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IL-12, IL-23 and IL-17 in IBD: Therapeutic and immunobiology targeting

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Abstract
The occurrence of multiple infections within the human body, such as gastroenteritis, is observed in a subset of patients who also experience inflammation-related conditions like ulcerative colitis. Traditionally, these conditions have been associated with an excessive response from Th2 or Th1 cells, respectively. However, recent studies have unveiled a noteworthy revelation in. the context of Inflammatory Bowel of Disease (IBD). It has been demonstrated that an enhancement in cytokine synthesis is facilitated by a distinctive subset of T cells, specifically Th17 cells, also known as helper cells. This discovery marks a pivotal development in the field of immunopathology. Furthermore, the role of interleukin (IL)-23 in amplifying Th17 cell responses, including those associated with inflammatory bowel disease, has yielded valuable insights into tissue damage pathways and has opened up new avenues for therapeutic strategies in various diseases, notably inflammatory bowel disease.
Recent research has also shed light on the potential dual nature of Th17- cytokines, such as IL-22 and IL-17A, which may exert protective effects without causing harm. This comprehensive review underscores the role played by cells of Th17 and IL-23 in the inflammatory processes occurring in various tissues, including those affected by intestinal infections and other related conditions.

Keywords: Cell Th17, IL-17, Cell of IL-23, IL-21, IBD

Introduction
The utilization of monoclonal antibodies targeting TNF as a therapeutic approach for managing Crohn'ss disease and other related conditions is well-documented [1]. However, despite substantial advancements in this field, optimizing the use of such drugs in the remains a pressing and often unmet clinical challenge. A significant portion either not respond to anti-TNF treatments or exhibit initial responses followed by subsequent loss of efficacy. Remarkably, it took approximately two from the initial licensing of anti-TNF. monoclonal antibodies for Crohn'ss disease until 2016 when both the Food and Drug Administration (FDA) and (EMA) approved the application of ustekinumab [2].
Ustekinumab, a modern cytokines-targeting agent, targets a shared cellular of both interleukin-12 (IL-12) and the interleukin-23 (IL-23). This review seeks to provide a comprehensive exploration of the underlying biology of cytokines and their pivotal role in disease. Furthermore, it delves into the rapidly evolving landscape of developments in this area, with particular emphasis on the period following the licensure of ustekinumab [2].
The review encompasses an array of clinical advancements and experimental data pertaining to monoclonal antibodies that target IL-23 (as opposed IL-12) in conditions and ulcerative colitis. Additionally, it touches upon promising early-stage studies aimed at identifying patient subgroups that may derive the greatest benefit from ustekinumab or IL-23-targeting agents. While further data regarding the application of ustekinumab in ulcerative colitis is eagerly anticipated, it is currently unavailable [3].

Materials and Methods
The initial phase of this review involved conducting an online websites search with the objective of identifying research studies elucidating the significance and functions of IL-23/IL-17 Axis in the Inflammatory Bowel Disease (IBD). A selection of articles was curated, focusing on diseases that are associated with the activity of cytokines. This assortment of articles encompassed a spectrum of conditions, including necrotic diseases, colon diseases, and various other infections.
The inclusion of research articles in the review was contingent upon their alignment with the following criteria: First, the articles were chosen based on the explicit reference to the

immunological importance attributed to these cytokines in the pathogenesis of diseases. Second, the selection considered the extent to which these studies shed light on the immunological treatment strategies for these diseases or emphasized the paramount importance and objectives underlying their investigation.

Results

Discovery (IL-12 and IL-23)

The inhibiting the IL-12-IL-23 is rooted in experimental data spanning over two decades, supported by genetic studies highlighting the pivotal role of components within the IL-12-IL-23 signaling pathway in the pathogenesis of Inflammatory Bowel Disease (IBD) [1]. The identification of IL-12 emerged from endeavors aimed at understanding cytokines derived from Natural Killer (NK) cells, which possess the capacity to inhibit colony formation from hematopoietic precursor cells [2]. Subsequent studies within the B-cell subgroup unveiled the cytokine's ability to activate natural killer cell functions, thus augmenting the immune response to mitogens [4]. Initially referred to as "NK stimulating factor," cytokine was later rebranded as IL-12. Investigations demonstrated that dendritic cell-derived IL-12 operates by inducing the downregulation (also known as TBX21) and promotes T-cell towards helper 1 (TH1) phenotype, accompanied by IFNγ production. Consequently [3, 4].

Experimental data have underscored the therapeutic potential of IL-12 modulation, either through neutralizing antibodies targeting the IL-12p40 subunit or inhibition of the protective IL-12p40 (IL12B) gene, in diverse immune-mediated including Allergic, collagen-induced arthritis, and models of infections. Consequently, IL-12 has emerged as a crucial therapeutic target [5]. Nevertheless, inactivation of the IL-12 subunit, IL-12p35, has been reviewed, with an emphasis on the necessity for its maintenance until the disease course becomes unequivocally exacerbated [6]. The identification of an interleukin-12p40 subunit's mathematical sequence, which pairs with a structurally distinct subunit, IL-12p35, yielded a novel active cytokine known as IL-23 [7]. It has become evident that IL-23, akin to IL-12, assumes a significant immune modulatory role. Its inactivation confers resistance against various immune-mediated disorders [8, 10]. Notably, IL-23 receptor signaling plays a pivotal role in the regulation of T helper 17 (TH17) cells, with IL-17A being a key pathogenic mediator [12]. The first clinical trial to test an anti-IL-12p40 antibody, briakinumab, in a group of Crohn's disease patients primarily targeting IL-12 underscores the evolving therapeutic strategies in this field [11].

IL-12 and IL-23 are members of the IL-12 cytokine group, which includes IL-35, an anti-inflammatory is produced by T-regulatory cells, and IL-27, which either enhances TH1 cell inhibits TH17 differentiation [13-16]. These cytokines exhibit heterogeneous receptors, with IL-12Rβ1 and IL-12Rβ2 comprising the IL-12 receptor, and IL-12Rβ1 or coupling to IL-23R in the case of the IL-23 receptor (Figure 1). IL-27, by both IL-12 and IL-23, engages in signaling cascades via distinct heterologous receptors [15, 16].

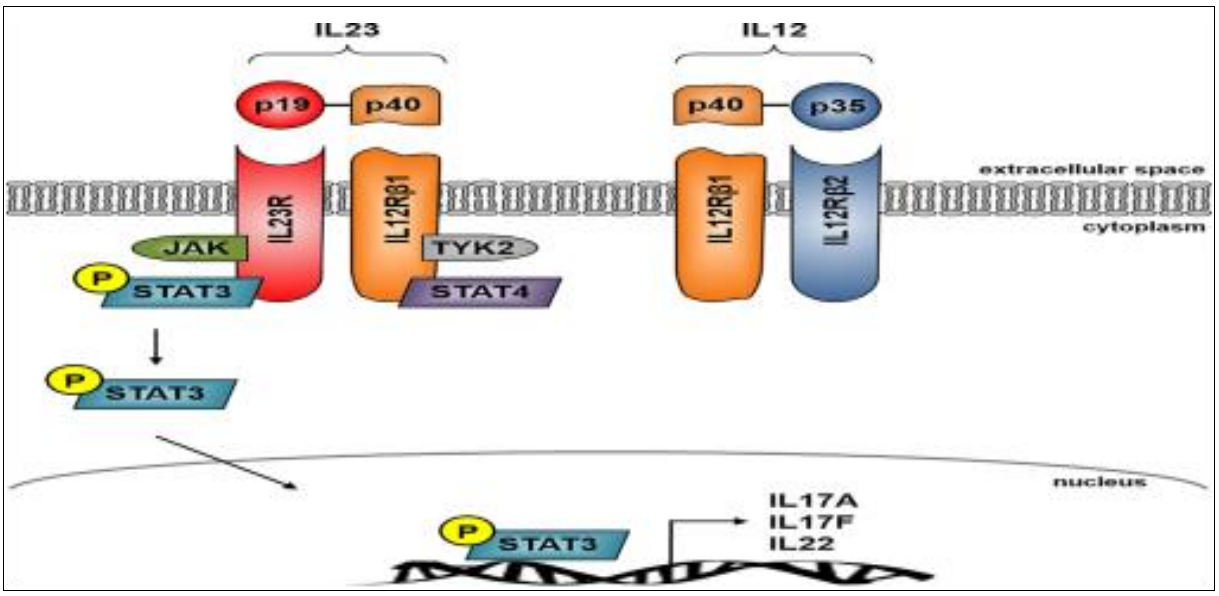

Fig 1: IL23 signaling. IL23 is Heterologous to the unique subunits p19 and p40, as well as IL12. IL23 refers to the receptor complex consisting of IL12Rb1 and IL23R subunits, but the IL23R, represented by the unique IL-12Rb1, also participates in the IL12 receptor complex

Important biological functions of IL-12 and IL-23

It is known that IL-12 exerts a wide range of important biological functions, such as initiating differentiation processes in CD4 + T cells, leading to the production of IFNγ-producing Th1 cell populations. These processes are contingent upon the involvement of various STAT4 transcription factors and T-bet [16]. Additionally, IL-12 plays role in hematopoietic progenitor cell proliferation and colony formation when combined with several other catalytic factors [16]. IL-12 enhances proliferation and affects the functionality of killer cells, NK T cells, and cytotoxic T cells. It also contributes to the conversion of B cells to a Th1-associated phenotype, impacting immunoglobulin production [17].

Because T cells lack the IL-23R receptor, unlike IL-12, IL-23 does not directly drive the development of Th17 cells. Instead, it engages in cytokine signaling, such as transforming growth factor (TGF), IL-1, and IL-6, and T-cell receptor interaction under particular environmental circumstances. As a result of this interaction, transcription

factors including retinoid receptor-related orphan receptor gamma t (RORt) are activated, which in turn enhances the production of crucial TH17 prototype genes like IL-17A and IL-23R. A positive feedback loop is created by the interaction of IL-23 with its receptors, which activates STAT3, encourages transcription through RORt, and supports the production of the TH17 gene, cell activation, and effector activities [18].

The balance between immunological and regulatory responses might be influenced by effector T cell responses because of their extraordinary adaptability and ongoing production of diverse and customized antibodies (19) (see Fig.)

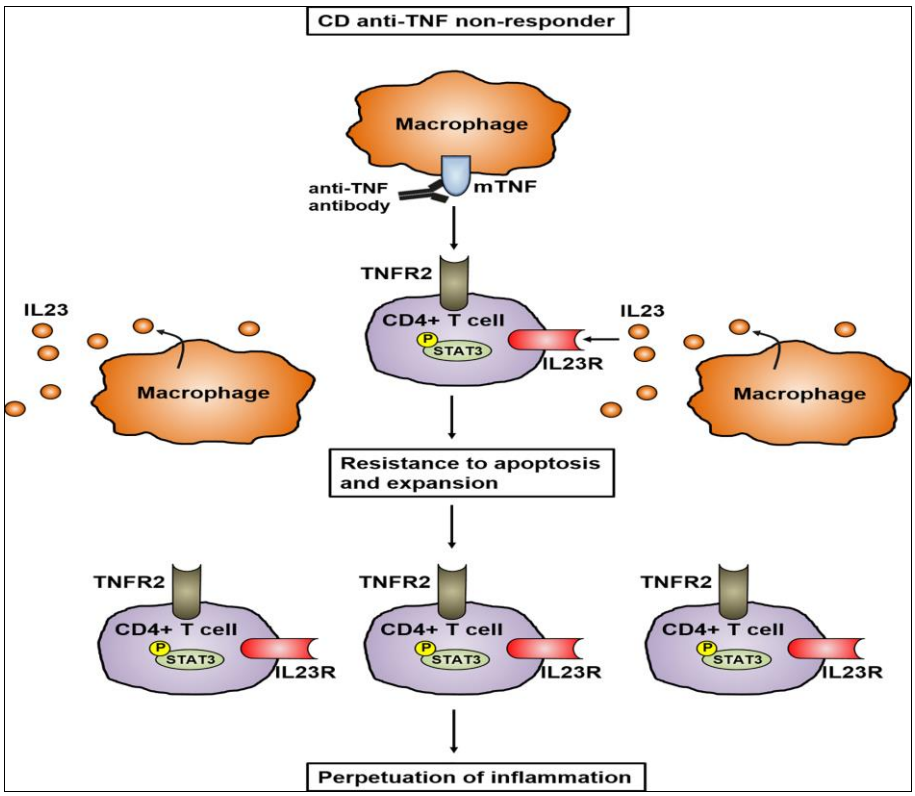

Fig 2: Anti-TNF resistant CD4+ T cells with IL23-mediated resistance to apoptosis. TNFR2-bearing CD4+ T cells that are anti-TNF refractory express the IL23R. Mucosal inflammation is caused by the IL23R on CD4+TNFR2+ T antibodies, which is produced by CD14+ macrophages

TH17 and its importance

In cases of chronic inflammation, polarized T cells are distinguished by their remarkable capacity to undergo phenotypic alterations and repolarization towards various destinies. This extraordinary adaptability is referred to as innate plasticity [21]. Several factors, including cytokine environments, metabolites, or microbial components, can influence the malleability of these cells. For instance, a cytokine-rich milieu can stimulate specific T-cell subsets, thereby fostering By the activation of many molecules, such as STAT proteins and different transcriptional regulators like FOS (Fosl2) and Interferon regulatory factor 4, plasticity is achieved. (IRF4) [22, 23].

Plasticity between Th1 and Th17 cells assumes a pivotal role in orchestrating immune responses within the gastrointestinal tract [24]. Moreover, numerous studies have suggested that Inflammatory Bowel Disease (IBD) is the presence of both Th1 and Th17 cells, or the accumulation of Th1 and Th17 cell populations within the mucosa of IBD patients. This phenomenon is accompanied by elevated levels of IFNγ and IL-17 when compared to a group characterized by co-expression of IFNγ and IL-17, which represents Th17 cells transitioning into Th1 cells. These findings underscore the substantial role played by Th17/Th1 plasticity in the pathogenesis of chronic intestinal infections [25].

Therapeutic methods have shown how important it is to block IL23 and IL17 signaling

Understanding the critical roles that IL23 and IL17 play in the pathophysiology of a variety of inflammatory bowel illnesses and other immune-related conditions, leading to the development of novel therapeutic approaches [26-28], a series of investigations were undertaken, focusing on p40 antibodies, which encompass the IL23 and IL12 subunits. Notable examples of such antibodies include briakinumab [29] and ustekinumab [30]. It has been demonstrated, as indicated in another study, that ustekinumab has exhibited efficacy in the treatment of patients afflicted with moderate to severe diseases, resulting in an elevated response rate [30].

Moreover, patients with Crohn's disease (CD), a condition characterized by anti-tumor necrosis factor factor therapy, have also been considered, particularly in cases involving severely ill patients manifesting features such as psoriasis lesions or skin infiltration of Th17 cells. Treatment with ustekinumab in these instances has led to a reduction in skin lesions {31}. The findings of these investigations have yielded promising results, underscoring the significance of ustekinumab treatment and its pivotal role in modulating the interplay between The etiology of infections and tissue necrosis involves IL23/IL23R and IL17/IL17R.

Furthermore, the maintenance of typical Th1 responses, which are supported by IL12, is made possible by the

selective targeting of the IL23p19 subunit. An antibody created to block IL23 should successfully inhibit IL23 in contrast to IL17, which has a direct role. This would stop the growth of pathogenic Th17 cells and eventually lessen inflammation brought on by cytokines linked to this cell subtype, such as IL17, IL21, and IL22.

Recent research has focused on the dramatic consequences brought on by blocking the IL23p19 subunit, building on the therapeutic success shown with targeted IL23 inhibition in disorders like psoriasis. Risankizumab, a humanized monoclonal antagonist, is a prime example of such a project [32].

Conflict of Interest

Not available

Financial Support

Not available

References

1. Duerr RH, *et al*. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314:1461–1463.
2. Kobayashi M, *et al*. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. J Exp. Med. 1989;170:827–845.
3. Macatonia SE, *et al*. Dendritic cells produce IL-12 and direct the development of Th1 cells from naïve CD4+ T cells. J Immunol. 1995;154:5071–5079.
4. Szabo SJ, *et al*. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000;100:655-669.
5. Segal BM, Dwyer BK, Shevach EM. An interleukin (IL)-10/IL-12 immunoregulatory circuit controls susceptibility to autoimmune disease. J Exp. Med. 1998;187:537–546.
6. Cua DJ, *et al*. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature. 2003;421:744–748.
7. Oppmann B, *et al*. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;13:715–725.
8. Cua DJ, *et al*. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature. 2003;421:744-748.
9. Yen D, *et al*. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin. Invest. 2006;116:1310–1316.
10. Mannon PJ, *et al*. Anti-interleukin-12 antibody for active Crohn's disease. N. Engl. J Med. 2004;351:2069-2079.
11. Patel DD, Kuchroo VK. Th17 cell pathway in human immunity: Lessons from genetics and therapeutic interventions. Immunity. 2015;43:1040–1051.
12. Vignali DA, Kuchroo VK. IL-12 family cytokines: Immunological playmakers. Nat. Immunol. 2012;13:722–728.
13. Collison LW, *et al*. The composition and signaling of the IL-35 receptor are unconventional. Nat. Immunol. 2012;13:290–299.
14. Hunter CA, Kastelein R. Interleukin-27: balancing protective and pathological immunity. Immunity. 2012;37:960–969.
15. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. Lancet. 2018;390(10114):2769–78. DOI: 10.1016/S0140-6736(17)32448-0.
16. Kamada N, Hisamatsu T, Okamoto S, Chinen H, Kobayashi T, Sato T, *et al*. Unique CD14 intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-gamma axis. J Clin Invest. 2008;118(6):2269-80. DOI: 10.1172/JCI34610.
17. Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. J Clin Invest. 2006;116(5):1218–22. DOI: 10.1172/JCI28508
18. Bunte K, Beikler T. Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Inflammatory Diseases. Int J Mol Sci. 2019;20(14):3394–418. DOI: 10.3390/ijms20143394.
19. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, *et al*. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;13(5):715–25. DOI: 10.1016/S1074-7613(00)00070-4.
20. Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S, Jijon H. Th17 plasticity and its relevance to inflammatory bowel disease. J Autoimmun. 2018;87:38–49. DOI: 10.1016/j.jaut.2017.12.004.
21. Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nat. Immunol. 2016;17:765–774.
22. Bernink JH, *et al*. Interleukin-12 and -23 control plasticity of CD127+ group 1 and group 3 innate lymphoid cells in the intestinal lamina propria. Immunity. 2015;43:146–160.
23. Zhao J, Lu Q, Liu Y, Shi Z, Hu L, Zeng Z, *et al*. Th17 Cells in Inflammatory Bowel Disease: Cytokines, Plasticity, and Therapies. J Immunol Res. 2021, 8816041. DOI: 10.1155/2021/8816041
24. Galvez J. Role of Th17 Cells in the Pathogenesis of Human IBD. ISRN Inflamm. 2014;2014:928461. DOI: 10.1155/2014/928461
25. Moschen AR, Tilg H, Raine T. IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. Nat Rev Gastroenterol Hepatol. 2019;16(3):185–96. DOI: 10.1038/s41575-018-0084-8.
26. Neurath MF. IL-23 in inflammatory bowel diseases and colon cancer. Cytokine Growth Factor Rev. 2019;45:1-8. DOI: 10.1016/j.cytogfr. 2018.12.002
27. Fragoulis GE, Siebert S, McInnes IB. Therapeutic Targeting of IL-17 and IL-23 Cytokines in Immune-Mediated Diseases. Annu Rev Med. 2016;67:337–53. DOI: 10.1146/annurev-med-051914-021944
28. Panaccione R, Sandborn WJ, Gordon GL, Lee SD, Safdi A, Sedghi S, *et al*. Briakinumab for treatment of Crohn's disease: results of a randomized trial. Inflamm Bowel Dis. 2015;21(6):1329–40. DOI: 10.1097/MIB.
29. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, *et al*. Antiinterleukin-12 antibody for active Crohn's disease. N Engl J Med. 2004;351(20):2069–79. DOI: 10.1056/NEJMoa033402
30. Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, *et al*. Anti-TNF antibody-

induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-gammaexpressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut. 2014;63(4):567–77. DOI: 10.1136/gutjnl-2012-302853

31. Feagan BG, Panes J, Ferrante M, Kaser A, D'Haens GR, Sandborn WJ, *et al*. Risankizumab in patients with moderate to severe Crohn's disease: An openlabel extension study. Lancet Gastroenterol Hepatol. 2018;3(10):671–80. DOI: 10.1016/S2468-1253(18)30233-4

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