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알도스테론에 의한 복막중피세포의 상피-중간엽 이행: NADPH oxidase와 미토콘드리아의 다른 역할

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신현수, 최예진, 김미진, 류은선, 최학선, 강덕희

Aldosterone-induced Epithelial-to-Mesenchymal Transition in Human Peritoneal Mesothelial Cells: Differential Role of NADPH Oxidase and Mitochondrial Function

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Introduction and Aims: Aldosterone (Aldo) is a final product of the activation of renin-angiotensin system, which is increasingly recognized as a player in the development of fibrosis of heart and kidney. Phenotype transition of peritoneal mesothelial cells, especially epithelial-to-mesenchymal transition (EMT) is one of the earliest phenomena of peritoneal fibrosis. The aim of this study was to examine the role of Aldo in EMT of peritoneal mesothelial cells and its potential mechanism involving an activation of local production of reactive oxygen species (ROS), MAPKinase and the receptor of epithelial cell growth factor (EGFR).

Methods: EMT of human peritoneal mesothelial cells (HPMCs) was assessed by the changes in the markers of epithelial and mesenchymal cells by real-time PCR, Western blotting and fluorescein immunocytochemistry. ROS production was examined by DCF-DA and MitoSOX staining. Effects of N-acetylcysteine, NOX inhibitor (diphenyleneiodonium, DPI), mitochondrial ROS blocker (Rotenone), ERK inhibitor (PD 98059), p38 MAPK inhibitor (SB203580), Src inhibitor (PP2), EGFR inhibitor (Erlotinib) and mineralocorticoid receptor (MR) antagonist (spironolactone) on Aldo-induced EMT were investigated.

Result: Aldo induced EMT of HPMC in a dose and time-dependent manner from 24 hours, which was preceded by an enhanced NOX mRNA expression and ROS production in 30 minutes of Aldo stimulation. MitoSOX staining revealed mitochondrial ROS production from 6 hours. Spironolactone, NAC and DPI ameliorated Aldo-induced EMT with an inhibition of the phosphorylation of Src, EGFR and ERK/p38 MAPK. PP2 and erlotinib inhibited EMT and mitochondrial ROS production in HPMC exposed to Aldo. Rotenone also alleviated Aldo-induced EMT, however did not affect the phosphorylation of EGFR and ERK/p38 MAPK.

Conclusion: Our data suggest that Aldo-induced EMT via ROS-dependent Src and EGFR phosphorylation, followed by ERK/p38 MAPK activation via MR-mediated increase in NOX expression in HPMC. Mitochondrial ROS also play a role in Aldo-induced EMT, but not mediated by the activation of Src/EGFR pathway.

Acknowledge: This work is supported by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST) (2010-0019866).

This work was supported by Hi Seoul Science (Humanities) Fellowship funded by Seoul Scholarship Foundation.

Key Words: 알도스테론, 상피-중간엽 이행, 미토콘드리아
Aldosterone, EMT, Mitochondria