Paeoniflorin-6'-O-benzene sulfonate inhibits macrophage pyroptosis via TLR4/ NLRP3/ GSDMD signaling pathway in adjuvant arthritis rats

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Abstract

Abstract Purpose. To investigate the mechanisms of macrophage pyroptosis mediated by TLR4/NLRP3/GSDMD signaling pathway in adjuvant arthritis (AA) rats and the role of Paeoniflorin-6'-O-benzene sulfonate (CP-25). Experimental Approach. AA model was induced in Wistar rats via complete Freund's adjuvant. Normal group, AA model group, CP-25 (50 mg/kg) group and MTX (0.5 mg/kg) group were included in this experiment. The co-expression of TLR4 and NLRP3 and membrane expression of GSDMD and NLRP3 in macrophages were detected by immunofluorescence assay. The expression of TLR4, the ratio of macrophage pyroptosis and M1/2-type macrophages were detected by Flow Cytomery. Cell morphology was observed by scanning electron microscopy. The levels of IL-18 and IL-1β cytokines in plasma and supernatant of cultured macrophage were detected by ELISA. The expression of TLR4, MyD88, NLRP3, Caspase-1, ASC and GSDMD in macrophages was detected by Western Blot. Key Results. Macrophage pyroptosis was found in AA rats; CP-25 has a therapeutical effect on AA rats by improving the joint inflammation and reducing the pathological process of the joints of AA rats; CP-25 can inhibit the pyroptosis of macrophages by down-regulate the expression of TLR4, MyD88, NLRP3, Caspase-1, ASC and GSDMD of macrophages in vivo; CP-25 inhibits LPS and ATP-induced macrophages pyroptosis by inhibiting the activation of TLR4/NLRP3/GSDMD signaling pathway in vitro. Conclusion and Implications. Macrophage pyroptosis was mediated through TLR4/NLRP3/GSDMD signaling pathway, and CP-25 can regulate macrophage pyroptosis by inhibiting TLR4/NLRP3/GSDMD signaling pathway, thereby improving synovitis in AA rats.

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