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혈관내피세포에서 산화 스트레스에 의한 monocyte chemoattractant protein-1 발현의 증가

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Hydrogen Peroxide Directly Stimulates Monocyte Chemoattractant Protein-1 (MCP-1) Expression in Vascular Endothelial Cells

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Background: Oxidative stress and the activation of chemokines including MCP-1 are known to be downstream mechanisms responsible for neointimal hyperplasia after creation of hemodialysis vascular access. Currently, however, the precise roles for individual reactive oxygen species (ROS) in mediating MCP-1 gene expression are poorly understood.
Methods: After stimulating the human umbilical vein endothelial cells with H_2O_2, cell viability, MCP-1 mRNA (by quantitative real-time PCR), MAPK activity (by Western blot), and transcription factors activities including NF-κB and AP-1 (by Western blot) were measured. Intracellular ROS production was analyzed by confocal microscopy using 2', 7'-dichlorofluorescin diacetate (DCF-DA). Apocynin and 2-thenoyltrifluoroacetone (TTFA) were used as anti-oxidants.
Results: Cell viability was over 90% when the cells were incubated with low concentration (≤0.5 mM) of H_2O_2 for short (≤4 hr) time, while it was less than 70% with high concentration (1 mM) of H_2O_2 or for long (>8 hr) time. H_2O_2 stimulated MCP-1 mRNA expression in a dose- and time-dependent manner with a peak at 4 hr. Confocal microscopic analysis using DCF-DA showed the anti-oxidants, apocynin or TTFA, abolished H_2O_2-induced intracellular ROS production. When the cells were pre-incubated with anti-oxidants, H_2O_2-induced MCP-1 mRNA expression was significantly inhibited. H_2O_2stimulated phosphorylation of p38 and JNK with a peak at 30 min, respectively. In addition, H_2O_2 stimulated phosphorylation of NFκB subunit, p65, and degradation of IκBα, and also stimulated phosphorylation of AP-1 subunits, c-Jun and c-Fos. When the cells were pre-incubated with SB203580 (P38 inhibitor), SP600 125 (JNK inhibitor), pyrrolidine dithiocarbamate (PDTC, NFκB inhibitor), or curcumin (AP-1 inhibitor), H_2O_2-induced MCP-1 mRNA expression was completely inhibited.
Conclusion: These data suggest that reactive oxygen species directly stimulate MCP-1 expression in vascular endothelial cells through the p38, JNK (cytoplasmic) and NFκB, AP-1 (nuclear) pathways. This study provides a new insight into the potential of anti-oxidants to prevent neointimal hyperplasia in the vascular access.

Key Words: 혈액투석, 산화 스트레스
Hemodialysis, Oxidative stress