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복막상피세포에서 TGFβ1에 의해 유도되는 NLRP3 Inflammasome을 통한 상피-중간엽 이행에 Paricalcitol의 효과

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Paricalcitol Attenuates TGFβ1-induced Epithelial-to-mesenchymal Transition (EMT) Via NLRP3 Inflammasome in Human Peritoneal Mesothelial Cells (HPMCs)

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Purpose: EMT is known as a key mechanism of peritoneal fibrosis in patients on peritoneal dialysis. The inflammasome is a multiprotein oligomer that promotes the maturation of proinflammatory cytokine, IL-1β and IL-18. The best characterized inflammasome is the NLRP3 inflammasome, which comprises the NLR protein NLRP3 (NLR family pyrin domain containing 3), the adapter ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) and pro-caspase-1. Paricalcitol, a selective agonist of vitamin D, is known to exert potent anti-fibrotic effect in organ fibrosis, however there are no studies about the role of paricalcitol on peritoneal fibrosis. Here we determine whether activation of the NLRP3 inflammasome is involved in TGFβ1-induced EMT and paricalcitol imposes any effect on peritoneal EMT.

Methods: EMT was evaluated by morphological changes of HPMCs and the expressions of E-cadherin and α-smooth muscle actin (α-SMA). Mechanisms responsible for peritoneal EMT such as generation of reactive oxygen species (ROS), phosphorylation of MAPKinase and NLRP3 inflammasome were investigated by WB and ICC. To investigate the role of NLRP3 inflammasome in EMT, the effect of NLRP3 gene silencing by a treatment of siNLRP3 or caspase inhibitor (Z-VAD-FMK, 10μM) on TGFβ1-induced EMT was examined in HPMCs.

Results: TGFβ1-induced EMT of HPMCs was associated with an up-regulation of NLRP3, ASC and procaspase-1 and an increased production of IL-1β and IL-18. TGFβ1-induced EMT was ameliorated by either siNLRP3 or caspase inhibitor. Paricalcitol also alleviated TGFβ1-induced EMT with a decrease in the expression of NLRP3 inflammasone components and the production of IL-1β and IL-18. TGFβ1 enhanced generation of ROS and phosphorylation of ERK1/2 and p38 MPAKinase. Interestingly, paricalcitol ameliorated TGFβ1-induced ROS generation and phosphorylation of MAPKiase. Anti-oxidants treatment ameliorated TGFβ1-induced activation of NLRP3 inflammasome.

Conclusions: Paricalcitol ameliorated TGFβ1-induced EMT of HPMCs via an oxidative stress-mediated activation of NLRP3 inflammasome. Modulation of NLRP3 inflammasome in peritoneal mesothelial cells could be a novel approach to protect the peritoneum from the development of EMT and peritoneal fibrosis in PD patients.

Key Words: 상피-중간엽 이행
Paricalcitol, EMT, Inflammasome