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Monocyte Chemoattractant Protein-1 (MCP-1)/CCR2 System is Involved in Epithelial-mesenchymal Transition of Peritoneal Mesothelial Cells

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Background: Monocyte chemoattractant protein-1 (MCP-1) and its receptor, CCR2,have been known to be directly involved in extracellular matrix synthesis in high glucose-stimulated mesangial cells in an autocrine fashion. Since the MCP-1/CCR2 system was present in peritoneal mesothelial cells (PMCs) and MCP-1 production was increased in PMCs under high glucose conditions, we presumed that the MCP-1/CCR2 system may play an important role in the pathogenesis of peritoneal fibrosis (PF).

Purpose: This study was undertaken to investigate the functional role of the MCP-1/CCR2 system in epithelial-mesenchymal transition (EMT) of PMCs and PF

Methods: In vitro,human PMCs (HPMCs) were incubated in M199 media containing 5.6 mM glucose (normal glucose, NG),NG+94.4 mM mannitol (NG+M), NG+recombinant human MCP-1 (10 ng/mL) (NG+MCP-1), or 100 mM glucose (high glucose, HG) with or without dominant negative mutant MCP-1 (mMCP-1) for 72 hours. In vivo, peritoneal catheter was inserted into 40 Sprague-Dawley rats, and saline (control group, n=10) or 4.25% PD solution (PD group, n=30) were infused.In the PD group, 20 rats were treated with empty lentivirus vector or lentivirus vector containing mMCP-1 intraperitoneally, once a week. After 4 weeks, peritoneum was removed for experiments. Western blot analysis was performed to evaluate fibronectin, E-cadherin, and α-smooth muscle actin (α-SMA) protein expression. PF was determined by Masson's trichrome (MT) staining.

Results: Fibronectin and α-SMA protein expression were significantly increased in HPMCs exposed to NG+MCP-1 and HG compared to NG cells, while E-cadherin protein expression was significantly decreased in NG+MCP-1- and HG-stimulated HPMCs ($p<0.05$). These changes in fibronectin, α-SMA, and E-cadherin expression in NG+MCP-1 and HG cells were significantly abrogated by mMCP-1 ($p<0.05$). In rats infused with PD solution, the expression of fibronectin protein and the ratio of α-SMA/E-cadherin protein expression of peritoneum were significantly higher compared to control rats ($p<0.05$). In addition, the thickness of mesothelial cell layer and the intensity of MT staining in the peritoneum of PD rats were significantly increased compared to control rats ($p<0.05$). These changes in PD rats were significantly ameliorated by the treatment with lentivirus containing mMCP-1.

Conclusion: These findings suggest that the MCP-1/CCR2 system is involved in peritoneal EMT and its inhibition may be a potential therapeutic target for PF.

Key Words: Peritoneal mesothelial cells, Epithelial-mesenchymal transition, Peritoneal fibrosis