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Can IL-23 be a good target for ulcerative colitis?

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ABSTRACT

A considerable percentage of patients with ulcerative colitis (UC) do not respond to therapies, including anti-tumor necrosis factor (TNF) drugs and vedolizumab, or lose response over time. Hence the continuing need to find new therapeutic strategies and novel drugs to control this chronic debilitating disease. Increased levels of interleukin (IL)-23 and T helper (Th) 17 cell cytokines have been found in intestinal mucosa, plasma, and serum of patients with inflammatory bowel disease (IBD). IL23-blocking has been shown to reduce the severity of inflammation in experimental colitis. Lastly, ustekinumab, a monoclonal antibody (mAb) to the p40 subunit of IL-12 and IL-23, has showed good efficacy and safety profile in patients with Crohn's disease (CD).

This review aims to discuss the available data on IL-23 and Th17 cell pathways in UC, in order to define the role of IL-23 as possible target for the treatment of UC.

1. Introduction

Ulcerative colitis (UC) is a chronic, relapsing-remitting, inflammatory bowel disease (IBD), that causes continuous mucosal inflammation of the colon, leading to organ damage and impaired quality of life [1]. In the last two decades, the introduction of biologic therapies have changed the natural history of UC, with a higher probability to achieve and maintain remission; nevertheless, there is still a considerable percentage of patients who do not respond to therapies [2].

Anti-tumor necrosis factor (TNF) drugs were the first class of biologics developed. They are currently available for intravenous (infliximab) or subcutaneous administration (certolizumab pegol, adalimumab and golimumab). However, about 30% of patients are primary non responders and another third of patients will become secondary non-responders, losing response over time [3].

The second class of biologics developed in UC in the last years is currently represented by vedolizumab. Unlike anti-TNFs, it acts blocking the integrin $\alpha 4\beta 7$ on leukocyte cells, thus reducing lymphocyte trafficking to intestinal mucosa. Vedolizumab is effective for induction and maintenance therapy in UC [4], but about 50% of patients do not respond to treatment or will lose response over time [5].

Hence the continuing need to find new therapeutic strategies and novel drugs to control this chronic debilitating disease.

Pathogenesis of UC is still poorly understood, but it is thought that environmental factors, such as microbiota, may provoke an aberrant immune response in subjects with a genetic predisposition, leading to chronic inflammation and finally to organ damage [6]. The excessive immune response has therefore been the target of most treatments for IBD, aimed at both reducing lymphocyte migration to inflammatory sites than blocking specific inflammatory cytokines, strategic keys in the development of inflammatory cascade.

In response to microbial pathogens, antigen-stimulated dendritic cells and macrophages produce interleukin (IL)-12 and IL-23, which in turn promote release of further cytokines, such as interferon gamma (IFN-γ), IL-17, IL-6, IL-1 and TNF [7]. In particular, IL-23 induces the differentiation of naïve $CD4^+$ T cells into T helper (Th) 17 cells, followed by activation of a cascade of pro-in-inflammatory cytokines, including IL-17 A, IL-17 F, IL-6 and TNF [8,9]. Increased levels of IL23 and Th17 cell cytokines have been found in intestinal mucosa, plasma, and serum of patients with IBD [10–12]. Variants in several genes encoding for IL23 and Th17 cell pathways have been associated with risk for IBD [13]. In particular,

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a variant of the IL23 receptor (IL23R) gene, that encodes an amino acid change from arginine to glutamine at position 381, has been observed to reduce the risk for IBD, due to a loss-of-function of IL23R, with decreased STAT3 signaling and Th17 cell responses upon exposure to IL23 [14]. IL23-blocking has been shown to reduce the severity of inflammation in experimental colitis [15–17]. Lastly, ustekinumab, a monoclonal antibody (mAb) to the p40 subunit of IL-12 and IL-23, has showed good efficacy and safety profile in patients with Crohn's disease (CD) [18].

Accordingly, IL-23 and IL-23/IL-17 axis may be a promising target in both CD and UC.

This review aims to discuss the available data on IL-23 and Th17 cell pathways in UC, in order to define the role of IL-23 as possible target for the treatment of UC.

2. IL-23 pathway

Intestinal wall, in particular the lamina propria layer, contains a complex population of immune cells that work constantly to maintain tolerance to luminal microbiota, but also to prevent entry of pathogens. In IBD, there is an infiltration and expansion of innate and adaptive inflammatory cells in intestinal wall. Activation and proliferation of neutrophils, macrophages, dendritic cells, natural killer (NK) T cells, innate lymphoid cells (ILCs), B and T lymphocytes lead to an increase of cytokines, such as TNF, IFN-γ, IL-1β, IL-6, IL-23 and Th-17 cell pathway cytokines, with an imbalance between anti-inflammatory and pro-inflammatory cytokines and development of chronic inflammation [19].

Naïve $CD4^+$ T cells can differentiate into several subsets of effector T cells, including Th1, Th2, Th17 and regulatory T cells [20]. Several studies of $CD4^+$ T-cell biology show that Th1 cells promote cellular immunity against intracellular pathogens (releasing cytokines such as IFN-γ); Th2 cells promote humoral immunity and response to helminth infections (producing IL-4, IL-5 and IL-13); Th17 cells regulate inflammatory response producing IL-17, a potent pro-inflammatory cytokine which, together with TNF-α and IL-1β, recruits neutrophils, inhibits chondrocyte metabolism and promotes osteoclastogenesis [21]. IL-17 comprises a family of six cytokines (IL-17 A to F) that signal through dimeric IL-17 receptors (IL-17 R A to E) [22]. They are also produced by NK T cells, intraepithelial and lamina propria γδ T cells and ILCs and, in turn, act on a variety of cells, including epithelial cells, fibroblasts and neutrophils [23]. Predominance of these T cells on regulatory T cells can cause intestinal inflammation [24]. In intestinal tissues from patients with IBD, it has been found an increase of levels of cytokines released by Th1 cells, such as IFN-γ and TNF; Th2 cells, such as IL-4, IL-5 and IL-13; TH9 cells, such as IL9 and IL21; and Th17 cells, such as IL-17, IL-21, IL-22 and IL-26 [19,25,26].

In the last year, it has been suggested that Th 17 cell pathways may have a predominant role in the development of chronic inflammation in IBD.

The IL-12 family, including IL-12, IL-23, IL-27 and IL-35, comprises cytokines that mediate the inflammatory response. They are mainly produced by dendritic cells and macrophages in response to exogenous stimuli [27,28]. IL-23 is a heterodimeric cytokine, composed by the p40 and p19 subunits. It binds to the heterodimeric receptor which consists of two portions, IL-12 Rβ1 and IL-23 R. It is produced by cells of the innate immune system, predominately inflammatory myeloid cells [29] (Fig. 1). IL-12 shares with IL-23 the p40 subunit and is additionally constituted by a specific subunit p35. It binds to its heterodimeric receptor, formed by IL-12 Rβ1, recognized by the p40 subunit, and by IL12Rβ2 (Fig. 1). Despite the similar chemical structure with IL-23, IL-12 has a different role. It is essential for developing immunity to intracellular pathogens and is involved in differentiating naïve $CD4^+$ T cells into Th1 cells. Finally it causes an increase of interferon-γ and TNF production by NK and T cells [20] (Fig. 2). IL-23 instead plays a key role in development of Th 17 cell pathways. It induces the differentiation of naïve $CD4^+$ T cells into Th17 cells and their release, IL-17 expression to response to infections in different mucosal tissues (Fig. 2). IL-23 plays an essential role in mucosal immunity and in normal intestinal homeostasis [30,31].

At the beginning, development of Th17 cells is induced by TGF-β and IL-6, the second stage is expansion under activation of IL-21 and finally, there is the stabilization phase driven by IL-23, generating the cytokine profile for the CD4 Th17 cell. Therefore, the Th17 cells' functions depend on the immunological environment in which they develop [32]. IL-23 signaling is mediated by the binding with its receptor that activates a specific intracellular signaling, the Janus-associated kinase (JAK), and signal transducer and activator of transcription 3 (STAT3), which regulate transcription of genes encoding for several cytokines, including IL-17, IL-21 IL-22, and IFN-γ [19,33]. IL-17 is involved to microbial defence, but can lead to chronic inflammation through recruitment and activation of other

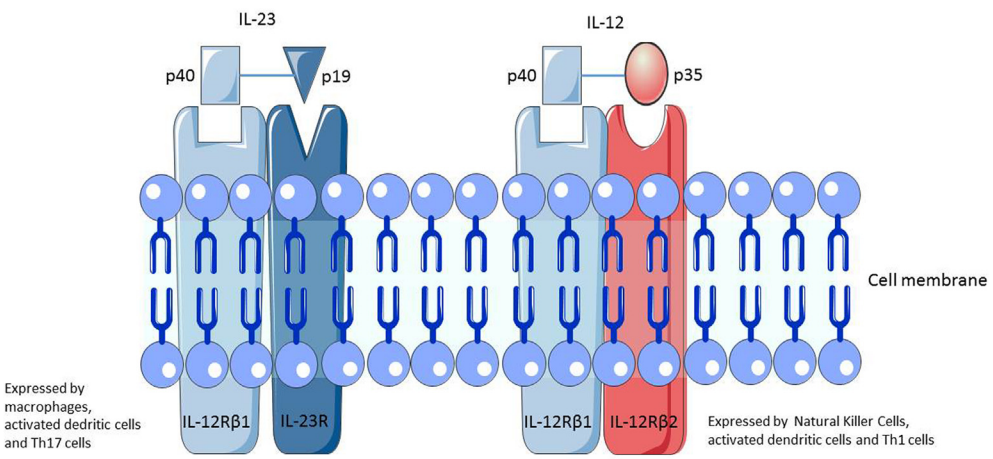

Fig. 1. Relationship between IL-23 and IL-12.
IL-23 is composed by the p40 and p19 subunits; IL-12 by the p40 and p35 subunits. The cytokines bind two different heterodimeric receptors, which share the IL-12Rβ1 portion recognized by the p40 subunit; the p19 subunit specifically binds the IL-23 R portion of the receptor complex; the p35 subunit binds the IL12Rβ2 portion. These two receptors are expressed by different cell populations, thus contributing to inflammation development and maintenance at different levels.

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