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Inhibition of p300/CBP-associated factor attenuates renal tubulointerstitial fibrosis through modulation of NF-kB and Nrf2

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Objectives: p300/CBP-associated factor (PCAF), a histone acetyltransferase, is involved in many cellular processes such as differentiation, proliferation, apoptosis and reaction to cell damage by modulating the activities of several genes and proteins through acetylation of either histones or transcription factors. Here, we examined a pathogenic role of PCAF and its potential as a novel therapeutic target in the progression of renal tubulointerstitial fibrosis induced by non-diabetic unilateral ureteral obstruction.

Methods:

Male C57BL/6 mice underwent left ureteral and received intraperitoneal injection of 0.5 mg/day garcinol or vehicle one day for 3 or 7 days after operation.

Results: Administration of garcinol, a PCAF inhibitor, reversed an increase in renal expression of total PCAF and histone 3 lysine 9 acetylation, and reduced positive areas of trichrome and α-smooth muscle actin and collagen content. A decrease in mRNA levels of transforming growth factor-β, matrix metalloproteinase (MMP) 2, MMP9 and fibronectin was followed by garcinol treatment. Furthermore, garcinol suppressed nuclear factor-κB (NF-κB) and pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β and IL-6 whereas it elevated nuclear expression of nuclear factor erythroid-derived 2-like factor 2 (Nrf2) and levels of Nrf2-dependent antioxidants including heme oxygense-1, catalase, superoxide dismutase 1 and NAD(P)H:quinone oxidoreductase-1.

Conclusions:

These results suggest that inhibition of the inordinately enhanced PCAF could mitigate renal fibrosis by redressing the aberrant balance between inflammatory signaling and antioxidant response through modulation of NF-κB and Nrf2.