Identification of tissue-resident memory T cells with pathogenic potency of Crohn's disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder of the gastrointestinal tract that consists of Crohn's disease and ulcerative colitis. In this study, we conducted a deep profiling of T cells in the gut mucosa of IBD patients and identified a subset of tissue-resident memory T cells (T_{RM}) that is specifically increased in Crohn's disease. These T cells are stimulated by cytokines that are abundant in the gut of IBD patients and secrete cytotoxic granules and IFN-γ. Inflammatory features of disease-specific T_{RM} are enhanced by their spatial proximity to gut epithelia. Moreover, the abundance of these T cells in the gut correlates with clinical scores, suggesting that the accumulation of this T cell subset is a pathological hallmark of Crohn's disease.

Background & Results

The development of therapeutic strategies has dramatically improved the remission rate of IBD, and enhancing long-term prognosis has become a new therapeutic goal. T_{RM} remain in non-lymphatic barrier tissues for extended periods and play a significant role in immune memory at the site of inflammation. The contribution of T_{RM} to the pathogenesis of IBD has been controversial, with conflicting results often been reported. In this study, we demonstrate that disease-specific CD4$^+$ T_{RM} are expressed in the gut of Crohn's disease patients and may contribute to the pathogenesis of the disease.

Profiling of T cells in the colonic mucosa of patients with Crohn's disease, ulcerative colitis, and colorectal cancer, using mass cytometry, revealed that CD161- and CCR5-expressing CD4$^+$ T_{RM} were significantly increased in Crohn's disease compared to other groups. Single-cell RNA sequencing analysis identified CD4$^+$ T_{RM} specifically expressed in the gut mucosa of Crohn's disease patients. This subset exhibited transcriptional signatures of cytotoxicity and Th1 effector activities. In vitro, disease-specific CD4$^+$ T_{RM}, stimulated with IL-12, IL-18, IL-7, and IL-15—cytokines known to be elevated in the gut mucosa of IBD—secreted high levels of Th1-type cytokines.

CD4$^+$ T_{RM} reside in close proximity to the gut epithelia. Co-culture of human gut organoids with disease-specific CD4$^+$ T_{RM} under cytokine stimulation resulted in elevation of LDH levels in the culture supernatant and increased the injury score of the organoids. These results suggest that disease-specific T cells may exacerbate inflammation and promote intestinal epithelial cell injury by secreting proinflammatory cytokines.

Significance of the research and Future perspective

A comprehensive analysis of immune cells at the site of inflammation in IBD will help elucidate the molecular mechanisms underlying the disease. As the disease specific T cells identified in this study represent potential therapeutic targets, understanding their characteristics and induction mechanisms could lead to the development of new therapeutic strategies.

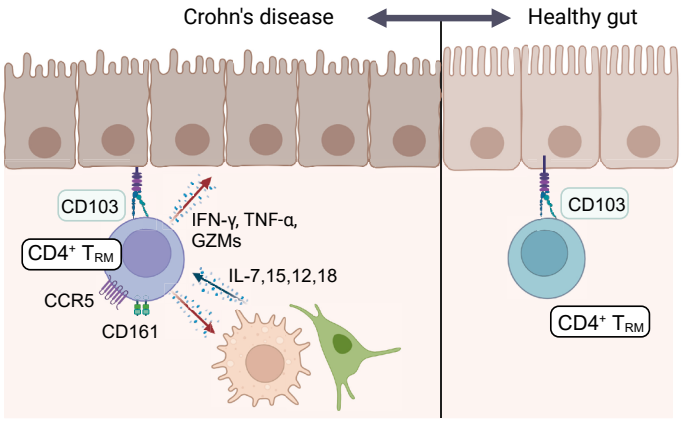

Fig. 1 Graphical Abstract

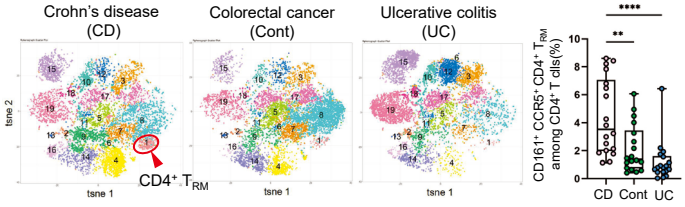

Fig. 2 Mass cytometry analysis of CD3$^+$ T cells

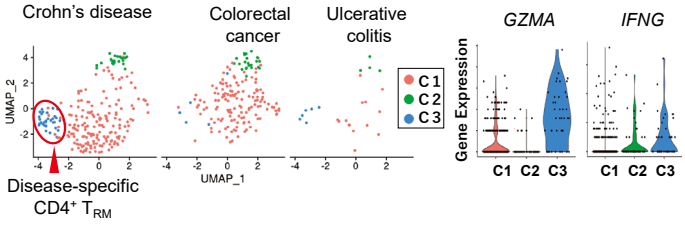

Fig. 3 Single-cell RNA-seq analysis of CD4$^+$ T_{RM}

Patent

Treatise

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Keyword inflammatory bowel disease, mucosal immunity, single-cell analysis, tissue-resident memory T cell