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Dipyridamole 抑制 PDGF 刺激人類腹膜細胞增生之機轉研究: 對 CKI 蛋白的影響

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Dipyridamole inhibits PDGF-stimulated human peritoneal mesothelial cell proliferation: effects on cyclin kinase inhibitors (CKI)

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Background. Cytokines-stimulated proliferation of human peritoneal mesothelial cells (HPMC) may contribute to the development of encapsulating peritoneal sclerosis (EPS), which is a serious complication in long-term peritoneal dialysis (PD) patients. We previously (*Kidney Int* 2001, Sep) had reported that dipyridamole (DP) inhibited HPMC proliferation by platelet-derived growth factor (PDGF). This inhibitory mechanism of DP may result from cell-cycle arrest of HPMC by DP. Cyclin-kinase inhibitors (CKI) negatively regulate the progression of cell-cycle. Two major classes of CKIs have been identified in mammalian cells: the INK4s ($p16^{INK4a}$, $p15^{INK4b}$, and $p19^{INK4d}$) and those able to inhibit all the CDKs ($p21^{Cip1}$, and $p27^{Kip1}$). While the $p27^{Kip1}$ have been investigated in HPMC, there is no report detailing the expression of the other CKIs in PDGF- and/or DP-treated HPMC. In this project, we will investigate whether the inhibitory effect of DP on PDGF-stimulated HPMC proliferation operated through modulations of these CKIs.

Methods. HPMC was cultured from human omentum. The expression of CKIs in various conditions of HPMC were determined by Western blotting.

Results. PDGF (20 μg/ml) stimulated proliferation of HPMC, which were significantly inhibited by DP in a dose-dependent and time-dependent manner. In PDGF-stimulated HPMC, the expressions of $p16^{INK4a}$ and $p19^{INK4d}$ remained constant until 8^{th} hr after PDGF then decreased. The protein level of $p15^{INK4b}$ remained low in the presence or absence of PDGF; in contrast, there is persistently high protein level of $p21^{Cip1}$ before and after treatment with PDGF. DP, at the dosage that inhibited PDGF-stimulated HPMC proliferation, did not alter the expressions of these CKIs ($p16^{INK4a}$, $p15^{INK4b}$, $p19^{INK4d}$ and $p21^{Cip1}$).

Conclusion. It seems that DP inhibited PDGF-stimulated HPMC proliferation through mechanisms other than modulations of these CKIs ($p16^{INK4a}$, $p15^{INK4b}$, $p19^{INK4d}$ and $p21^{Cip1}$) in HPMC.