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Statin이 복막중피세포의 상피-중간엽이행에 미치는 영향

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The Effect of Statin on Epithelial-Mesenchymal Transition in Peritoneal Mesothelial Cells

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Background: Accumulating evidence has suggested that epithelial-mesenchymal transition (EMT) is involved in renal or peritoneal fibrosis. Among numerous factors leading to EMT, activation of RhoGTPases via mevalonate pathway is reported to play a role in renal EMT. Recently, statins have been highlighted in various aspects due to their pleiotropic actions besides cholesterol-lowering effects. However, it is currently unknown whether statin therapy may inhibit peritoneal dialysis-related EMT.

Methods: In vitro, human peritoneal mesothelial cells (HPMCs) were exposed to media (control), media+simvastatin (1 μM), or 4.25% peritoneal dialysis fluid (PDF, Dianeal®, Baxter Incorporation, Singapore) with or without simvastatin (1 μM). Dose of simvastatin was determined using the MTT assay. Cell morphology was analyzed under an inverted phase-contrast microscope. Protein expression of EMT markers such as E-cadherin and α-smooth muscle actin (α-SMA) and fibronectin in HPMCs were evaluated by Western blot analysis. To explore whether activation of mevalonate pathway is involved inperitoneal EMT, protein expression of RhoGTPases in the membrane and cytosolic fractions was determined by Western blot analysis in HMPCs after 4.25% PDF stimulation.

Results: Compared to control cells, E-cadherin expression was significantly decreased, while α-SMA and fibronectin expression were significantly increased in HPMCs exposed to 4.25% PDF, and these changes were significantly abrogated by simvastatin ($p<0.05$).Similar changes of EMT markers were induced after geranyl-geranyl pyrophosphate (GGPP, 5 μM) treatment. In addition, the cobblestone-like appearance of normal mesothelial cells was converted into a fibroblast-like morphology after stimulation with 4.25% PDF, and this myofibroblast phenotype were reversed by simvastatin.Western blot analysis after separation of membrane and cytosolic fractions revealed that 4.25% PDF increased protein expression of RhoA and Rac1 in the membrane fractions and statin attenuated these changes.

Conclusion: This study demonstrated that peritoneal dialysis-related EMT was mediated through the activation of mevalonate pathway and statin treatment attenuated EMT. Further studies using in vivo model are required to validate our findings.

Key Words: 스타틴, 상피-중간엽이행, 복막중피세포
Statin, EMT, Mesothelial Cells