammasat University Klong Nung, Klong Luang, Pathumtani, Thailand 12121

Background: Renal ischemia reperfusion injury (IRI) is the major cause of acute renal failure. One striking feature of renal IRI is an increase in interstitial fluid, caused by vascular leak. Accompanying interstitial infiltration could reflect increased vascular permeability. Recent studies have shown that angiopoietin-1 (Ang-1) is vascular genesis factor counteract with vascular endothelial growth factor to prevent vascular leakage and inflammation. Hyaluronan (HA) is the high capacity water-binding component of the extracellular matrix and leads to the extravasations of inflammatory cells by interact with CD44.

Methods: We evaluated the effect of IRI in mice and observe the expression of two factors that regulate permeability. We studied renal function, pathological changes, proteins expression (immunohistochemical staining, western blots) and mRNA (real time RT-PCR) in renal IRI at 24 and 48 hr after ischemia was induced by clamping the both renal artery for 30 minutes compare with normal.

Results: At 24 hr post renal IRI, serum BUN/Cr was significantly increase compared with normal mice correlated with pathology exhibit significant severe tubular epithelial cell (TEC) necrosis, peritubular capillary congestion and mild interstitial infiltration and edema. The pathology at 48 hr post renal IRI, showed severe TEC necrosis capable with increased serum BUN/Cr level and increased degree of interstitial infiltration and edema compared with 24 hr post renal IRI. In normal kidney, Ang-1 was strongly present in glomerulus and peritubular capillary, and HA is absent in cortex but present in the medulla and papilla. At 24 and 48 hr post IRI, kidney showed progressive reduced Ang-1 staining but increase HA staining in cortex and medulla, compared to normal. Like a mirror, western blots analysis showed that Ang-1 expression significantly decreased to 75% at 24 hr post IRI and progressive decreased to 65% at 48 hr post IRI compared to normal kidney. By real time RT-PCR, Ang-1 expression significantly decreased 7 fold at 24 hr post IRI and the decreased was sustained at 48 hr post IRI compared to normal kidney.

Conclusion: These results suggest that loss of Ang-1 contributes to increased permeability and inflammation of microcirculation in renal IRI.