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RESEARCH HIGHLIGHT

RIG-I has guts: Identification of a role for RIG-I in colitis development

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Countries in North America and Europe have the highest incidence of inflammatory disorders of the gastrointestinal tract. The prevalence of inflammatory bowel diseases (IBD), which comprise Crohn's disease (CD) and ulcerative colitis (UC), now ranges from 10-200 cases per 100 000 individuals [1]. Although new therapeutic approaches have been developed to improve current treatments, the etiology of this disorder remains elusive. Crohn's disease and ulcerative colitis are known to show similar clinical and pathological characteristics; however it is now believed that these two forms of IBD are entirely different. Epidemiological studies have revealed that these differences might be explained by the fact that environmental and genetic factors play important roles in the pathogenesis and susceptibility to IBD [1]. Over the years, significant advances in the study of IBD had been made through the analysis of patient-based studies and murine models of intestinal inflammation [1]. One important feature characterizing IBD is the alteration of mucosal immunity, caused by effector T cell dysfunction and aberrant pro-inflammatory cytokine production. Indeed, mice with mutations in genes regulating T-cell immune responses or expressing specific transgenes were shown to develop spontaneous colitis. These murine models have greatly contributed to our understanding of human IBD [1].

Interestingly, genetic linkage studies have demonstrated that the gene coding for G protein subunit Gi2 alpha (Gαi2) is located within an IBD susceptible locus on chromosome 3p21 [2] and therefore is a potential candidate for IBD development in humans. In 1995, Rudolph *et al*. observed that Gαi2-deficient mice developed spontaneous inflammatory bowel disease closely resembling ulcerative colitis in humans [3]. The authors also demonstrated that an increase in the production of pro-inflammatory T_H1 cytokines such as IL-12, TNF-α and IFN-γ in the intestinal mucosa of these Gαi2-deficient mice led to a dysregulation in T cell activation. In fact, overproduction of these cytokines resulted in an upregulation of effector T cells and downregulation of naïve T cells, suggesting an important role for Gαi2 in the negative regulation of T cell response [4]. Further phenotypic analysis revealed that the number of Peyer's patches, which are the primary site for antigen encounter in the gut and specialised sites for initiation of mucosal immune responses [5], was also decreased in Gαi2-deficient mice.

In a recent issue of *Cell Research*, Wang Yi *et al*. [6] report that disruption of the retinoid acid-inducible gene-I (RIG-I) in mice leads to a colitis-like phenotype that is associated with the downregulation of Gαi2 expression. RIG-I is an intracellular pathogen-recognition receptor (PRR) that recognizes a variety of RNA viruses and triggers the innate antiviral response independent of the Toll-like receptor (TLR)-dependent pathways. RIG-I contains a DExD/H box RNA helicase domain and two caspase activation and recruitment domains (CARD). Binding of dsRNA and specifically 5′-triphosphate containing RNA to its DExD/H box leads to IFN production in response to viral infection via its interaction with downstream signalling protein MAVS and activation of IRF-3 and NF-κB (reviewed in [7]).

Wang Yi *et al*. successfully generated RIG-I-deficient mice through the deletion of exons 4 to 8 of the *RIG-I* gene. Interestingly, mice generated using this strategy were viable and fertile, in contrast to a previously reported study by Kato *et al*. [8], where $RIG^{-/-}$ mice were severely affected by *RIG-I* gene ablation and died during embryogenesis. These striking phenotypic differences between the two studies likely reflected the disruption of different regions of the *RIG-I* gene. Nevertheless, the generation of these knockout mice provides a valuable alternate mouse model

for the study of the mechanisms underlying IBD.

Wang Yi *et al*. demonstrate that RIG$^{-/-}$ mice experience a decrease in body weight and histological analysis of the colons of these mice reveals a colitis-like phenotype that correlates with severe damage and inflammatory infiltration in the colon mucosa. Consistent with previous observations that a decreased number of Peyer's patches was associated with the development of colitis [9], this study also demonstrated that the number and size of Peyer's patches were significantly reduced in RIG$^{-/-}$ mice. The authors then asked if RIG$^{-/-}$ mice display an altered regulation in T cell activation, as observed in other murine models of IBD such as Gαi2$^{-/-}$ mice. Similar to Gαi2$^{-/-}$ mice, RIG-I deficiency leads to an increase in splenic CD4^{+} and CD8^{+} effector T cells and a decrease in naïve T cells, suggesting that RIG-I plays an essential role in the regulation of T cell activation. As Gαi2- or RIG-I-deficient mice display similar phenotypes, the possible link between Gαi2 function and RIG-I was further evaluated. The authors demonstrated that Gαi2 expression is decreased in various tissues, as well as in T and B cells isolated from spleens of RIG$^{-/-}$ mice. Moreover, reporter assays demonstrated that RIG-I overexpression induced Gαi2 promoter activity, thus indicating that RIG-I regulates the transcriptional activity of Gαi2. Regulation of the Gαi2 promoter by RIG-I may be mediated by the activation of the NF-κB pathway [10].

In summary, the report by Wang Yi *et al*. underlines the importance of Gαi2-deficiency in the development of colitis. RIG-I may be a key player in the regulation of Gαi2 expression and thus RIG-I deficiency may contribute to the pathogenesis of IBD. Future work investigating RIG-I expression levels in individuals suffering from ulcerative colitis would further test this idea. Strikingly, another intracellular pathogen sensor − NOD2 − has also been associated with the development of Crohn's disease. Indeed, mutations of the *NOD2* gene − also known as caspase-recruitment domain protein 15 (CARD15) − have been shown to occur exclusively in patients with Crohn's disease and not in patients with ulcerative colitis (reviewed in [1]). Altogether, these studies highlight the involvement of pattern recognition receptors in the pathogenesis of inflammatory bowel disease. Although further research is required to enhance our knowledge of the exact causes of IBD pathogenesis, these findings will ultimately contribute to the development of new therapies.

References

1 Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nature reviews 2003; **3**:521-533.
2 Hampe J, Lynch NJ, Daniels S, *et al*. Fine mapping of the chromosome 3p susceptibility locus in inflammatory bowel disease. Gut 2001; **48**:191-197.
3 Rudolph U, Finegold MJ, Rich SS, *et al*. Ulcerative colitis and adenocarcinoma of the colon in G alpha i2-deficient mice. Nature genetics 1995; **10**:143-150.
4 Huang TT, Zong Y, Dalwadi H, *et al*. TCR-mediated hyper-responsiveness of autoimmune Galphai2(-/-) mice is an intrinsic naive CD4(+) T cell disorder selective for the Galphai2 subunit. International immunology 2003; **15**:1359-1367.
5 Ohman L, Franzen L, Rudolph U, Birnbaumer L, Hornquist EH. Regression of Peyer's patches in G alpha i2 deficient mice prior to colitis is associated with reduced expression of Bcl-2 and increased apoptosis. Gut 2002; **51**:392-397.
6 Wang Y, Zhang HX, Sun YP, *et al*. Rig-I(-/-) mice develop colitis associated with downregulation of Galphai2. Cell Res 2007; **17**:858-868.
7 Takeuchi O, Akira S. Signaling pathways activated by microorganisms. Current opinion in cell biology 2007; **19**:185-191.
8 Kato H, Sato S, Yoneyama M, *et al*. Cell type-specific involvement of RIG-I in antiviral response. Immunity 2005; **23**:19-28.
9 Spahn TW, Herbst H, Rennert PD, *et al*. Induction of colitis in mice deficient of Peyer's patches and mesenteric lymph nodes is associated with increased disease severity and formation of colonic lymphoid patches. The American journal of pathology 2002; **161**:2273-2282.
10 Arinze IJ, Kawai Y. Transcriptional activation of the human Galphai2 gene promoter through nuclear factor-kappaB and antioxidant response elements. J Biol Chem 2005; **280**:9786-9795.