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6-bromo-indirubin-3'-oxime (6-BIO) attenuates lipopolysaccharide-induced inflammation and fibrosis through inhibition of Src tyrosine phosphorylation in the human renal proximal tubular epithelial cells.

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Objectives:

The bacterial endotoxin, lipopolysaccharide (LPS) as a potent pro-inflammatory stimulator, is associated with inflammatory responses of acute kidney disease and leading to fibrosis of chronic kidney disease. We investigated whether 6-BIO, a glycogen synthase kinase-3β inhibitor, attenuates inflammation and fibrosis in LPS-induced kidney injury in human proximal tubular (HK2) cells.

Methods: The effects of 6-BIO in LPS-induced cell inflammation and fibrosis were determined using human renal proximal tubular epithelial (HK-2) cells. The effects of LPS and 6-BIO on cell viability were determined using EZ-CyTox assays. The protein and mRNA expression of MCP-1, PAI-1, Collagen I, Collagen IV, CTGF, Src, PI3K/AKT, STAT3, MAPK, and NF-κB was determined by semiquantitative immunoblotting and RT-PCR. Receptor tyrosine kinase and intracellular staining of INF-γ was determined by using flow cytometry and confocal laser microscopy.

Results:

LPS treatment induced increased expression of MCP-1 and INF-γ, as well as PAI-1, Collagen I, Collagen IV, CTGF in HK-2 cells. There was a marked activation of the non-receptor tyrosine kinase, Src, in response to LPS. Furthermore, LPS-treatment induced the activation of AKT, STAT3, p-ERK1/2, p-p38, and p-JNK MAPK pathway as well as NF-κB nuclear transactivation. Inhibition of Src activity using a glycogen synthase kinase-3β inhibitor, 6-BIO significantly attenuated the protein expression of Src tyrosine phosphorylation, AKT, MAP kinase (MAPK), NF-κB activation, and MCP-1 in LPS treated HK-2 cells.

Conclusions:

Treatment of 6-BIO may exert anti-inflammatory and anti-fibrotic effect via controlling JAK/STAT, PI3K/AKT, MAPK, and NF-κB signal pathways through the suppression of Src tyrosine phosphorylation in LPS-treated HK-2 cells.