해외연수발표

# 급성 허혈성 신손상에서 발생하는 선천적 면역반응의 감시자로서의 pericytes

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# Pericytes, as the Innate Immune System Sentinels Following Ischemic Acute Kidney Injury

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Pericytes are perivascular mesenchymal originated cells which are attached to endothelial cells. Surrounding and connected with capillary network and endothelial cells, pericytes are generally involved in the development and stabilization of vascular network. However, recent studies have shown that pericytes are much more than a structural stabilizer.

In the kidney, pericytes are relatively abundant, consisting approximately 2.5 to 5% of kidney cell population. After kidney injury, pericytes detach from endothelial cells and migrate into the interstitial space. Genetic fate mapping studies marking FoxD1 lineage cells have shown evidence that in response to kidney injury, migrated pericytes undergo transition into myofibroblasts. After detachment, endothelial cells become unstable, leading to rarefaction of the kidney. Furthermore, recent study on the pericytes of the skin by Alon et al, have suggested that pericytes may guide the extravasation of leukocytes to the site of tissue injury.

To understand the mechanism of pericytes following kidney injury, innate immune responses following sterile ischemic injury were investigated. Sterile inflammation following kidney ischemic reperfusion injury activates the innate immune system, initiating inflammatory process and eventual myofibroblast activation in the kidney. In previous study (Campanholle et al, PLOS one 2013), we have demonstrated that Toll-like receptor (TLR) -2/-4 and Myd88 signaling required for the activation of proinflammatory cascade were dispensable in the myeloid cell activation in kidney injury, and were rather important in regulating the activation of mesenchymal cells (pericytes). DAMPs prepared from experimental IRI kidney activated TLR/Myd88 signaling in kidney pericytes, and resulted in secretion of proinflammatory cytokines. DAMPs also activated NLRP3 inflammasome in pericytes leading to IL-1β and IL-18 secretion. IL-1β production required Myd88 dependent priming in pericytes. In addition, pericytes responded to released IL-1β, amplifying inflammatory and profibrotic response. In vivo, Myd88 deletion specific to pericytes significantly attenuated tissue injury, fibrogenesis and innate immune activation following ischemia reperfusion injury. Pericytes act as sentinel sensors of tissue injury in the kidney, actively modulating signals through activation of innate receptors, inflammatory and fibrogenic responses via Myd88 dependent mechanism.