Dual role of Th17 cells in Crohn’s disease

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Abstract
Crohn’s disease (CD) is a chronic relapsing, destructive inflammatory disease of the gastrointestinal (GI) tract, the cause of which remains still unknown. Accumulating evidence suggests that CD results from the imbalance between pro- and anti-inflammatory agents and the overactivity of T helper (Th)1. It seems that major cause of GI inflammation is an IL-12-driven Th1 response, which results in the generation of IFN-γ, the key inflammatory mediator. Recently, however, much attention has also been given to the possible involvement of Th17 cells in the pathogenesis of CD. This mini-review is aimed to summarize the current knowledge on the dual role of Th17 cells in CD.

Key words: IBD, Crohn’s disease, Th17, IL-17, Th1/Th2/Th17.

Introduction
Crohn’s disease (CD) is a chronic relapsing, destructive inflammatory disease of the gastrointestinal (GI) tract, the cause of which remains still unknown. In Europe, CD incidence rates vary between 0.7 (Croatia) and 9.8 (Scotland) cases per 100,000 persons-years, while prevalence ranges from 8.3 (Croatia) to 214 (UK) [1]. Undoubtedly, CD is of multifactorial nature, involving genetic predispositions, environmental factors, intestinal microbial flora and the immune system. Accumulating evidence suggests that CD results from the imbalance between pro- and anti-inflammatory agents and the overactivity of T helper (Th)1 and possibly Th17 cells [2]. Some data also suggest that the defect within the regulatory T cell compartment might be at least partially responsible for the imbalance [3]. This mini-review is aimed to summarize the current knowledge on the potential role of Th17 cells in the pathogenesis of CD.

Th1/Th2 paradigm in CD
The current view on CD is that inflammation is caused by an IL-12-driven Th1 response, which results in the generation of interferon-γ (IFN-γ), the key inflammatory mediator [2]. The predominance of Th1 response is consistent with the presence of granulomas in CD patients, which is a well-described outcome of Th1-related immune response [4]. This view has also been supported by multiple IBD mouse models of CD [1]. A large number of CD4+ T cells that highly express T-bet and STAT-4, the Th1-master regulators, have been found in the intestinal mucosa of CD patients [5, 6]. CD4+ T cells in the intestinal lamina propria of CD patients produce large amount of IFN-γ and lower amount of IL-4 than that of healthy control [6]. Macrophages in the intestinal lamina propria of CD patients produce large amount of IL-12 [7]. Lymphocytes in the intestinal lamina propria of CD patients express elevated levels of IL-12R, and produce large amount of IFN-γ in response to IL-12 [8]. Similar picture can be found in the peripheral blood of CD patients [9]. The most convincing evidence that CD is a Th1-cytokine mediated disease, however, is the efficacy of biologic therapies directed against tumor necrosis factor (TNF)-α, IL-12 and IFN-γ [10].

Th17 cells
Recently, much attention has also been given to the possible involvement of Th17 cells in the pathogenesis of CD [11, 12]. This newly identified subset of T-helper cells distinct from Th1/Th2 produce various proinflammatory cytokines, including IL-17A, IL-17F, IL-21, IL-22 and TNF-β and play an important role in the protective immunity against the extracellular pathogens such as bacteria and...
Th17 cells differentiate in the presence of IL-6 and transforming growth factor (TGF)-β, through the expression of retinoic-acid-receptor-related orphan receptor (ROR)γt [13]. While TGF-β drives Smad signaling, IL-6 activates STAT3 pathway, which promotes the expression of RORγt, a master regulator of Th17 cells. IL-21, in turn, seems to be an important cytokine for the differentiation of Th17 cells. IL-6 promotes the production of IL-21 from Th17 cells independent of RORγt, and then IL-21 upregulates the expression of RORγt through the activation of STAT3 pathway. This process provides a positive feedback in the differentiation of Th17 cells, and is called an amplification. Although IL-21 is not essential for the polarization of Th17 cells, it is necessary for their amplification. The key cytokine responsible for stabilization and expansion of Th17 cells, in turn, is the member of IL-12 cytokine, IL-23. This cytokine is produced by professional antigen-presenting cells (APCs) during the inflammatory response to both pathogenic and nonpathogenic stimuli [14]. Also intestinal microbiota is essential for the development of Th17 cells, since mice in germ-free condition are characterized by lower percentage of this subset [15]. Th17 cells play a crucial role for the protective immunity against intestinal pathogens. A high expression of IL-23 has been found in mucosa of human ileum, as well as an upregulation of Th17 cells in the human GALT [16].

Potential role of Th17 cells in CD

IL-17A, often referred to as IL-17, is a main proinflammatory cytokine produced by Th17 cells. It has been reported that Th17 subset is deeply involved in the pathogenesis of various diseases that were thought to be either Th1 or Th2 dominant previously. IL-17A is upregulated in and has been associated with several autoimmune diseases including inflammatory bowel disease (comprising CD and UC), rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis and multiple sclerosis [11]. Its involvement in other pathological inflammatory conditions like uveitis, cystic fibrosis, chronic obstructive pulmonary disease and other inflammatory airway diseases, allograft rejection, cancer, and intraperitoneal abscesses and adhesions has been also implied [11]. Mounting evidence seems to support the view that Th17 cells are somehow involved in CD pathogenesis. A high expression of IL-17A mRNA was found in intestinal mucosa of CD patients [17]. The elevated fecal IL-17A levels were found in active CD, accompanied by high percentage of IL-17A and IL-23 producing cells in lamina propria of CD patients [12]. Several mouse studies have identified IL-23 as a major driver of intestinal inflammation via inflammatory mediators including IL-17A and IL-6 [17-19]. A genome-wide association study (GWAS) has indicated that IL-23R and five additional genes involved in Th17 differentiation are associated with susceptibility to CD [17]. It is not clear how IL-23R polymorphism might predispose to CD, however the identification of both disease-protective and risk-associated variants of the gene suggests that the IL-23 signaling may play a crucial role in maintaining immune homeostasis in the intestine. Also, recently conducted phase II clinical trials have reported that blockage of p40, the shared subunit of IL-12 and IL-23, is effective in CD treatment, and has a therapeutic effect similar to that of anti-TNF-α therapy [20, 21]. The anti-p40 antibodies were assumed to abrogate IFN-γ mediated intestinal inflammation through blockage of IL-12, however the other possibility implies that inflammation attributed to IL-12 is mediated by IL-23 and its downstream cytokines IL-17A and IL-22. All these data have provided support for the idea that IL-17A plays a major role in CD pathogenesis and its inhibition might represent a potential approach for treating active course of the disease.

Although these observations suggest the importance of the IL-23/IL-17 axis in CD, the exact role of IL-17 in the pathogenesis of disease remains unclear, since also its protective role in the intestine inflammation has been proposed based on T cell dependent and T cell independent models of colitis [22, 23]. This view is supported by the poor therapeutic effect accompanied by a higher rate of adverse events compared to placebo group obtained in recent phase II clinical trial of anti-IL-17 therapy in active CD patients [24]. It should be remembered that Th17 cells constitute a heterogeneous subpopulation, differing in properties and functions [2]. There is evidence that differentiation of Th17 cells in the absence of IL-23 leads to Th17 cells producing a strong anti-inflammatory cytokine, IL-10 [25]. Th17 cells induced in the presence of IL-1β, on the contrary, have a unique mRNA profile and increased capacity to induce inflammation [26]. In milieu lacking TGF-β, IL-12 and IL-23 Th17 cells acquire the capacity to produce IFN-γ [2].

Of great importance for immune homeostasis is also a somewhat reciprocal relationship of Th17 cells with regulatory T cells through their shared use of TGF-β as a differentiation factor [27-29]. Current data demonstrate that active CD is, like many other autoimmune diseases, characterized by a numerical and/or functional defect of a regulatory T cell subpopulation [9, 30, 31]. In spite of the presence in the inflamed GI tract of CD patients, their number and/or suppression function is probably insufficient to control an ongoing inflammation [30]. It is suspected that generation of these cells is inhibited by active blocking by Th17 cells and chronic overproduction of Th17 cytokines [14]. It is also worth noting that in some circumstances Th17 cells can acquire strong immunosuppressive capabilities [32]. These regulatory Th17 cells are IL-17A+ FoxP3- and suppressive capacity is dependent on IL-10, TGF-β and cytotoxic T lymphocyte antigen 4 (CTLA4) [32]. Another study has reported the isolation of regulatory Th17 cells expressing Foxp3 and exhibiting strong suppressive activity from the lamina propria of CD patients [33]. There is also evidence that regulatory T cells and Th17 cells may play com-
limentary roles in the intestinal homeostasis. In vitro studies have indicated that regulatory T cells can promote the development of Th17 cells in a TGF-β-dependent manner [34, 35]. Regulatory T cells themselves can be induced to secrete IL-17 in vitro [35].

Conclusions

Standard treatment of CD includes immunosuppression with corticosteroids, thiopurines, or methotrexate, and anti-TNF therapy for patients with persistent disease activity [36]. Although most CD patients respond to anti-TNF therapy, secondary failures due to intolerance or loss of initial response are common [37, 38]. Thus, novel therapies based on different mechanisms are needed. In spite of the fact that various clinical trials with antibodies to IL-17A have reported therapeutic benefit in multiple patients populations, especially with rheumatoid arthritis and psoriasis, the poor outcome obtained in recent clinical trial in active CD patients indicate that the role of Th17 cells and IL-17A might be much more complex and unique in the intestine. It appears that the local cytokine milieu at site of inflammation is the key factor in the development of Th17 cells and their conversion into distinct subtypes characterized by different levels of proinflammatory activity and playing potentially opposing roles. It seems to be particularly relevant to the immune homeostasis of GI tract. Therefore, further research is needed to elucidate the role of Th17 cells and its downstream cytokines in the pathogenesis of CD.

References