KSN 2018
Seoul, Korea · May 17 - 20

Abstract Type : Oral
Presentation No. : OR 08 CK-09

Protective effect of DNA methyltrasferase inhibitor against progressive renal tubulointerstitial inflammation and fibrosis

Eun Sil Koh[1], Soojeong Kim[2], Minyoung Kim[1], Seok Joon Shin[4], Cheol Whee Park[3], Ho-Shik Kim[2], Sungjin Chung[5]
[1]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Yeouido St. Mary's Hospital, Korea, Republic of
[2]Department of Biochemistry & Molecular Biology, School of Medicine, The Catholic University of Korea, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Incheon St. Mary's Hospital, Korea, Republic of
[5]Department of Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States

Objectives:

Renal fibrosis is the final common pathway of virtually all progressive kidney diseases and correlates with the aggravation of renal function. However, the contribution of DNA methylation to the process of renal fibrosis is not clarified. The current study examined the impact of DNA methyltransferase (Dnmt) inhibitor on the progression of inflammation and fibrosis in kidneys of mice with unilateral ureteral obstruction (UUO).

Methods: Zebularine (225 mg/kg/day), a Dnmt inhibitor, or vehicle was administred to male C57BL/6 mice intraperitoneally for 3 or 7 days after UUO operation.

Results: Administration of zebularine significantly attenuated renal tubulointerstitial fibrosis and inflammation as assessed by trichrome, α-smooth muscle actin, collagen IV, transforming growth factor-β1 staining both at 3 and 7 days after UUO. This was accompanied by alleviation of mRNA expression level of Dnmt. Zebularine downregulated mRNA expression levels of matric metalloproteinase (MMP) 2, MMP9 and fibronectin, and it also suppressed nuclear factor-κB (NF-κB) and pro-finlammatory cytokines such as tumor necrosis factor-α, interleukin (IL) – 1β and IL-6 in obstructed kidneys. Furthermore, zebularine treatment upregulated the nuclear expression of nuclear factor erythroid-derived 2 like factors 2 (Nrf2) and its subsequent antioxidant downstreams such as heme oxygenase-1, catalase, superoxide dismutase 1 and NAD(P)H: quinone oxidoreduates-1 in UUO kidneys.

Conclusions:

Our findings suggest that Dnmt inhibition could restore the disrupted balance in pro-inflammatory pathway and antioxidant defence mechanism and alleviate renal fibrosis.