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Pentoxifylline 調整 TGF-β在人類腹膜表面細胞內之訊息傳遞模式

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Pentoxifylline Modulates Intracellular Signaling of TGF-β in Cultured Human Peritoneal Mesothelial Cells

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Background. Peritoneal matrix accumulation is characteristics of encapsulating peritoneal sclerosis (EPS), which is a serious complication in long-term peritoneal dialysis (PD) patients. We previously (*Kidney Int* 2000, Jun) had reported that TGF-β stimulates expression of type I and III collagen mRNA in cultured HPMC, and was attenuated by pentoxifylline (PTX). However, this inhibitory mechanism remains undetermined. The SMAD family and the mitogen-activated protein kinase (MAPK) (ERK1/2, JNK and $p38^{HOG}$) pathways have been shown to participate in TGF-β signaling. In this study, we investigated the molecular mechanisms involved in the inhibitory effects of PTX on TGF-β induced collagen gene expression in HPMC.

Methods. HPMC was cultured from human omentum by an enzyme digestion method. Expression of collagen α1(I) mRNA was determined by northern blotting. The SMAD proteins and the MAPK kinase activity were determined by Western blotting.

Results. TGF-β stimulated collagen α1(I) mRNA expression of HPMC was inhibited by PTX. The Smad2, ERK1/2 and $p38^{HOG}$ pathways were activated in response to TGF-β. However, TGF-β displayed no activation of the JNK pathway in HPMC. Addition of PD98059 and SB203580, which blocked activation of ERK1/2 and $p38^{HOG}$ MAPK respectively, suppressed TGF-β-induced collagen α1(I) mRNA expression. At concentration (17 μg/ml) that inhibited collagen gene expression, PTX suppressed ERK1/2 and $p38^{HOG}$ MAPK activation by TGF-β. In contrast, PTX had no effect on TGF-β-induced activation of Smad2, under the same concentration.

Conclusion. PTX inhibits TGF-β-induced collagen gene expression in HPMC through modulations of the ERK1/2 and $p38^{HOG}$ MAPK pathways. Our study of PTX may provide therapeutic basis for clinical applications in prevention of EPS.