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Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

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Low dose colchicine inhibits the NLRP3 inflammasome activation to protect kidney fibrosis

Ga Young Heo[1], Gyuri Kim[2], Ju Yeon Park[2], Jaejin Ryu[2], Bo Young Nam[2], Hyung Woo Kim[1], Jung Tak Park[1], Tae-Hyun Yoo[1], Shin-Wook Kang[1], Seung Hyeok Han[1]
[1]Department of Department of Internal Medicine, Institute of Kidney Disease Research, Yonsei University College of Medicine, Korea, Republic of
[2]Department of Severance Biomedical Science Institute, Yonsei University College of Medicine, Korea, Republic of

Objectives : Chronic kidney disease (CKD) is a progressive disease characterized by renal fibrosis. Recent studies have reported that the NOD-like receptor, pyrin domain containing 3 (NLRP3) inflammasome has emerged as a potential contributor to kidney injury. Colchicine has been shown to suppress NLRP3 inflammasome assembly and the effects of inflammatory cells. However, it remains unknown whether low-dose colchicine can inhibit kidney fibrosis via suppressing the NLRP3 inflammasome pathway.
Methods : In vitro, renal tubular epithelial cells (RTECs) were isolated from C57BL/6 mice. Fibrosis markers and NLRP3 inflammasome were examined in RTECs stimulated with TGF-β (10 ng/ml) for 48h with or without treating with colchicine (0.1, 1 uM). In vivo, mice were divided into 4 groups: control without colchicine, control with colchicine, CKD without colchicine, and CKD with colchicine. CKD model was induced by administering an adenine diet. Colchicine groups were treated with colchicine 0.5mg via osmotic pump and were sacrificed after 3 weeks. Bone marrow-derived macrophages (BMDMs) were isolated. Fibrosis markers and NLRP3 inflammasome were examined in tissue and BMDMs. The oligomerization of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-mediated cross-linking assay was performed in BMDMs.
Results : In vitro, RTECs stimulated with TGF-β increased the expression of fibrotic and cell injury markers and showed activation of the NLRP3 pathway. After treating with colchicine, NLRP3 inflammasome and fibrotic markers were decreased. In vivo, the activation of the NLRP3 inflammasome and kidney fibrosis were increased in the CKD group mice. However, these were significantly decreased in the CKD with colchicine group. Oligomerization of NLRP3 with ASC was significantly increased in BMDMs from the CKD mice model; while significantly decreased by colchicine treatment.
Conclusions : Colchicine attenuated kidney inflammation and fibrosis in a mouse model of adenine-induced kidney injury via inhibiting NLRP3 inflammasome assembly and activation.

Figure1 (1).jpg

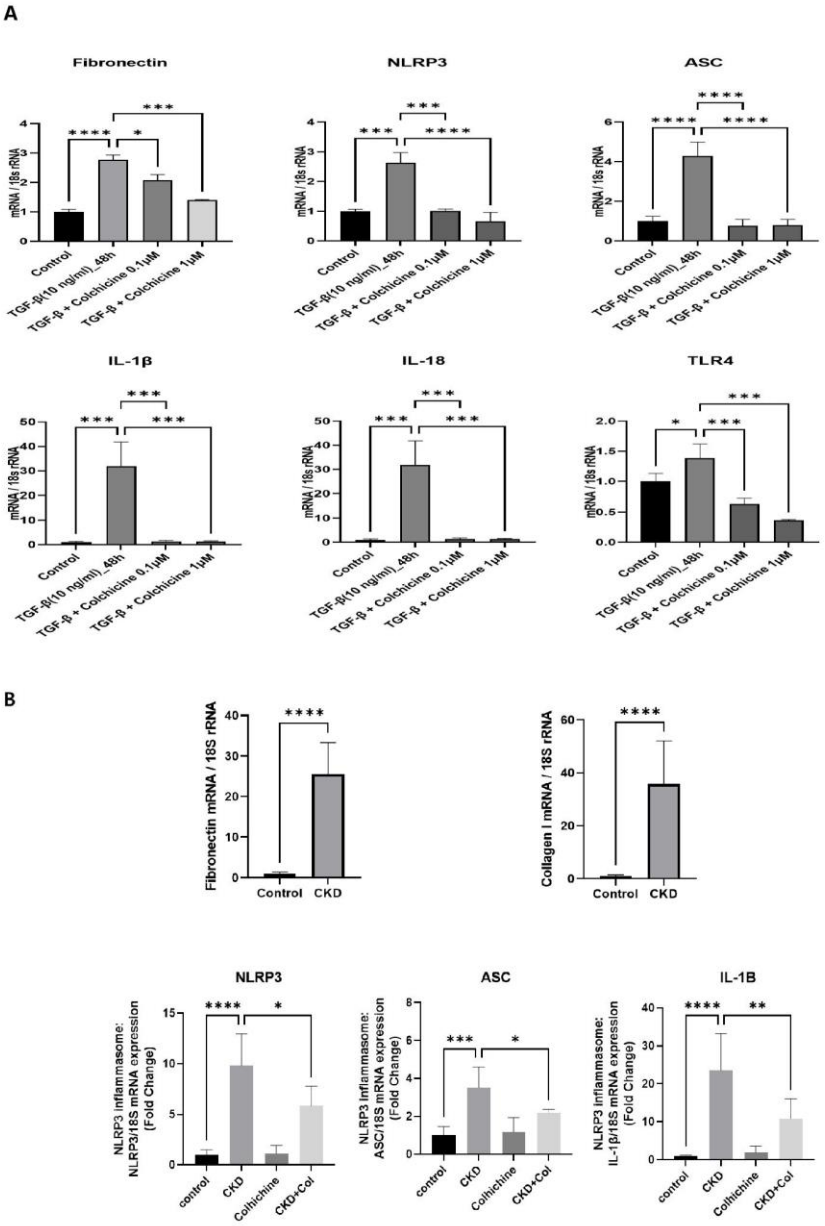
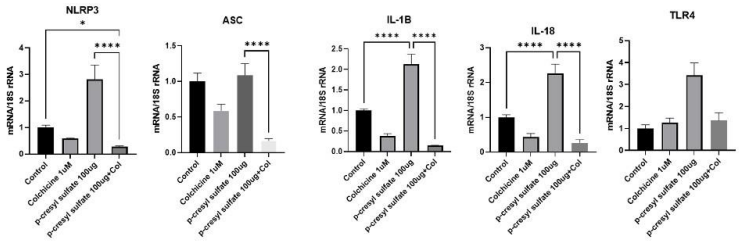
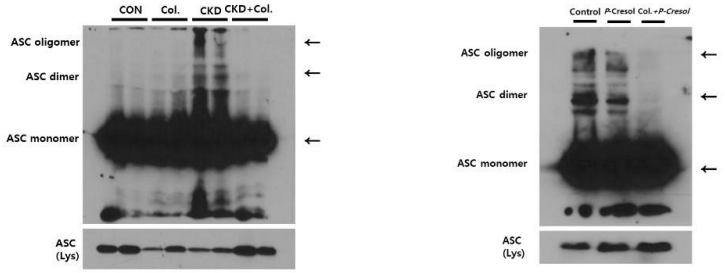


Figure1 (1).jpg

A


NLRP3
ASC
IL-1B
IL-18
TLR4
mRNA/18S rRNA
Control
Colchicine 1uM
p-cresyl sulfate 100ug
p-cresyl sulfate 100ug+Col

B


CON
Col.
CKD
CKD+Col.
ASC oligomer
ASC dimer
ASC monomer
ASC (Lys)
Control
P-Cresol
Col.+P-Cresol