외국 연수회원 발표

Chronic Microvascular Dysfunction Following I/R Injury -the effect of MMP-9 inhibition-

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In ischemic rat kidney models, it has been reported that increased MMP-9 activity was associated with degradation of occludin in endothelial cells and MMP inhibitor ABT-518 attenuatedincrease of microvascular permeability in acute stage of I/R injury. These studies suggest that MMPs have some role in endothelial injury and vascular permeability in acute I/R injury.

It is recently known that the MMP-9 induce the liberation of cleavage fragment of the C-terminal globular non-collagenous (NC1) domain of α-1 chain of type IV collagen into circulation, and the cleaved fragment function as a potent angiogenesis inhibitor, arresten (Kalluri et al, 2005). Arresten could induce apoptosis in cultured endothelial cells (Mier JW et al, 2003). We investigated the role of MMP-9 in the microvascular rarefaction that occurs 4 weeks after I/R injury and the mechanism involved. We found that MMP-9 inhibition preserved cablin stained paratubular capillary basement membrane at 30 days after I/R injury. The protective effect of MMP-9 inhibition on microvascular dropout seemed to occur through the modulation of the balance of the angioregualtory protein expression. We observed that VEGF protein expression decreased in ischemic kidney tissue, and MMP-9 inhibition attenuated thedecrease of VEGF. The angioinhibitory protein, arresten was expressed at the ischemic kidney tissue at 24 h and 2 weeks after I/R injury and this was also reduced by MMP-9 inhibition.

This understanding about the pathophysiology of ischemia-induced microvascular dropout and the preservative role of MMP-9 inhibition would provide the specific therapeutic target to ameliorate the chronic vascular alteration that occurs following AKI and potentially other etiologies of chronic kidney disease.