Suppression of the expression of ubiquitin ligase RNF183 ameliorates dextran sodium sulfate-induced colitis

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Background: Ubiquitin ligase (E3) is the most critical enzyme in the ubiquitination machinery for forming polyubiquitin chains as it participates in the regulation of substrate preference and degradation rate. We previously identified 37 RING-finger-type ubiquitin ligases containing transmembrane domain. We further investigated the tissue distribution of these 37 ubiquitin ligases; consequently, we identified the novel kidney-specific ubiquitin ligase RNF183. It has recently been reported that RNF183 expression is upregulated in intestinal epithelial cells in inflammatory bowel disease (IBD) patients and in trinitrobenzene sulfonic acid-induced colitis mice. The study suggested that RNF183 promotes intestinal inflammation via NF- κ B pathway activation. However, the physiological significance of inhibiting RNF183 expression has not yet been explored.

Methods: The RNF183 expression level in colitis mice exposed to 2% and 3.5% dextran sulfate sodium (DSS) for 1, 3, and 5 days by quantitative PCR. The level of inflammation was evaluated by quantitative PCR in terms of changes in inflammatory marker levels and by hematoxylin-eosin staining. The level of inflammation between wild-type (WT) and RNF183 knockout (KO) mice exposed to DSS was compared.

Results: Significant reduction in body weight and shortening in colon length were observed in DSS-treated mice at 5 days after exposure. RNF183 mRNA levels were significantly upregulated in DSS-induced colitis mice at 1 and 3 days after exposure and were most highly upregulated at 5 days. Although the levels of inflammatory markers, such as IL-1 β and TNF- α , also significantly increased at 5 days after exposure, their levels were not significantly changed at 1 day after exposure. From this, we speculate that RNF183 was not upregulated as a downstream target of the inflammatory response. In contrast, RNF183 KO mice with DSS-induced colitis exhibited less inflammatory response than WT mice as the colon length was longer, inflammatory cell infiltration was attenuated, and the inflammatory marker levels were lower.

Conclusions: Taken together, our findings suggest that RNF183 plays important roles in the onset and/or exacerbation of DSS-induced colitis. Therefore, we propose that IBD can be prevented by inhibiting RNF183 expression or activity.