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Anti-inflammatory effects of Platycodin D on dextran sulfate sodium (DSS) induced colitis and E. coli Lipopolysaccharide (LPS) induced inflammation

Ruiqi Guo [a], Qingyu Meng [a], Baisen Wang [a], Fan Li [a,b,c,d,e,*]

[a] Department of Pathogenobiology, The Key Laboratory of Zoonosis, Chinese Ministry of Education, College of Basic Medicine, Jilin University, Changchun, China
[b] The Key Laboratory for Bionics Engineering, Ministry of Education, Jilin University, China, Changchun, China
[c] Engineering Research Center for Medical Biomaterials of Jilin Province, Jilin University, Changchun, China
[d] Key Laboratory for Health Biomedical Materials of Jilin Province, Jilin University, Changchun, China
[e] State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Xinjiang, China

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ABSTRACT

Platycodin D (PLD) is a saponin found in *Platycodon grandiflorum*, which has been reported to have anti-inflammatory effects. However, the effects of PLD on ulcerative colitis (UC) remain unknown. In this study, PLD showed the potential to reduce inflammation, ameliorate intestinal damage, and maintain intestinal integrity in DSS-induced colitis. However, the beneficial effect of PLD was reduced when macrophages were depleted, indicating the key role of macrophages in the beneficial effect of PLD in DSS-induced colitis. Meanwhile, we found that PLD inhibited the expression of M1 markers and promoted the expression of M2 markers in colon. Similarly, we found PLD significantly attenuated the levels of pro-inflammatory cytokines, increased the level of anti-inflammatory cytokine and altered macrophage proportions in LPS-stimulated RAW 264.7 cells *in vitro*. Moreover, treating LPS-stimulated RAW 264.7 cells with PLD increased the activation of the PI3K/Akt signaling pathway and decreased activation of NF-κB pathway. Furthermore, we found that the anti-inflammatory and macrophage polarization regulatory effects of PLD was Adenosine 5′-monophosphate-activated protein kinase (AMPK)-dependent. These results indicate that PLD attenuates DSS-induced colitis and LPS-induced inflammation, and the mechanism behind the phenomenon may be regulating macrophage polarization via activation of AMPK. Our study provides a theoretical basis for PLD to be used as a potential treatment of colitis.

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic non-specific intestinal inflammatory diseases of unknown origin, including ulcerative colitis (UC) and Crohn's disease (CD), which has emerged as a global challenge [1]. However, the pathogenesis and pathophysiology of IBD are not completely clear at present. IBD may be caused by abnormal immune responses in intestinal mucosa, intestinal microbiota, intestinal mucosal barrier damage, genetic susceptibility and environmental factors [2,3]. UC is an autoimmune-related inflammatory bowel disease of unknown origin that occurs in the rectum and colon. The therapy strategies used to treat UC include 5-aminosaliculic acid drugs, corticosteroids and immunosuppressants. However, due to differential patient responses, adverse reactions, complications, or the high cost of these treatments, there is an urgent need to develop new drugs and therapeutic strategies [4,5].

Macrophages are crucial for innate immunity, immune homeostasis, and tissue repair [6–8]. Macrophage polarization occurs when macrophages are activated by signals including different cytokines, microbial product or other biomolecules in tissue microenvironment. Activated

Abbreviations: PLD, Platycodin D; DSS, Dextran sulfate sodium; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; LPS, Lipopolysaccharide; DAI, Disease activity index; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; TNF-α, Tumor necrosis factor alpha; IL-6, Interleukin 6; IL-1β, Interleukin 1β; IL-10, Interleukin 10; TJP1, Tight junction protein 1; OCLN, Occludin; iNOS, Inducible nitric oxide synthase; Arg1, Arginase; CCK8, Cell Counting Kit-8; PBS, phosphate-buffered saline; TBST, Tris Buffered saline Tween; Clod-lipo, Clodronate Liposomes; PBS-lipo, PBS Liposomes; ELISA, Enzyme-linked immunosorbent assay; RT-PCR, Reverse transcription and real-time PCR.

* Corresponding author.
E-mail addresses: guorq18@mails.jlu.edu.cn (R. Guo), qymeng20@mails.jlu.edu.cn (Q. Meng), wangbs18@mails.jlu.edu.cn (B. Wang), lifan1965@163.com, lifan@jlu.edu.cn (F. Li).

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