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A characterization of pro-inflammatory cytokines in dextran sulfate sodium-induced chronic relapsing colitis mice model

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ABSTRACT

Repeated cycles of dextran sulfate sodium (DSS) administration in mice, inducing chronic relapsing colitis, have been used to mimic human ulcerative colitis (UC). However, no systematic characterization of pro-inflammatory cytokines in these DSS mice has been reported. In this study, the development of colitis was examined by assessment of the disease severity and inflammation in the colon of C57BL/6 mice that received DSS. ELISA was used to analyze the levels of pro-inflammatory cytokines in serum, colon, spleen and supernatant of cultured splenocytes. mRNA levels of the above cytokines in colon and mesenteric lymph node (MLN) were measured with RT-PCR. The mice receiving three cycles of 2% DSS over a 43-day period showed a fluctuating appearance of diarrhea and bloody feces, and a significant reduction in body weight and colon length. When compared with normal control mice, an increase in TNF-α level in serum was detected in the DSS mice, along with a decrease in the amounts of TNF-α, IL-17, IL-1β and IL-6 in the colonic tissue. However, mRNA levels of these cytokines were found to be significantly increased in the colon while decreased in the MLN of the colitis mice. Further, the ELISA assay suggested a pronounced increase of TNF-α production by cultured splenocytes with PMA/ionomycin re-stimulation but no increase in its presence in spleen tissue upon DSS challenge. In conclusion, we have systematically demonstrated the dysregulation of pro-inflammatory cytokines in the DSS-induced chronic relapsing colitis model, which will provide markers to test emerging therapeutic strategies by this model.

1. Introduction

Ulcerative colitis (UC) is one form of inflammatory bowel disease (IBD), which is a chronic inflammatory disorder of the colon with unknown mechanisms [1]. Both understanding of the pathogenesis of UC and treatment options have dramatically increased in recent years through the use of experimental models [2]. Currently, most of these UC models are based on chemical administration, immune cell transfer, gene knockout (KO), or IL-17 or HLA B27 transgenic animals among others [3,4]. Due to a rapid onset of inflammation, technical simplicity, and no artificial genetic deletions or manipulations that are usually not found in humans, chemically induced models are the most commonly used [5–8].

Dextran sodium sulfate (DSS) is a chemical that is widely used to induce colitis. Its use was first reported in 1990 by Okayasu and colleagues [9]. They described a model in which mice orally receiving three to five cycles of DSS developed chronic colitis with decreases in body weight and colon length [9,10]. This chronic relapsing DSS colitis model is simple and affords a high degree of uniformity and reproducibility of most lesions in the distal colon. This DSS animal model has been used to investigate pathophysiological mechanisms and is a valuable tool to test emerging therapeutic strategies in the preclinical phase [11–14].

Herein we perform the first comprehensive analysis of a broad spectrum of cytokines from three cycles of a 2% DSS induced-chronic relapsing colitis model in mice. This study defines a cytokine profile in the perpetuation of disease pathogenesis, demonstrating the utility of cytokine profiling as a quantitative measure of disease severity in the chronic relapsing colitis model. These changes in cytokine production can be used to assess therapeutic strategies in preclinical studies for UC.

Abbreviations: CD, Crohn's disease; DAI, disease activity index; DSS, dextran sodium sulfate; ELISA, enzyme-linked immunosorbent assay; FBS, fetal bovine serum; H&E, hematoxylin & eosin; IBD, inflammatory bowel disease; IL, interleukin; PMA, phorbol 12-myristate 13-acetate; RT-qPCR, quantitative real-time reverse-transcription polymerase chain reaction; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis

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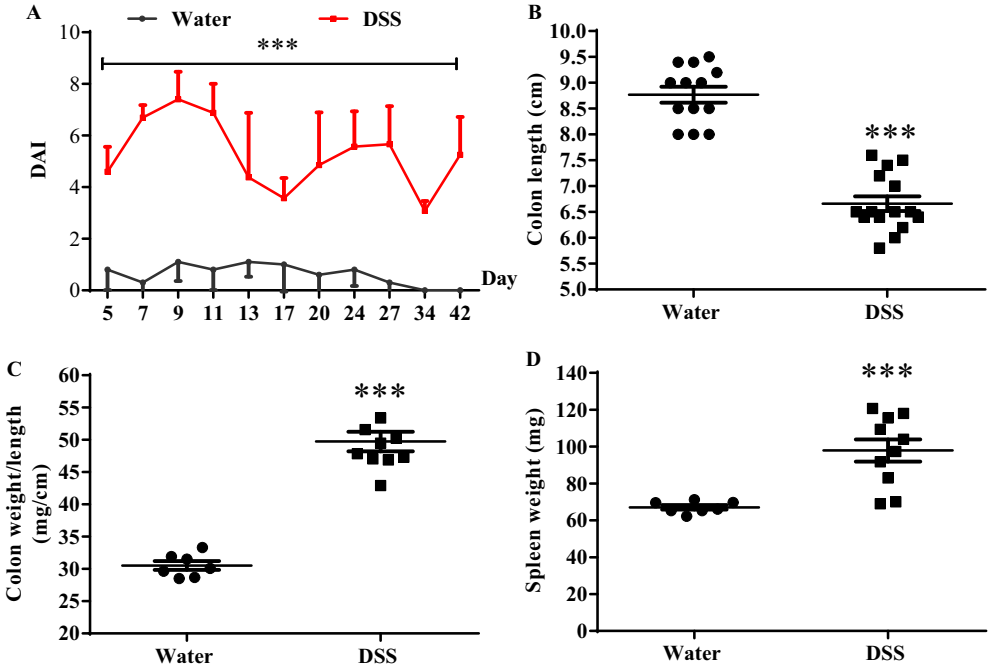

Fig. 1. Clinical severity of mice with dextran sulfate sodium (DSS)-induced chronic colitis. Clinical disease scores were measured (A). The length of colon (B) was recorded and weight of colon and spleen (C and D) were measured when mice were euthanized. $^{*}P < 0.05$, $^{***}P < 0.001$ compared with water group; $n = 13$ and 15 mice in water and DSS group respectively.

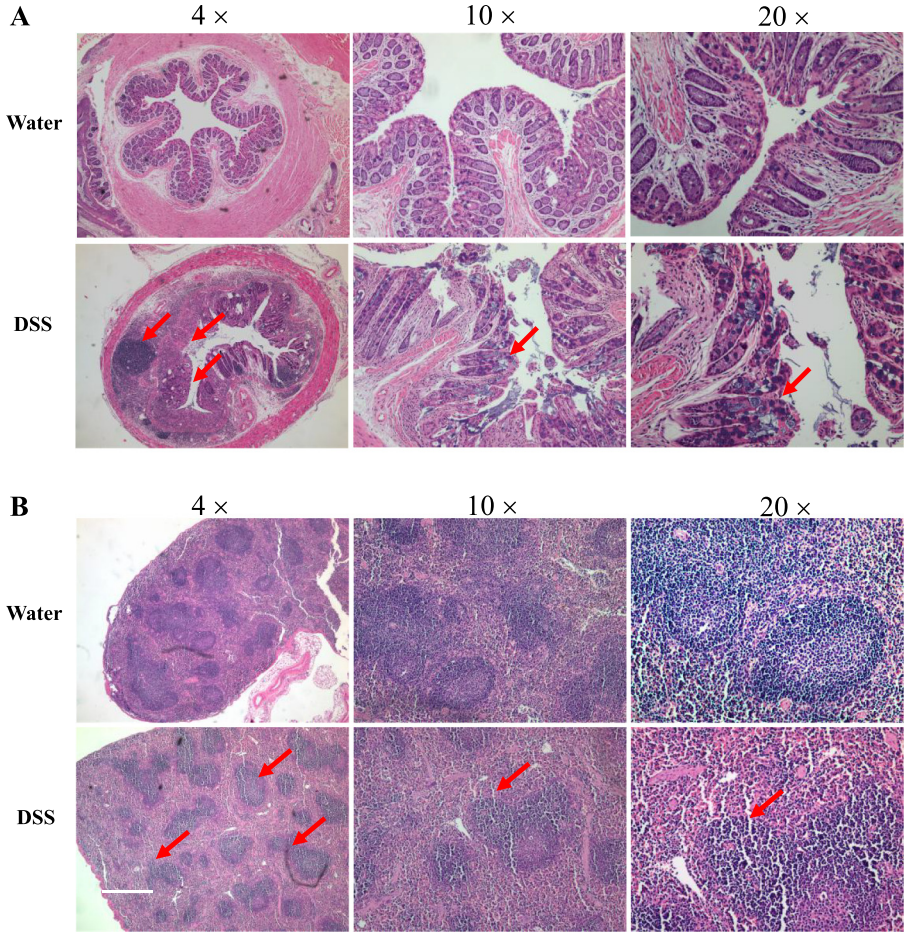

Fig. 2. Histological changes of colon and spleen of mice with dextran sulfate sodium (DSS)-induced chronic colitis. Paraffin-embedded colon (A) and spleen (B) sections were stained with H&E for light microscopic assessment. The marked epithelial destruction and intense inflammatory infiltration in colon and moderate white pulp hyperplasia in spleen are indicated by arrows in red. $n = 6$ mice in each group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)