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MCP-1/CCR2 시스템이 신섬유화에 미치는 직접적 영향

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강혜영, 남보영, 김성훈, 엄재은, 박지민, 오미연, 이미정, 박정탁, 한승혁, 유태현, 강신욱

MCP-1 Directly Induces Renal Tubulointerstitial Fibrosis Independently of Monocytes/Macrophages Infiltration

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Background: Previous studies have demonstrated the importance of monocyte chemoattractant protein-1 (MCP-1) and its receptor, C-C chemokine receptor 2 (CCR2), in the pathogenesis of various inflammatory and fibrotic diseases via the recruitment and activation of monocytes/macrophages. Recently, however, accumulating in vitro evidence has indicated that MCP-1 per se may act directly on renal cells via CCR2. Therefore, the results of a number of former studies showing the impacts of MCP-1/CCR2 blockade on renal injury may be partly attributed to a direct inhibitory effect of MCP-1 on renal cells, but it has never been clarified in vivo to date.

Methods: In vivo, lenti-empty or lenti-MCP-1 virus was injected intravenously in monocytes/macrophages-depleted mice and RS102895, a specific inhibitor of CCR2, was delivered for 4 weeks via subcutaneously-implanted osmotic mini-pumps. At the time of sacrifice, blood and renal tissue were collected for further experiments. In vitro, NRK-52E cells were cultured in DMEM media with or without MCP-1. To examine the direct effect of MCP-1 on extracellular matrix (ECM) synthesis along with the role of CCR2, MCP-1-treated NRK-52E cells were also incubated with or without RS102895 and CCR2 siRNA. The protein expression of fibronectin, type I collagen and CCR2 in cultured NRK-52E cells, and the whole kidney were evaluated by Western blot, and the mRNA expression of fibronectin and type I collagen was assessed by real-time PCR. MCP-1 concentrations in serum and the whole kidney were determined by ELISA. Immunohistochemistry (IHC) for fibronectin, type I collagen and F4/80 and Masson's trichrome staining were examined.

Results: The significant increases in fibronectin and type I collagen protein expression in monocytes/macrophages-depleted mice injected with lenti-MCP-1 virus were significantly ameliorated by CCR2 inhibition using osmotic mini-pumps containing RS102895. In vitro, the protein expression of fibronectin and type I collagen were significantly increased in NRK-52E cells exposed to MCP-1, and these increases were significantly abrogated by RS102895 or CCR2 siRNA.

Conclusion: These findings suggest that the MCP-1/CCR2 system is directly involved in MCP-1-induced renal fibrosis and blockade of the MCP-1/CCR2 system can be a promising approach to treat various kidney diseases such as diabetic nephropathy, of which MCP-1-induced renal fibrosis is involved in the pathogenesis.

Key Words: MCP-1, 신섬유화, 단핵구/대식세포
MCP-1, Renal Fibrosis, Monocytes/Macrophages