Sphingosine-1-phosphate receptor type 4 (S1PR4) deficiency differentially affects acute and chronic intestinal inflammation in a murine colitis model

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Introduction

Immunological, genetic and environmental factors contribute to the development of chronic inflammatory bowel diseases (IBD). The common pathophysiological pathway of IBD appears to be an impaired tolerance of the immune system to epitopes of commensal or pathogenic components of the intestinal flora or food components. Only recently, various B cell populations have been shown to be involved in the regulation of IBD development. We have recently shown that S1PR4 mediated signalling impacts peritoneal B cell migration and the development of B cell follicules in a murine knock-out model. In this study, we investigate the role of S1PR4 in the development of acute and chronic intestinal inflammation.

Methods

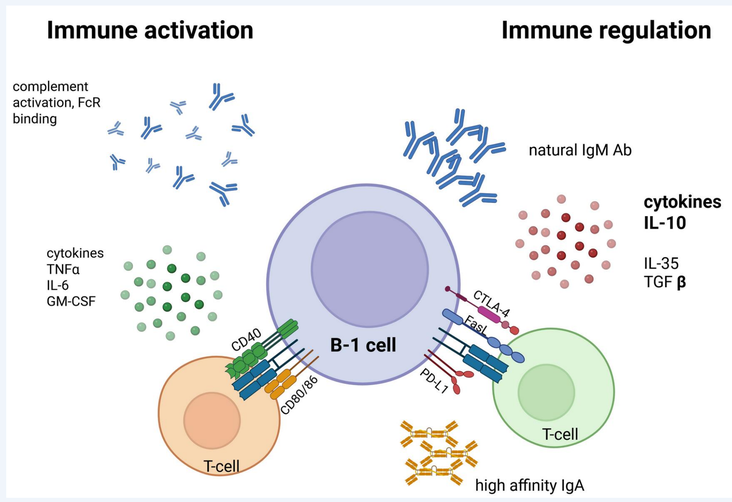

Figure 1: Functional overview of peritoneal B-1 cells in immun activation and immun regulation. Modified from Suchanek and Clatworthy, Frontiers in Immunology (2023) under Creative Commons license.

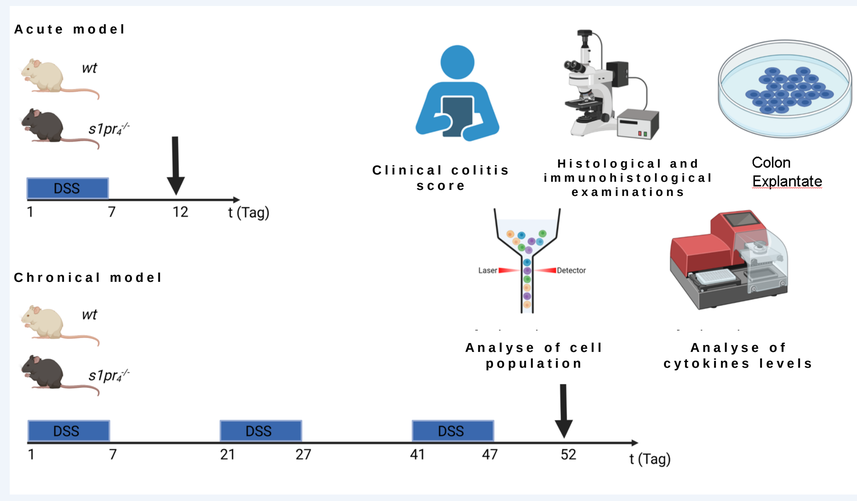

Figure 2: Schematic overview of our experimental setting. Acute and chronical colitis was chemically induced in *s1pr*$_4^{-/-}$ and *wildtype* (wt) *C57Black/6* mice by oral DSS administration. Created with BioRender.

Results

Clinical disease activity and intestinal weight-length Index

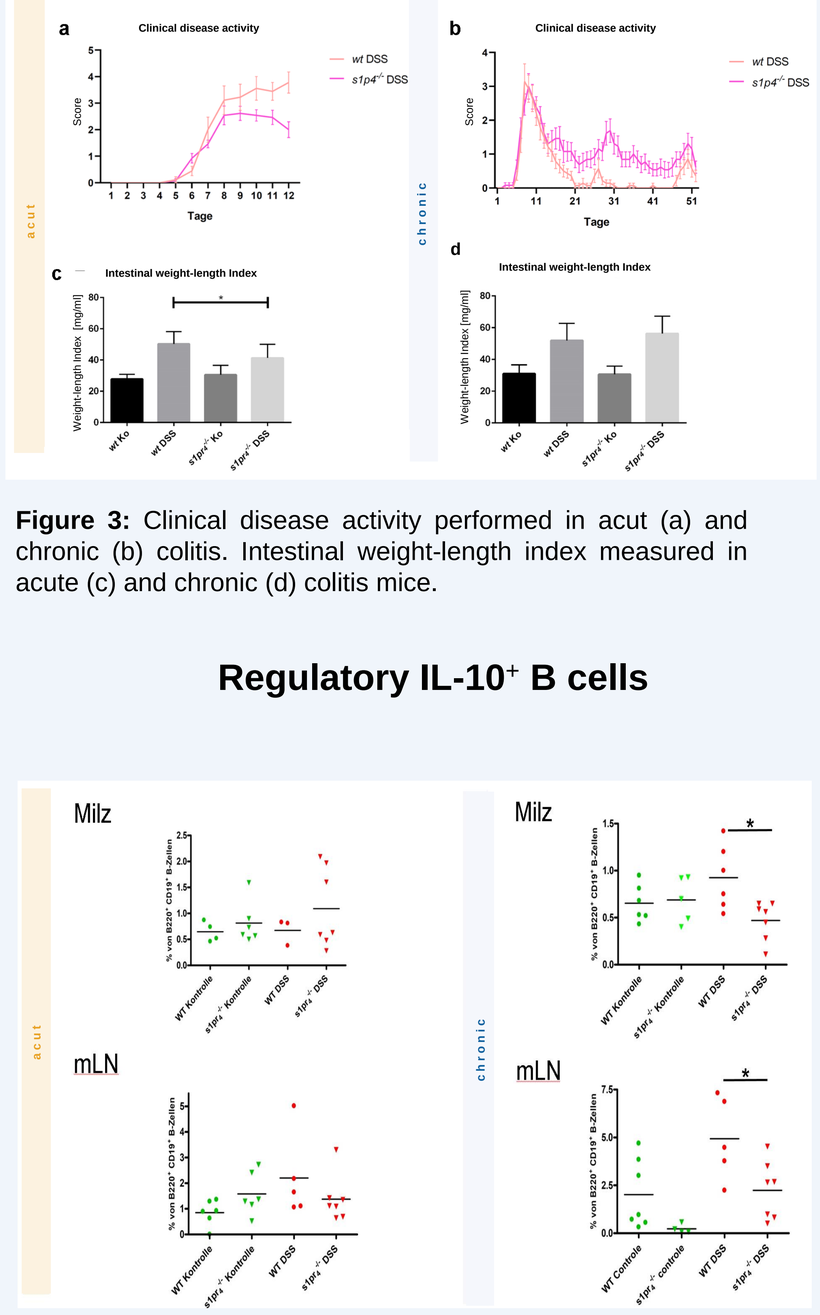

Figure 3: Clinical disease activity performed in acut (a) and chronic (b) colitis. Intestinal weight-length index measured in acute (c) and chronic (d) colitis mice.

Histopathology

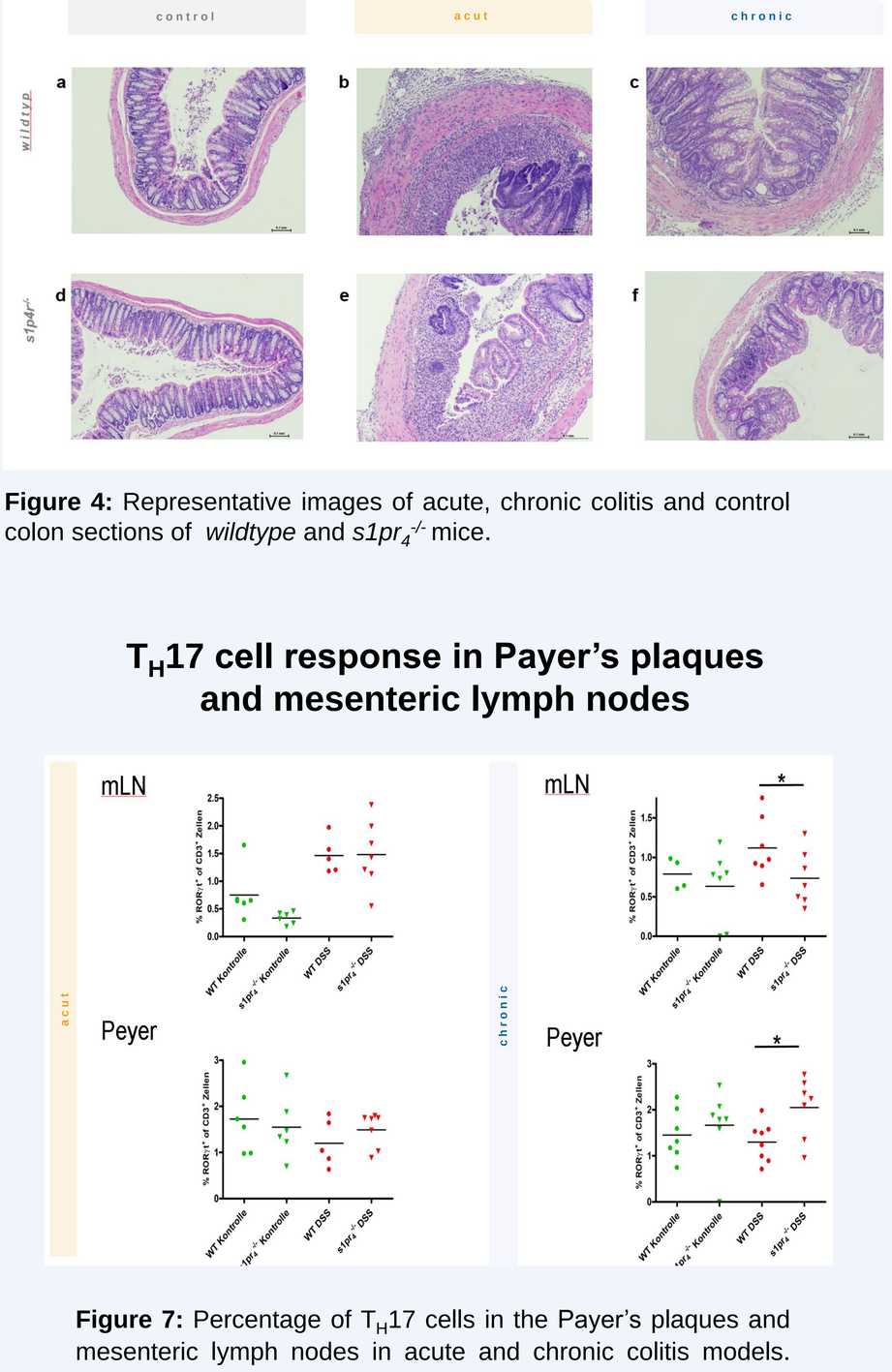

Figure 4: Representative images of acute, chronic colitis and control colon sections of *wildtype* and *s1pr*$_4^{-/-}$ mice.

Histopathology Index

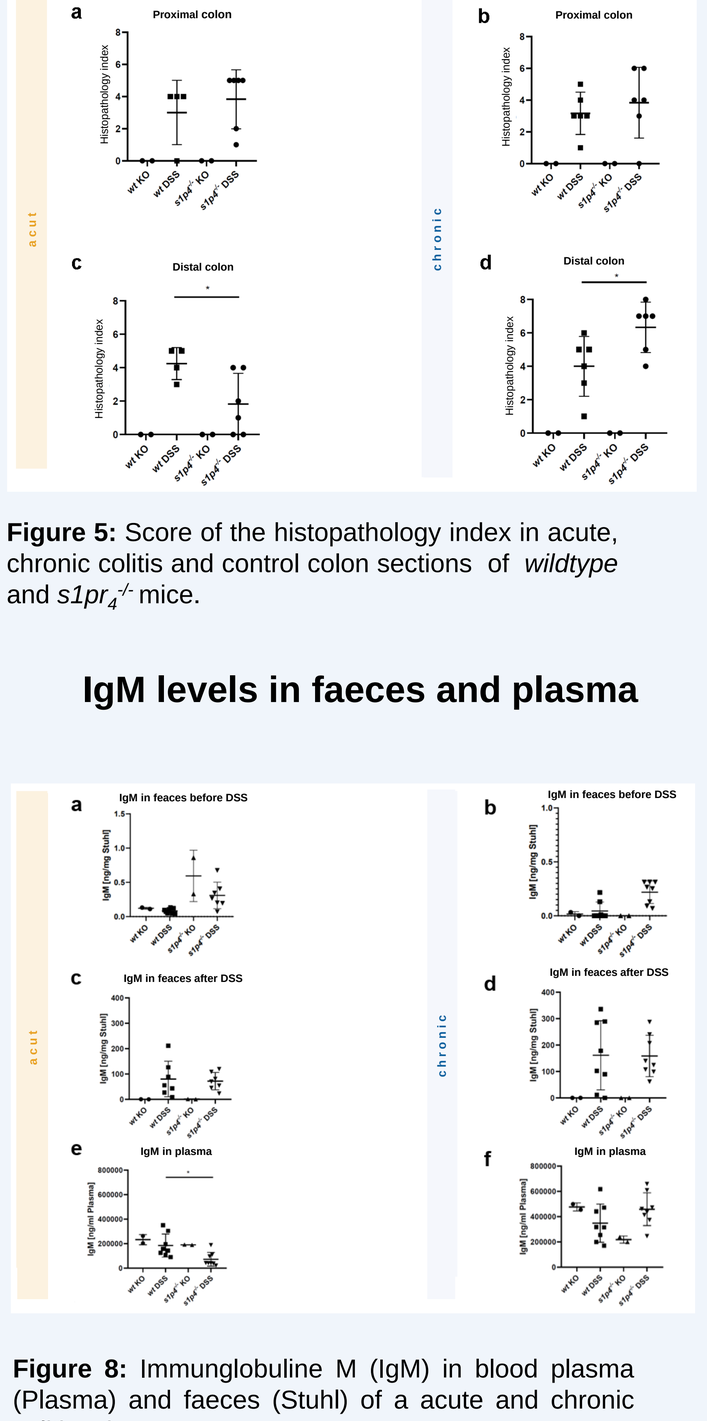

Figure 5: Score of the histopathology index in acute, chronic colitis and control colon sections of *wildtype* and *s1pr*$_4^{-/-}$ mice.

Regulatory IL-10$^+$ B cells

Figure 6: Percentage of IL-10$^+$ B cells in the spleen and mesenteric lymph nodes in acute and chronic colitis models. IL-10$^+$ B cells identified as B220$^+$ CD19$^+$ IL10$^+$.

T$_H$17 cell response in Payer's plaques and mesenteric lymph nodes

Figure 7: Percentage of T$_H$17 cells in the Payer's plaques and mesenteric lymph nodes in acute and chronic colitis models. T$_H$17 cell identified as CD3$^+$ CD4$^+$ CD45$^+$ RORγt$^+$.

IgM levels in faeces and plasma

Figure 8: Immunglobuline M (IgM) in blood plasma (Plasma) and faeces (Stuhl) of a acute and chronic colitis mice.

* $p < 0.05$

Conclusions: Inhibition of S1PR4-mediated signalling attenuates acute inflammation in a murine model of acute colitis, while it accentuates histopathological changes in a model of chronic intestinal inflammation. Our data suggest that altered regulatory B cells numbers and altered T$_H$17 response are implicated in the increased inflammatory response in the chronic model, while no differences in the production of natural IgM could be detected. The mechanims leading to increased inflammatory activity in the acute model remain to be clarified. S1PR4 may thus represent a potential therapeutic target for agonists and antagonists in the appropriate clinical setting.