P-209

STZ로 유도된 당뇨병성 쥐의 대식세포 침투와 신장섬유화에서의 ATF3의 역할

질병관리본부 국립보건연구원 대사영양질환과

김규희, 김원호

ATF3 Plays as a Potent Activator of Macrophage Infiltration and Renal Fibrosis in Streptozotocine-induced Diabetic Rats

Gyu Hee Kim, Won-Ho Kim

National Institute of Health Center for Biomedical Sciences Division of Metabolic Disease

Renal tubulointerstitial fibrosis is considered as the final outcome of progressive chronic kidney diseases and is closely associated with peritubular inflammation; however, the exact molecular mechanisms involved in peritubular inflammation-mediated renal fibrosis are still not elusive. We assessed here the role of ATF3 on streptozotocine-induced diabetic kidney failure and especially, signaling of inflammatory factors and macrophage infiltration during the processing of fibrosis. STZ-injected rats exhibited renal dysfunction, as evidenced by increased volume of renal glomerulus, thickened basement membrane, and increased mesenterium mass. ATF3 and MCP-1 expression was correlatively increased in kidney tissue of STZ-injected rats, which is associated with the activation of macrophage infiltration and ECM accumulation. In NRK-52E cells, TNF-α-induced fibrotic gene expression was potentiated by ATF3, which were attenuated by ATF3 siRNA. Also, ATF3 determined TNF-α-induced activation of NF-κB, which subsequently led to increase the expression of several inflammation-related proteins, such as MCP-1, ICAM-1, VCAM-1. The critical roles of ATF3 on the regulation of NF-κB-dependent MCP-1 expression were confirmed by performing luciferase assay using wild-type or mutated MCP-1 promoter constructs. TNF-α-induced transcriptional activation of MCP-1 and their potentiation by ATF3 were detected only in the cells transfected with pMCP-1-514 (enh), which contains two copy of NF-kB binding sites, but not in pMCP-1-514(enh)mutA or pMCP-1-514(enh)mutB-transfected cells. The macrophage cells cocultured in upper chamber were migrated into the TNF-α treated NRK-52E cells of lower chamber, which were abolished by ATF3 depletion or anti-TNF-α antibody. Here, we know that ATF3 may play as an important regulator of renal fibrosis by enhancing ECM accumulation and macrophage infiltration, and thereby reveals a new aspect of the therapeutic mechanisms involved in DN.

Key Words: 당뇨병신증질환, ATF3, MCP-1
Diabetic nephrophaty, ATF3, MCP-1