FMC 연구비

실험적 복막투석 모형에서 스타틴의 상피-중간엽 이행 억제 효과

국민건강보험공단 일산병원[1], 연세대학교 의과대학 BK21[2], 연세대학교 의과대학 내과학교실[3]

장태익[1], 이순하[2], 남보영[2], 강혜영[2], 팽지선[2], 김성훈[2], 오형중[3], 유태현[3], 강신욱[2,3], 한승혁[3]

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

Tae-Ik Chang[1], Soon Ha Lee[2], Bo Young Nam[2], He Young Kang[2], Jisun Paeng[2], Seonghun Kim[2]
Hyung Jung Oh[3], Tae-Hyun Yoo[3], Shin-Wook Kang[2,3], Seung Hyeok Han[3]

NHIC Ilsan Hopital[1]
Brain Korea 21 Project for Medical Science Yonsei University College of Medicine[2]
Yonsei University College of Medicine Department of Internal Medicine[3]

Background: Statins have recently been highlighted due to their pleiotropic actions besides cholesterol-lowering effects. However, it is currently unknown whether statin therapy may inhibit peritoneal dialysis-related epithelial-mesenchymal transition (EMT).

Methods: In vitro, human peritoneal mesothelial cells (HPMCs) were exposed to media (C), media + simvastatin (1 μM), or 4.25% peritoneal dialysis fluid (PDF) with or without simvastatin. In vivo, PD catheters were inserted into 32 Sprague-Dawley rats, and saline (C, n=16) or 4.25% PDF (PD, n=16) was infused for 4 weeks. Eight rats from each group were treated with 5 mg/kg/day of simvastatin intraperitoneally. Protein expression of E-cadherin, α-SMA, Snail, and fibronectin in HPMCs and the peritoneum were evaluated by Western blot analysis. To explore whether activation of mevalonate pathway is involved in peritoneal EMT, protein expression of RhoGTPases in the membrane and cytosolic fractions was determined by Western blot analysis in HMPCs after 4.25% PDF and simvastatin treatment.

Results: Compared to C groups, E-cadherin expression was significantly decreased, while α-SMA and fibronectin expression were increased in HPMCs exposed to 4.25% PDF, and these changes were abrogated by simvastatin ($p< 0.05$). In addition, the cobblestone-like appearance of normal mesothelial cells was converted into a fibroblast-like morphology after 4.25% PDF treatment, which was reversed by simvastatin. This EMT-like change was also observed in HPMCs treated with geranyl-geranyl pyrophosphate (5 μM). 4.25% PDF significantly increased protein expression of RhoA and Rac1 in the membrane fractions, which were decreased by simvastatin ($p<0.05$). In PD rats, E-cadherin/α-SMA ratios in the peritoneum were significantly decreased, whereas fibronectin expression was increased ($p<0.05$) compared to C rats. The thickness of the mesothelial layer and the intensity of Masson's trichrome staining in the peritoneum were also significantly higher in PD rats than in C rats ($p<0.05$). These changes in PD rats were abrogated by simvastatin.

Conclusion: This study demonstrated that PD-related EMT was mediated through the activation of mevalonate pathway and statin treatment attenuated EMT changes in 4.25% PDF-stimulated HPMCs and PD rats.

Key Words: 스타틴, 복막중피세포
Statin, Peritoneal mesothelial cells