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SIRT2 Regulates Lipopolysaccharide-induced Renal Tubular CXCL2 and CCL2 Expression Through Mitogen-activated Protein Kinase Phosphatase-1 and p38/JNK Signaling

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SIRT2, a NAD-dependent histone deacetylase, is involved in genomic instability, carcinogenesis and genomic instability. However, its role in renal inflammatory injury has not yet been demonstrated. In this study, we explored the expression pattern of CXCL2 and CCL2 in kidney tissues from $Sirt2^{-/-}$ and $Sirt2^{+/+}$ mice and in proximal tubular cell lines. We found that CXCL2 and CCL2 were significantly down-regulated at both mRNA and protein levels in kidneys of $Sirt2^{-/-}$ mice compared to those in $Sirt2^{+/+}$ mice after administration of lipopolysaccharide (LPS). Supporting the observation, CXCL2 and CCL2 expression was decreased in MPT cells treated with SIRT2-siRNA compared to control-siRNA. Moreover, overexpression of SIRT2 in MPT cells using adenovirus significantly increased the expression of CXCL2 and CCL2 at mRNA and protein level after treatment with LPS. Renal myeloperoxidase activity, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 levels were decreased in $Sirt2^{-/-}$ mice. In addition, SIRT2-knockdown in MPT cells increased mitogen-activated protein kinase (MAPK) phosphatase-1 acetylation while suppressing MAPK signaling. SIRT2 regulated p65 binding to the promoters of CXCL2 and CCL2. Taken together, these findings indicate that SIRT2 is associated with expression of renal CXCL2 and CCL2 and that regulation of SIRT2 might be an important target for renal inflammatory injury.

Key Words: SIRT2, LPS, 염증
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