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메포민은 산화스트레스를 개선함으로써 복막 중피의 섬유화를 완화한다

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Metformin Attenuated Phenotype Transition and Fibrosis of Peritoneal Mesothelium Via an Amelioration of Oxidative Stress

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Introduction and Aims: Phenotype transition of peritoneum has been regarded as an early mechanism of peritoneal fibrosis. Metformin, 5'-adenosine monophosphate (AMP)-activated protein kinase activator, is a drug widely used to treat type 2 diabetes and also a key player in the regulation of energy hemostasis. Metformin has recently received a new attention due to its therapeutic effect in oncology by inhibiting epithelial-to-mesenchymal transition (EMT). We investigated the effect of metformin on EMT of HPMC and cellular mechanism for this beneficial effect of metformin on peritoneal EMT and fibrosis.

Methods: EMT was evaluated by morphological changes of HPMCs and the expressions of epithelial cell marker, E-cadherin and mesenchymal cell marker, α-smooth muscle actin (α-SMA) after stimulation of TGF-β1 (1 ng/mL) with or without metformin (1 mM) by real time PCR, western blotting and immunocytochemistry. Intracellular reactive oxygen species (ROS) were analyzed by DCF-DA, NADPH activity, NADPH oxidase mRNA expressions, and MitoSoxR staining. Activation of Smad2/3, Erk1/2, p38 MAPK, nuclear translocation of β-catenin and snail expression were assessed by western blotting and immunocytochemistry. Effect of metformin on peritoneal thickening, EMT and an expression of markers of oxidative stress was also investigated in animal model of peritoneal dialysis in 12 Sprague-Dawley rats.

Results: TGF-β1 induced EMT in HPMC was ameliorated by metformin. TGF-β1 significantly increased the ROS generation and NOX activity from 30 minutes, and mitochondrial ROS production from 6 hours. TGF-β1 increased the phosphorylation of smad2/3 and MAPK at 30 minutes and 3 hours, respectively, which was followed by nuclear translocalization of β-catenin and snail up-regulation in HPMC. Metformin ameliorated ROS production, the activation of smad2/3 and MAPK, and snail expression. In animal model of peritoneal dialysis, oral administration of metformin decreased peritoneal thickening and EMT with an increase in ratio of reduced to oxidized glutathione and the expression and activity of superoxide dismutase in peritoneal dialysate whereas it decreased the expression of nitrotyrosine in peritoneum and 8-hydroxy-2'-deoxyguanosine in dialysate in 8 weeks of peritoneal dialysis.

Conclusions: Metformin protected the peritoneum from phenotype transition and fibrosis via an amelioration of oxidative stress.

Key Words: 메포민, 표현형 전이, 섬유화, 산화스트레스
Metformin, Phenotype transition, Fibrosis, Oxidative stress