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Colchicine attenuates kidney injury via modulating on the NLRP3 inflammasome pathway

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Objectives : Chronic kidney disease (CKD) is a progressive loss of kidney function driven by inflammation and fibrosis, ultimately leading to kidney failure. Chronic inflammation plays a crucial role in CKD progression. Colchicine, a well-known anti-inflammatory drug, has emerged as a therapeutic option in various inflammatory diseases. However, its role in CKD remains unclear.

Methods : A CKD animal model was established in C57BL/6 mice by feeding a 2% adenine-containing diet. Colchicine (0.3 mg/kg/day) or saline was administered intraperitoneally for 4 weeks. RNA sequencing of kidney tissue was performed to capture molecular signatures associated with the therapeutic mechanism of colchicine in CKD. In vitro, renal tubular epithelial cells (RTECs) were treated with TGF- β and bone marrow-derived macrophages (BMDMs) were exposed to p-cresol sulfate. Colchicine was administered to evaluate its protective effects. Fibrosis markers and NLRP3 inflammasome pathway were examined in kidney tissue, RTECs and BMDMs.

Results : Adenine-fed CKD mice exhibited systemic inflammation, as evidenced by increased circulating levels of inflammatory cytokines including TNF- α , IL-6 and IL-1 β . Colchicine treatment significantly reduced these inflammatory markers. In the kidney tissues of adenine-fed mice, prominent fibrotic change and macrophage infiltration were observed, both of which were significantly attenuated by colchicine treatment. These improvements were accompanied by reduced albuminuria and improved kidney function. RNA sequencing revealed that colchicine modulated key inflammatory pathways, including the NF- κ B, cytokine-cytokine receptor interaction and NOD-like receptor signaling pathway. Notably, colchicine treatment significantly decreased the expression levels of NLRP-3 inflammasome pathway components in adenine-fed mice, TGF- β -treated RTECs and PCS-treated BMDMs. Mechanistically, colchicine directly inhibited the interaction between NLRP3 and ASC in TGF- β -treated RTECs and PCS-treated BMDMs, resulting in decreased NLRP inflammasome assembly, as demonstrated by oligomerization cross-linking assay and proximity ligation assay.

Conclusions : This study demonstrated that colchicine can attenuate kidney injury and fibrosis in adenine-induced CKD mice via inhibiting NLRP3 inflammasome assembly and activation.

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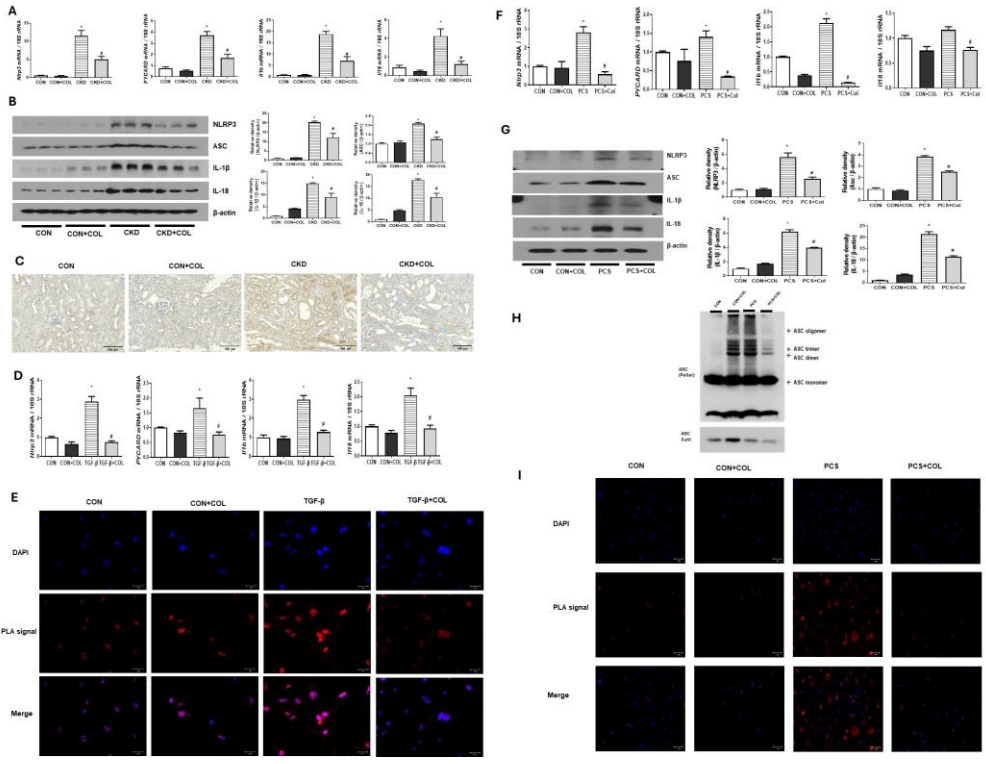


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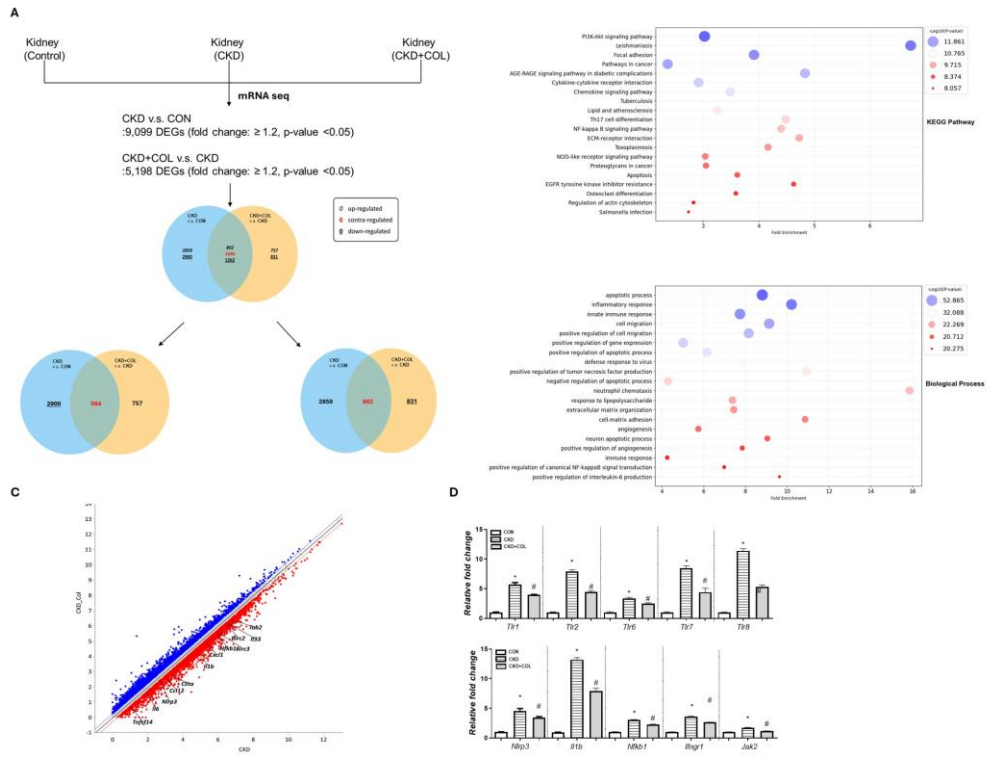


Figure 2 provides a detailed bioinformatics analysis of the mRNA-seq data. Panel A illustrates the overlap of differentially expressed genes (DEGs) between CKD vs. CON (9,099 DEGs) and CKD+COL vs. CKD (5,198 DEGs). Panels B and C show the enrichment of these DEGs in KEGG pathways and Biological Processes, respectively. Panel D presents bar graphs of the relative fold change for selected genes, including Tfr1, Tfr2, Tfr6, Tfr7, Tfr9, Nlrp3, Il1b, Nlrp1, Il1r1, and Jak2, comparing CON, CKD, and CKD+COL groups.