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Mitochondrial DNA augments the inflammatory response in acute kidney injury

Haena MOON, Jung-woo SEO, Dong-jin KIM, Seon-hwa PARK, Yu ho LEE, Yang-gyun KIM, Kyung-hwan JEONG, Ju-young MOON, *Sang-ho LEE

division of nephrology, department of internal med, Kyung Hee university school of medicine, Korea, South

Objectives : Pathogenesis of acute kidney injury (AKI) is involved in the activation of systemic inflammation as well as local inflammation. Damage-associated molecular patterns (DAMPs) was suggested as one of possible mediator in the activation of systemic inflammation. However, the role and mechanism of circulating mtDNA, which contains unmethylated CpG DNA and can be released in tissue injury, was not extensively evaluated in the pathogenesis of AKI. This study was aimed to clarify the role of circulating mtDNA on the activation of systemic inflammation, which is common clinical feature of AKI.

Methods : Bilateral ischemia-reperfusion injury (IRI) was induced in C57BL/6 mice. To confirm whether mtDNA activates macrophages, Primary cultured bone marrow-derived macrophages (BMDMs) was stimulated with mtDNA, which was isolated from mouse kidney. Furthermore, using confocal microscopy, migration of circulating mtDNA into macrophage was also assessed.

Results : The circulating mtDNA was significantly elevated at 24 hours after reperfusion comparing to that of control and 6 hours after reperfusion. mtDNA alone did not induce the secretion of pro-inflammatory cytokines in the primary cultured BMDMs. In contrast, mtDNA combination with LPS significantly increased the secretion of IL-6 and TNF-α in the BMDMs, compared to LPS alone. We also observed that the co-localization of mtDNA and TLR9 on endosome as well as the intracellular entry of mtDNA was enhanced in the cells treated with the combination.

Conclusions : Circulating mtDNA was increased in animal model of AKI, and the mtDNA could augment the cytokine release from the activated macrophage through TLR9 activation.

Keywords : Acute kidney injury, mitochondrial DNA, inflammation, damage-associated molecular patterns