

인간 대동맥 내피세포에서 mycophenolic acid가 TNF- α 에
 의한 MCP-1의 발현 증가를 중재하는
 spleen tyrosine kinase의 활성화에 미치는 영향

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The Role of Mycophenolic Acid for Spleen Tyrosine
 Kinase Activation in TNF- α -induced MCP-1
 Upregulation in Cultured Human Aortic Endothelial Cells

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Purpose : Spleen tyrosine kinase (Syk) plays an important role in the inflammation. Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil, is known to have anti-oxidant effect. Reactive oxygen species (ROS) serve as a major mediator of intracellular signaling of pro-inflammatory cytokine including tumor necrosis factor- α (TNF- α). However, the effect of MPA on Syk has not been fully understood. This study was performed to evaluate the role of MPA for Syk in TNF- α -induced monocyte chemoattractant protein-1 (MCP-1) production in cultured human aortic endothelial cells.

Methods : The expression of MCP-1 mRNA and MCP-1 protein were measured by RT-PCR and ELISA, respectively. Intracellular ROS production was measured using 2'7'-dichlorofluorescein diacetate. Activation of AP-1 and NF- κ B were assessed by electrophoretic mobility shift assay (EMSA). Tyrosine phosphorylation of Syk was examined by Western blot analysis.

Results : TNF- α increased MCP-1 at both mRNA and protein levels. TNF- α -induced MCP-1 mRNA expression was inhibited by N-acetylcysteine (NAC), Syk inhibitors (BAY 61-3606, Syk inhibitor 574711), Syk-siRNA and MPA. TNF- α -induced MCP-1 protein production was also inhibited by Syk inhibitors and MPA. TNF- α increased DNA binding activity of AP-1 and NF- κ B, whereas both AP-1 and NF- κ B decoy oligodeoxynucleotides downregulated TNF- α -induced MCP-1 mRNA expression. TNF- α increased ROS generation, which was inhibited by NAC and MPA, but not by Syk inhibitors. TNF- α increased tyrosine phosphorylation of Syk, which was attenuated by NAC and MPA. Syk inhibitors had no effect on TNF- α -induced DNA binding activity of NF- κ B. In contrast, NAC and Syk inhibitors attenuated TNF- α -induced DNA binding activity of AP-1.

Conclusion : TNF- α induced MCP-1 expression via activation of AP-1 and NF- κ B. AP-1 was mediated through ROS, followed by Syk. MPA exerts anti-inflammatory effect by inhibiting MCP-1 expression via suppression of ROS and Syk.

Key Words : MCP-1, Mycophenolic acid, Spleen tyrosine kinase