심포지엄 X

Importance of Renal Endothelial Cells in Acute Kidney Injury : the Role of Angiopoietin-1

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Acute kidney injury, characterized by rapid decline in glomerularfiltration rate is associated with high morbidity and mortality. Despite new insights into the pathogenesis of acute renal failure, morbidity and mor tality has not declined in decades. Injury to the renal microvasculature may be a major factor in the progression of renal disease, thus protection of endothelial cells in renal vasculature may have a therapeutic role in acute kidney injury.

Endothelial dysfunction is an important pathogenetic mechanism in acute kidney injury in sepsis. Endothelial injury in lipopolysaccharide-induced endotoxemia can be associated with renal hemodynamic changes such as alteration of renal blood flow, vascular resistance, and glomerular filtration rate. Thus, regulation of renal endothelial cell dysfunction may have a beneficial role in preventing acute kidney injury from endotoxemia.

Ischemia followed by reperfusion induces microvascular endothelial cell injury, leading to the loss of functions such as regulation of vascular tone, tissue perfusion, permeability, and inflammation in kidney. Improvement of this endothelial dysfunction could be a good approach to treating ischemia/reperfusion-induced renal injury.

COMP-angiopoietin-1 (COMP-Ang1) is a variant of native angiogenic factor Angiopoietin-1 engineered to have higher activity in phosphorylation of Tie2, angiopoietin-1 receptor. COMP-Ang1, a soluble, stable, and potent factor in Tie binding, has anti-inflammatory and antipermeability functions.

We evaluated the protective effect of COMP-Ang1 in a lipopolysaccharide-induced endotoxemia and an ischemia/reperfusion renal injury model.

COMP-Ang1 prevented the lipopolysaccharide-induced decrease of renal blood flow and mean arterial pressure, and improved the glomerular filtration rate. COMP-Ang1 also mitigated the effects of lipopolysaccharide on renal intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 protein expression, the number of ER-HR3-positive macrophage infiltrating in the kidney, serum nitrate/nitrite levels, renal inducible nitric oxide synthase protein expression, the induction of tubular epithelial reactive oxygen and nitrogen species, and renal microvascular permeability.

COMP-Ang1 preserved renal peritubular capillaries after ischemia/reperfusion injury without recruiting pericytes. Pretreatment with COMP-Ang1 attenuated the increase of blood urea nitrogen and serum creatinine levels after ischemia/reperfusion. In addition, the morphologic examination indicated less tubular injury in mice pretreated with COMP-Ang1 than in those treated with the vehicle. COMP-Ang1 treatment reduced the increase in the number of Gr-1-positive neurtrophils or ER-HR3-positive macrophages infiltrating kidneys, increased phosphorylation of Akt, and preserved renal tissue perfusion flow and microvascular permeability. Furthermore, COMP-Ang1 decreased renal interstitial fibrosis 30 days after the ischemia/reperfusion injury.

In conclusion, COMP-Ang1 can be a possible endothelial cell-targeted therapy for preventing ischemia/reperfusion- or endotoxemia-induced acute kidney injury.