KSN 2020
FULLY VIRTUAL MEETING

Abstract Submission No. : IL-9091

Dynamic regulation of APE1/Ref-1 in vascular inflammation

Byeong Hwa Jeon
Chungnam National University School of Medicine, Korea, Republic of

Byeong Hwa Jeon, MD, Ph.D.

Research Institute for Medical Sciences, Department of Physiology, College of Medicine, Chungnam National University, 266 Munhwa-ro, Jung-gu, Daejeon 35015, Korea. E-mail: bhjeon@cnu.ac.kr

Vascular inflammation plays a key role in the pathogenesis of vascular diseases such as atherosclerotic disorders. The vascular inflammatory is a series of complex interactions between inflammatory cells or stimuli and defense cells, such as macrophages and endothelial cells. Among the antioxidative defense mechanisms, apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1), a multifunctional protein that can be secreted from cells, is a key regulatory antioxidant system in cells. APE1/Ref-1 functions as an apurinic/apyrimidinic endonuclease in the DNA base repair pathway. APE1/Ref-1 also regulates the redox activity of several transcription factors such as activator protein-1 (AP-1). The formation of disulfide bonds in APE1/Ref-1 is important in redox activity with cysteine residues C65 and C93 playing key roles in the thiol-mediated redox reactions. A novel function of APE1/Ref-1 in endothelial cells inhibited hypoxia-reoxygenation-induced apoptosis by modulating cytoplasmic rac1-regulated ROS generation and inhibited TNF-α-induced vascular cell adhesion molecule-1 in endothelial cells. Moreover, APE1/Ref-1 inhibits balloon injury-induced neointimal formation in rats, suggesting that it has an anti-inflammatory function in the vascular endothelium. Mitochondrial APE1/Ref-1 contributes to the protective role of protein kinase C-induced mitochondrial dysfunction in endothelial cells. Furthermore, the redox function of APE1/Ref-1 prevents inorganic phosphate-induced calcification of vascular smooth muscle cells by inhibiting oxidative stress and osteoblastic differentiation. Since the concept of APE1/Ref-1 secretion was established, functions of extracellular APE1/Ref-1 with respect to leading anti-inflammatory signaling were focused. Recombinant human APE1/Ref-1 with reducing activity induced a conformational change in TNF-α receptor by the thiol-disulfide exchange as well as inhibition of Toll-like receptor and/or IL-1 receptor signaling. Under endotoxemic conditions, multiple organ failure is caused by uncontrolled inflammatory responses such as cytokine storms or cytokine overproduction. Recently, we demonstrated *in vivo* activity of extracellularly secreted APE1/Ref-1, which exerts inhibitory effects on lipopolysaccharide (LPS)-induced inflammation and has a potential for treating LPS-induced endotoxemia or systemic inflammation such as cytokine storms. Interestingly, the secreted APE1/Ref-1 inhibited the LPS-induced pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, and chemotactic cytokines such as monocyte chemoattractant protein-1, suggesting that the secretory APE1/Ref-1 inhibits LPS-induced cytokine production. Taken together, it suggested that the secreted APE1/Ref-1 could be used as a serological biomarker and/or therapeutic biomolecules against vascular inflammation.