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# IL-23 in inflammatory bowel diseases and colon cancer

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ABSTRACT

Studies in recent years have identified a pivotal role of the cytokine IL-23 in the pathogenesis of inflammatory bowel diseases (IBD: Crohn´s disease, ulcerative colitis) and colitis-associated colon cancer. Genetic studies revealed that subgroups of IBD patients have single nucleotide polymorphisms in the IL-23R gene suggesting that IL-23R signaling affects disease susceptibility. Furthermore, increased production of IL-23 by macrophages, dendritic cells or granulocytes has been observed in various mouse models of colitis, colitis-associated cancer and IBD patients. Moreover, in several murine models of colitis, suppression of IL-12/IL-23 p40, IL-23 p19 or IL-23R function led to marked suppression of gut inflammation. This finding was associated with reduced activation of IL-23 target cells such as T helper 17 cells, innate lymphoid cells type 3, granulocytes and natural killer cells as well as with impaired production of proinflammatory cytokines. Based on these findings, targeting of IL-23 emerges as important concept for suppression of gut inflammation and inflammation-associated cancer growth. Consistently, neutralizing antibodies against IL-12/IL-23 p40 and IL-23 p19 have been successfully used in clinical trials for therapy of Crohn´s disease and pilot studies in ulcerative colitis are ongoing. These findings underline the crucial regulatory role of IL-23 in chronic intestinal inflammation and colitis-associated cancer and indicate that therapeutic strategies aiming at IL-23 blockade may be of key relevance for future therapy of IBD patients.

## 1. IL-23 and IL-23 receptor signaling

The cytokine IL-23 was discovered in 2000 when a novel p19 protein was described that interacts with the p40 protein subunit of IL-12 to form a p19/p40 heterodimer [1]. IL-23 belongs to the IL-12 cytokine family together with IL-12 p35/p40, IL-27 EBI3/p28 and IL-35 EBI3/p35. Additional studies revealed that IL-23 binds to a specific receptor via its N-terminal immunoglobulin domain [2]. This IL-23 receptor is composed of a common subunit, IL-12Rβ1, and a second protein required for IL-23 signaling, denoted IL-23Rα [1,3,4]. While the former protein is also responsible for IL-12 p35/p40 signaling, the use of the IL-23Rα chain is restricted to IL-23 signaling. Upon IL-23 binding to its receptor the Janus kinases JAK2 and Tyk2 become activated followed by activation and nuclear translocation of the transcription factors signal transducer and activator of transcription 3 (STAT3) and 4 (STAT4) [1,5]. In contrast, IL-12R signaling in naïve T cells induces STAT4 rather than STAT3 activation.

IL-23 is produced by various immune cells such as dendritic cells and macrophages upon Toll-like receptor signaling in tissues [1,6,7]. Additionally, in the gut, several pathways have been delineated that suppress IL-23 function. For instance, intestinal regulatory T cells (Treg) may engage MHC class II molecules on CX3CR1 + macrophages via LAG3, an immune checkpoint receptor, to impair IL-23 production [8,9]. Moreover, Vitamin D downregulated IL-23R expression on innate lymphoid cells type 3 and reduced IL-23R signaling [10]. In addition to antigen-presenting cells, tissue-infiltrating neutrophils have been identified as a potential source of IL-23 production [7].

Functional studies identified specific functions of IL-23 that partially differ from IL-12 p35/p40. While IL-12 preferentially acts on naïve T cells, IL-23 mainly activates memory T cells expressing the IL-23 receptor. Consistently, IL-23 was capable to induce strong proliferation of both murine and human memory T cells [1,4]. Memory T cells expressing the IL-23 receptor produce Th17 cytokines such as IL-17 A, IL-17 F and IL-22 indicating that IL-23 is a key factor perpetuating Th17 cell activation and cytokine production [11]. These effects of IL-23 on Th17 cytokine production could be enhanced by prostaglandin-E2 or IL-1beta [12]. In addition to T cells, neutrophils may respond to IL-23 stimulation by upregulating IL-23 receptor expression and

*Abbreviations:* CD, crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; CRC, colorectal cancer

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activation of the transcription factor retinoid acid receptor-related orphan receptor γ t (RORγt) and aryl-hydrocarbon receptor (Ahr). Such stimulation finally led to neutrophil activation and IL-23-mediated induction of neutrophil IL-17 and IL-22 production [13].

Subsequent studies focusing on the function of IL-23 showed that this cytokine regulates both innate and adaptive immune signals in tissue homeostasis and various disorders. Moreover, ubiquitous transgenic expression of the IL-23 p19 subunit caused multiorgan inflammation and premature death in mice indicating an important function of IL-23 as driver of inflammatory processes [14]. Consistently, IL-23 has been implicated in the pathogenesis of chronic inflammatory disorders such as psoriasis, psoriatic arthritis and inflammatory bowel diseases and drugs targeting IL-23 p19 have been used in clinical studies for these disorders [15]. In this review, we will focus on the role of IL-23 in intestinal homeostasis and inflammatory bowel diseases.

## 2. IL-23 in intestinal homeostasis

In healthy mice, high constitutive IL-23 p19 production was noted in the small bowel with particularly high expression in the terminal ileum. This marked constitutive expression was associated with high expression of p40 mRNA as well as p40 and IL-23 p19/p40 proteins [16]. The cells constitutively producing IL-12 p40 were identified as CD8alpha and CD11b double-negative CD11c + lamina propria dendritic cells that represent a major cell population in the lamina propria of the small intestine, but not in the colon. The preferential production of IL-23 in the distal small bowel creates a specific local cytokine environment that creates a hotspot for IL-23 sensitive target cells in this area. As IL-23 is preferentially produced under homeostatic conditions in the small intestine, Th17 cells are present in this area where they may acquire a regulatory phenotype with in vitro and in vivo immunosuppressive properties (regulatory Th17 cells) [17]. Such regulatory Th17 cells may produce anti-inflammatory cytokines such as IL-10 and TGF-beta that are known to counteract mucosal inflammation [18,19]. Additionally, intestinal epithelial cells (IECs) can express the IL-23 receptor under homeostatic conditions and may respond to IL-23 stimulation with production of antimicrobial peptides and IL-22 that support intestinal barrier function [20]. Consistently, mice deficient in IL-23R expression in intestinal epithelial cells (Il23R(ΔIEC)) were found to exhibit reduced Reg3b expression and had lower IL-22 levels and a disturbed colonic microflora with an expansion of flagellated bacteria. Therefore, IL-23 production may contribute to mucosal homeostasis by acting on specific intestinal target cells carrying the IL-23R.

Foxp3$^+$ regulatory T cells (Treg cells) have been recently shown to control intestinal IL-23 production via latent activation gene-3 (LAG-3), an immune checkpoint receptor-expressed on the surface of Treg cells. Interaction between LAG-3 and MHC class II caused immunosuppression of CX3CR1$^+$ tissue-resident macrophages and prevented colitis by innate lymphoid cells (ILCs) type 3. Such ILC3 belong to the lymphoid lineage but lack T cell receptors on their surface and may produce cytokines such as IL-17A and IL-22. Thus, these findings indicate that gut homeostasis is based on local communication between Treg cells and resident CX3CR1$^+$ macrophages that controls intestinal IL-23 production and activation of ILC3 [8,9].

## 3. IL-23 in rodent models of inflammatory bowel diseases

Studies in recent years revealed elevated levels of IL-23 in models of experimental colitis, including DSS colitis, TNBS colitis, Helicobacter-hepaticus colitis and T cell transfer colitis [21–24], consistent with the idea that IL-23 may play an important role in the pathogenesis of colitis. IL-23 was mainly produced by CD11c + monocytes and macrophages upon microbial stimulation (e.g. LPS, heat-killed bacteria) [24,25]. LPS-induced IL-23 production by macrophages could be suppressed by IFN-gamma [26]. Functional studies identified ILCs, T lymphocytes and hematopoietic stem and progenitor cells (HPSC) as major targets of IL-23-driven gut inflammation [27]. These findings encouraged studies on the effects of neutralizing IL-23 in experimental colitis in vivo.

Before the discovery of IL-23, studies used neutralizing antibodies against the p40 subunit of IL-12 that are now known to block IL-12 and IL-23 simultaneously. P40 blockers were found to be very effective in suppressing activity of experimental colitis in various mouse models. For instance, in the murine TNBS model, antibodies targeting p40 effectively suppressed mucosal inflammation and proinflammatory cytokine production [28]. Although these data indicated efficacy of suppressing IL-12 and IL-23 in experimental colitis, the functional relevance of the individual cytokines remained to be determined, however [29]. In this context, Imamura et al. [30] compared the efficacy of neutralizing antibodies against an IL-23-specific receptor subunit with neutralizing anti-IL-12/IL-23 p40 antibodies in T cell transfer colitis. Both antibodies caused comparable suppression of mucosal inflammation in experimental colitis suggesting that IL-23 rather than IL-12 is a crucial driver of transfer colitis. Similarly, studies in p19, p35 and p40-deficient mice showed that Helicobacter hepaticus-triggered T cell-dependent colitis is triggered by IL-23 rather than IL-12 [31]. Furthermore, Yen et al. [22] noted that the absence of p19 suppressed colitis in IL-10 knockout mice, while p35 deficiency had little or no effect. In addition, Cox and coworkers observed reduced DSS colitis activity in p19 and IL-23R knockout mice as compared to wild-type mice [32]. Finally, Uhlig et al. [33] found that innate immune cell-mediated colitis induced by agonistic CD40 antibody treatment in T and B cell-deficient mice was suppressed by p19 blockade. In this model, IL-23 regulated activity of intestinal inflammation in colitis, while IL-12 controlled wasting disease and serum cytokine production but not mucosal immunopathology.

In addition to monoclonal antibodies, various groups have tested alternative concepts to suppress IL-23 expression and function. In this regard, andrographolide, the main active component of the plant *Andrographis paniculata (Kalmegh),* suppressed IL-23 production and gut inflammation in experimental colitis as well as mucosal levels of RORgammat, pSTAT3 and Th17 cytokines [34]. Similarly, Bastaki et al. [35] tested the protective effects of turmeric (Curcuma longa, CL) on acetic acid-induced colitis in rats. This treatment reduced both MPO and IL-23 levels in the colonic mucosa and improved signs of colitis activity. Other options might consist of the generation of bacteria suppressing IL-23 expression or producing IL-23 blockers locally in the inflamed gut in colitis. In this context, Chen et al. observed that the administration of *Lactobacillus acidophilus* suppressed IL-23 and Th17 cytokine production in experimental DSS colitis [36]. Moreover, another group recently generated a recombinant *Lactococcus lactis* strain that produces IL-23-specific protein blockers, denoted ILP binding proteins [37]. Such proteins have been developed to suppress the binding of IL-23 to its receptor and might be used in the future for topical treatment of IL-23-dependent colitis forms. Moreover, a recent study [38] engineered lactic acid bacteria (Lb. salivarius) with the ability to simultaneously bind to IL-17 A, IL-23 and TNF. Accordingly, three different cytokine-binding non-Ig scaffolds were expressed in L. lactis and used in cell culture to suppress the activity of these cytokines. Additional studies [39] showed that mouse p40 peptide-based vaccines may prevent TNBS-induced murine colitis. Specifically, the p40 vaccine induced high antibody levels to IL-12 and IL-23 and thereby reduced intestinal inflammation and fibrosis. Moreover, such therapy downregulated proinflammatory cytokine production in colonic tissues. Another group developed a p19 peptide-based vaccine for colitis therapy [40]. Treatment of mice with TNBS colitis with this vaccine led to suppression of IL-23 production and colitis activity suggesting that vaccines might be used to target IL-23 function in inflammatory bowel diseases (IBD).

In contrast to the above situations where IL-23 plays a key pathogenic role in experimental colitis, a protective role of IL-23 in gut inflammation has been noted in specific circumstances. For instance, C57Bl6 LacZ knockin mice deficient for IL-23 p19 were highly

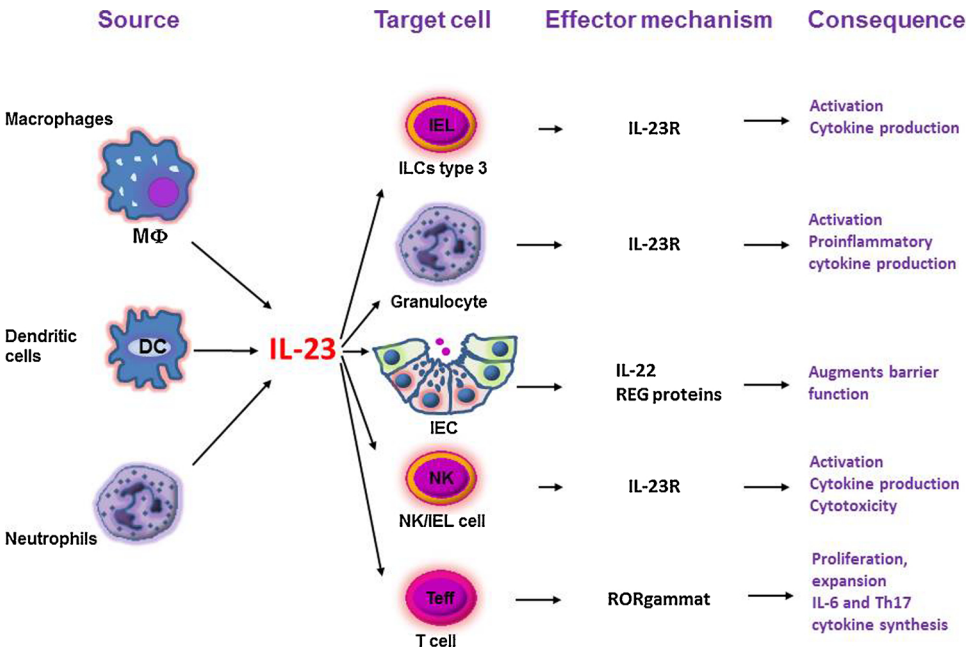


**Fig. 1.** Source of IL-23, IL-23 targets and consequences of IL-23R signaling in gut inflammation. IL-23 in colitis is produced by various immune cell types and exerts its pleiotropic effects via various target cells (Innate lymphoid cells (ILC), intraepithelial lymphocytes (IEL), natural killer (NK) cells, T cells, intestinal epithelial cells (IECs) and granulocytes). The effects of IL-23 signaling on these target cells are highlighted.

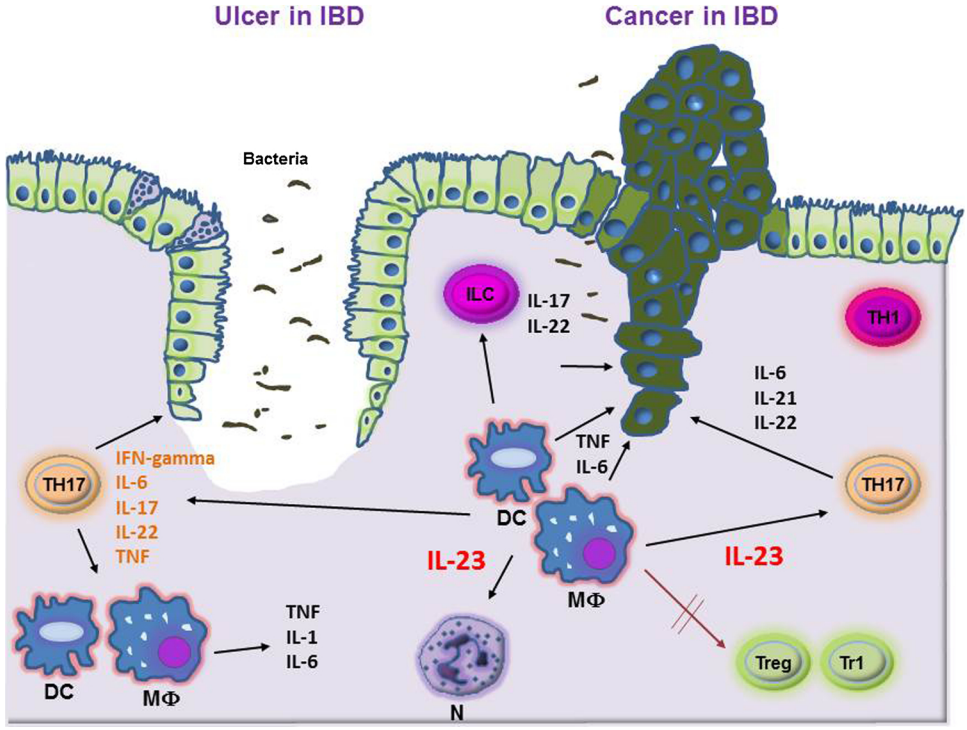


**Fig. 2.** A key regulatory role of IL-23 in experimental colitis and IBD. IL-23 in IBD and experimental colitis is mainly produced by dendritic cells (DC) and macrophages (MP). In paediatric IBD, granulocytes have been identified as another key source of IL-23 production. IL-23 has various target cells in the mucosa including T lymphocytes subsets, innate lymphoid cells and granulocytes, and thereby may promote mucosal inflammation..

susceptible for the development of experimental T cell-mediated TNBS colitis and showed augmented colitis activity compared to wild-type controls [23]. Mechanistic studies revealed that dendritic cells from p19-deficient mice produce elevated levels of IL-12 p35/p40 in the absence of IL-23 p19. The functional relevance of this observation was underlined by the finding that in vivo blockade of IL-12 in IL-23-deficient mice rescued mice from augmented colitis activity. These data indicated cross-regulation and suppression of IL-12 expression by IL-23 in dendritic cells as protective regulatory pathway in colitis. Other examples of a protective role of IL-23 in colitis comprise experiments in T cell transfer colitis in which mice deficient in IL-23R showed augmented colitis activity [41] and studies in DSS colitis in which mice with deficient IL-23R expression in intestinal epithelial cells (Il23R (ΔIEC)) showed augmented mucosal inflammation [20,32]. Further studies revealed impaired mucosal IL-22 levels in the latter mice and showed that administration of IL-22-Fc or Reg3b rescues DSS-treated Il23R(ΔIEC) mice. Effects of Reg3b in this context were mediated by induction of neutrophil-dependent IL-22 production. Thus, IL-23R signaling in IECs may control barrier-protective and anti-inflammatory immune pathways in experimental colitis (Fig. 1).

## 4. Functional role of IL-23 in experimental colitis

The above studies highlighted a pivotal proinflammatory role of IL-23 in driving mucosal inflammation in most murine models of colitis. However, the effect of IL-23 or IL-23R blockade in experimental colitis

could not be explained by IL-17 A neutralization, as IL-17 A or IL-17RA blockade had no protective effect on colitis activity or caused even aggravated mucosal inflammation in various models of colitis [42–45]. Subsequent functional studies showed that IL-17 A regulates epithelial tight junction proteins such as occludin and thereby strengthens barrier function. Conversely, suppression of IL-17 A function caused impaired barrier function and led to exacerbation of colitis activity. Gut protective IL-17 A was produced by gamma/delta T cells in the colonic lamina propria and this production was IL-23 independent [44]. Indeed, IL-23 blockade did not affect IL-17 A production by gamma/delta T cells.

As the above findings indicated that the protective effects of IL-23 blockade are independent from IL-17 A, additional studies analyzed further proinflammatory effects of IL-23 in colitis. These studies revealed that IL-23 drives intestinal T cell proliferation, promotes effector T cell accumulation and enhances the emergence of polyfunctional Th17 cell populations (Figs. 1–2). Such cells may produce simultaneously IL-17A and IFN-gamma or GM-CSF, IL-17 A plus IFN-gamma [46]. While IFN-gamma production by T cells may augment proliferation of haematopoietic cells in colitis, GM-CSF from these cells has been suggested to induce accumulation of neutrophils and monocytes in the colon, causing local inflammation by producing proinflammatory cytokines such as TNF or IL-1. In several models of T cell-mediated colitis, p19- or anti-IL-23R antibody treatment as well as p19 deficiency reduced production of IL-6 [22,30] suggesting that IL-23 signaling controls IL-6 production in addition to the Th17 cytokines IL-17 A and IL-22. Nevertheless, the effects of IL-23 on the Th17 cell lineage appear to be of key relevance, as targeting of RORgammat suppressed Th17 cytokine production and mucosal inflammation in T cell transfer colitis [45,47].

Activation of IL-23R signaling suppressed the differentiation or activation of Foxp3$^+$ Treg cells and IL-10-producing Tr1 cells indicating that IL-23 affects the balance between pro- and anti-inflammatory T cell subsets in colitis (Fig. 2). In addition, in a murine model of colitis mediated by innate immune cells (anti-CD40-treated Rag2$^{-/-}$ mice) [48], anti-IL-23R antibody treatment regulated expression of pro- and anti-inflammatory genes such as S100A8, S100A9, regenerating protein 3β (REG), REG3γ, lipocalin 2 (LCN2), and macrophage migration inhibitory factor (MIF). Finally, the proinflammatory effects of IL-23 in T cell transfer colitis and *H. hepaticus*-induced colitis were dependent on hematopoietic stem cells (HSCs) which expanded via GM-CSF [27]. These findings indicated that hematopoietic stem and progenitor cells represent a major target of the IL-23-driven inflammatory axis in colitis. Finally, innate lymphoid cells (ILCs) have been identified as targets of IL-23 in colitis [49]. In fact, IL-23 induced the expansion of ILCs and their production of IL-17 A and IFN-gamma and these cells expressed Thy1 and Sca-1 suggesting that an IL-23 driven ILC population controls activity of experimental colitis. Consistently, Eken et al. [41] found that IL-23R signaling in ILCs promotes colitis development in experimental anti-CD40 antibody-induced acute innate colitis in Rag1 knockout mice. This pathogenic function of IL-23R signaling was mediated via IL-22, as neutralization of IL-22 protected mice from colitis and administration of IL-22 to IL-23R-deficient animals restored disease activity.

Further studies aimed at the identification of inducers of IL-23 and IL-23R expression in experimental colitis. In DSS colitis, it was found that the micro RNA miR-155 controls expression of Est-1 with subsequent regulation of IL-17 and IL-23 levels [50]. Consistently, lentiviral overexpression of miR-155 caused augmented DSS colitis activity associated with decreased Est-1 levels and elevated IL-23-mediated Th17 activation. Another group suggested that the micro RNA miR-29 downregulates IL-23 by targeting IL-12p40 directly and IL-23p19 indirectly via suppression of ATF2 [51]. In miR-29-deficient mice, augmented DSS colitis was noted that was accompanied by elevated IL-23 and Th17 cytokine levels. Additional experiments demonstrated that the G protein-coupled receptor Gpr109a suppresses microbiota-dependent IL-23 production by colonic dendritic cells in colitis and thereby activation of ILC3 [52]. Consistently, *Gpr109a*$^{-/-}$*Rag1*$^{-/-}$ mice exhibited spontaneous colonic inflammation with elevated numbers of IL-17-producing Rorγt$^+$ ILCs and this phenotype could be prevented by genetic inactivation of Rorγt. Moreover, the Gpr109a agonist Niacin suppressed IL-23-dependent ILC3 activation number in a Gpr109a-dependent manner underlining the functional relevance of the Gpr109-a pathway for IL-23 activation of ILCs in colitis. Another study [53] revealed that the endogenous inflammatory protein HMGB1 promoted dendritic cells via TLR2/4 signaling to produce IL-23 during colitis followed by activation ILC3s and production of IL-17 and IL-22. Consistently, anti-HMGB1 antibody-treated mice had reduced cytokine levels and ameliorated experimental colitis. Finally, the Janus kinase Tyk2 regulated IL-12 and IL-23 cytokine levels in experimental colitis and Tyk2 deficiency protected from DSS and TNBS colitis [54].

IL-23R levels in transfer colitis were dependent on the AP-1 transcription factor JunB that additionally controlled levels of RORγt by facilitating DNA binding of Batf at the Rorc locus [55]. Functionally, T lymphocytes lacking JunB failed to induce IL-23- and Th17-mediated experimental colitis highlighting the relevance of JunB for the IL-23/Th17 pathway. Further studies demonstrated that the transcription factor T-bet suppressed IL-23R expression in colitis [56]. This concept was underlined by the finding that the absence of T-bet causes unrestrained Th17 cell differentiation and activation characterized by high amounts of IL-17 A and IL-22.

## 5. IL-23 in IBD-associated colon cancer

Chronic inflammatory disorders such as IBD may predispose to cancer development. In the context of IBD, various studies in recent years have highlighted the fact that chronic intestinal inflammation in these patients may lead to development of colorectal cancer (CRC). Key risk factors for CRC development in IBD comprise the number of flares and the presence of primary sclerosing cholangitis [57–59]. Moreover, the extent of the disease is an important factor regulating the incidence of CRC where patients with inflammation of the entire colon (pancolitis) have a higher risk than patients with limited colitis (e.g. proctitis).

Several studies have looked at the molecular mechanisms driving development of colitis-associated colon cancer. These studies have highlighted a key role of proinflammatory cytokines such as IL-6, that are released during gut inflammation, for cancer growth by activation of intracellular transcription factors such as NF-kappaB and STAT-3 [60,61] (Fig. 2). Additional studies revealed that IL-23 production in the mucosa was increased in colitis-associated neoplasia [62]. Furthermore, expression of IL-23 correlated with levels of the transcription factor Batf, a known inducer of Th17 cells. Subsequent functional studies in Batf-deficient mice demonstrated a crucial role of Batf for development of colitis-associated colon tumors. Tumor growth in Batf-deficient mice was induced by treatment with hyper-IL-6 (designer fusion protein of IL-6 and sIL-6R) [62] indicating that Batf and IL-23 mediate their effects at least in part by inducing IL-6 production and tumor growth.

Another study [63] revealed that the NADPH oxidase protein p47phox regulates IL-23 production during development of experimental colitis-associated neoplasias. Deficiency of p47phox in mice resulted in impaired IL-23 expression and protection from colitis-associated tumors. While reconstitution of wild-type mice with p19-deficient bone marrow protected from colon cancer, transplantation of wild-type bone marrow into p19 knockout mice led to elevated susceptibility to tumor growth. These findings highlighted an important role for p47phox in driving IL-23 production and tumor growth in experimental colitis.

In addition to a role for IL-23 in colitis-associated colon cancer, recent studies have also noted a regulatory function of this cytokine in carcinogenesis of sporadic colorectal cancer. In fact, Grivennikov et al. [64] found that IL-23 signalling promotes tumour growth and progression in colorectal tumors via effects on a protumoural Th17 cytokine signature. Tumour-associated myeloid cells were found to produce

IL-23 in areas with barrier defects and translocation of microflora into the mucosa. These effects were also noted in early tumors and adenomas of the colon suggesting that the IL-23 signaling pathway is an important regulator of early carcinogenesis and tumor growth.

## 6. IL-23 and IL-23R in human IBD

### 6.1. -Genetic studies

Various studies in recent years have addressed the expression and functional role of IL-23 in patients with IBD. Furthermore, genetic variants affecting IL-23 function and IL-23R have been studied [65,66]. A pilot study in 547 patients [65] identified an association between variants of the IL23R gene on chromosome 1p31 and ileal Crohn´s disease (CD). Specifically, an uncommon coding variant (p.Arg381Gln) conferred strong protection against this disease and additional non-coding IL23R variants were independently associated with the risk for development of CD. Subsequent replication studies confirmed IL23R associations in independent cohorts of patients with IBD suggesting that the risk for development of both CD and ulcerative colitis (UC) is affected by IL-23R variants [65–68]. Consistently, a large case-control study in 727 IBD patients revealed that development of CD is associated with the IL-23R variant G149R, while UC patients had an association with G149R and Q3H. Additionally, an association with IL-17 A variants and UC was noted. Another study [69] found that the protective IL-23R R381Q variant in exon 9 was associated with CD in children. This variant may lead to decreased IL-23-dependent IL-17 production and may impair STAT3 and Th17 activation in IBD thereby explaining the observed protective effect of this variant. Further studies using a candidate gene approach noted that single nucleotide polymorphisms (SNPs) leading to genetically determined high activity of the IL-23/IL-17 pathway were associated with increased risk of both CD and UC [70]. Moreover, SNPs causing genetically determined high activity of TLR1 and TLR5 were associated with an increased risk of IBD suggesting that microbial drivers of IL-23 expression may additionally modulate the risk for chronic intestinal inflammation.

In spite of the large number of studies showing an association of IL-23R SNPs with the risk of IBD in independent patient cohorts, it should be noted that some studies did not detect associations between IL-23R polymorphisms and the risk for IBD development. For instance, a study from Iran in 85 UC patients [71] showed no associations between various IL-23R polymorphisms and UC. Thus, the contribution of IL-23R variants to IBD development may show regional differences. Nevertheless, there is substantial evidence from various genetic studies that IL-23R variant play an important role in the pathogenesis of IBD highlighting the need to study the expression and function of the IL-23/IL-23R signaling pathway in these disorders.

### 6.2. -Expression of IL-23 and IL-23R

Several studies addressed the levels of IL-23 in the serum of IBD patients. A study by Gheita et al. [72] noted a significant, almost two-fold increase of IL-23 serum levels in IBD patients compared to control patients with higher average levels in CD versus UC patients. Particularly high serum levels were observed in patients with peripheral or axial arthritis suggesting that IL-23 might be involved in controlling the development of arthritis in IBD. Another study by Rafa and coworkers [73] revealed a significant positive correlation between IL-23 serum levels and nitric oxide (NO) levels in IBD, particularly in CD patients, consistent with a proinflammatory role of IL-23 in IBD. Finally, further studies detected higher serum levels of IL-23 in UC compared to control subjects [74–76]. Additionally, the serum levels of IL-23 showed a positive correlation with the disease severity in UC and the reduced ratio of Treg/Th17 cells in peripheral blood mononuclear cells. Collectively, these findings showed augmented IL-23 serum levels in IBD patients.

To study the production of IL-23 by cells in the lamina propria, several groups have analyzed IL-23 mRNA and protein expression in intestinal samples from IBD patients. Expression of IL-23p19 mRNA was increased in inflamed mucosa of CD compared with UC and healthy controls [77]. Another study found upregulated IL-23 p19 mRNA expression in IBD with correlation between p19 and IL-17 A levels in UC and p19 and IFN-gamma levels in CD [78]. Furthermore, treatment of CD patients with neutralizing anti-TNF antibodies resulted in further induction of IL-23 mRNA expression in the intestine of patients with lack of clinical response to anti-TNF therapy [79] suggesting that IL-23 may cause molecular resistance to such therapy.

Subsequent studies using immunohistochemistry revealed that IL-23 p19 expressing cells were mainly CD68 expressing macrophages or dendritic cells. Consistently, myeloid dendritic cells from CD patients produced higher levels of IL-23 and lower levels of IL-10 than controls when stimulated via Toll-like receptors and bacterial products [80]. Elevated production of IL-12 p40 was particularly noted by dendritic cells from CD patients with NOD2 polymorphisms in response to adherent invasive E. coli [51]. Furthermore, Kamada et al. [81] demonstrated that CD macrophages expressing CD14 produce higher amounts of IL-23 than those of UC or control patients. Additionally, Fuss et al. [82] found that IL-23 production was increased by cultured lamina propria macrophages from CD patients as compared to controls. In these cells, IL-23 production can be markedly augmented by commensal bacteria stimulation [83] suggesting that microbial stimuli in the lamina propria may be crucial inducers of IL-23 production in IBD. Furthermore, macrophage-dependent production of IL-23 in IBD appears to be dependent on TNF [84]. In fact, it was found that the anti-TNF antibodies infliximab and adalimumab form complexes with soluble TNF with consecutive binding of such complexes to the Fc-gamma receptor on macrophages thereby reducing mucosal IL-23 production in IBD.

In contrast to the above studies in adult patients that noted mainly dendritic cells and macrophages as source of IL-23 in IBD, another study in paediatric patients found that tissue-infiltrating neutrophils were the main source of IL-23 [85]. Specifically, colonic neutrophils expressing C-X-C motif (CXC)R1 and CXCR2, known receptors for the CXC ligand 8 (CXCL8) chemokine family, produced IL-23 in IBD patients. These findings suggested that the cellular source of IL-23 in IBD may depend on the duration or the stage of the disease.

Several studies analyzed the expression of IL-23R and Th17-associated transcription factors in IBD: Kobayashi et al. [78] and Liu et al. [77] detected increased expression of the IL-23R in lamina propria T cells in IBD. Furthermore, Schmitt et al. [79] noted elevated levels of IL-23R mRNA and IL-23R expressing lamina propria CD4 + T cells in non-responders to anti-TNF therapy in CD. Additional experiments indicated that the expression of the Th17-associated transcription factor RORC is augmented in CD and UC lamina propria $CD4^+$ T cells suggesting the presence of IL-23R driven Th17 cells in IBD. However, another study found that intestinal mRNA levels of the transcription factor Batf rather than RORgammat are increased together with IL-23 mRNA levels in UC but not in CD patients [62].

### 6.3. -Functional role of IL-23

Various studies in recent years have attempted to clarify the functional role of IL-23 in the pathogenesis of IBD. In this context, IL-23 has been identified as key activator of mucosal CD161 Th17 cells carrying the IL-23R. For instance, IL-23 stimulation of lamina propria T cells was shown to induce IL-17 production in UC [78] and CD patients [83] or to promote production of IFN-gamma, TNF and IL-17 A in IBD patients [77]. Effects of IL-23 stimulation in mucosal T cells could be augmented by tumor necrosis factor-like protein 1 A (TL1 A), a member of the TNF superfamily [83]. Additionally, in CD patients, IL-23-induced IFN-gamma production by T cells was found to further induce IL-23 levels indicating the presence of an IL-23/IFN-gamma feedback loop [81]. IL-23 stimulation resulted in increased expression of RORC in mucosal T

cells in IBD suggesting that this cytokine perpetuates and stabilizes local Th17 commitment. Finally, IL-23 has been shown to suppress production of IL-10 by lamina propria mononuclear cells and blockade of IL-23 resulted in higher IL-10 production [86]. This findings suggested that local overexpression of IL-23 suppresses the production of IL-10, which might contribute to reduced production of IgA and impaired barrier function in IBD patients.

A very recent study implicated the functional role of IL-23 in controlling clinical response to anti-TNF therapy in CD via specific effects on mucosal T cells [79]. While responders to anti-TNF therapy had comparable expression levels of IL-23R on mucosal T cells to non-responders prior to anti-TNF therapy, there was a significant upregulation of IL-23 p19 and IL-23R expression in anti-TNF non-responders during therapy. This finding was associated with an accumulation of apoptosis-resistant mucosal TNFR2 +IL23R + T cells that produced both Th1 and Th17 cytokines. Subsequent studies showed that anti-TNF-induced apoptosis of mucosal T cells is blocked by IL-23 leading to an expansion of IL-23R expressing mucosal T cells. This expansion was associated with molecular resistance to anti-TNF therapy in CD suggesting that IL-23 is a promising target in anti-TNF refractory patients.

Another target cell population for IL-23 in IBD consists of ILCs. In the inflamed intestine of CD patients, Geremia and coworkers [87] identified an increase of IL-23 responsive $CD127^{+}CD56^{-}$ ILCs, whereas no changes were noted in UC patients as compared to controls. This ILC population was characterized by augmented proinflammatory cytokine expression suggesting that IL-23 driven ILCs may contribute to intestinal inflammation in CD.

In addition to T cells and ILCs, NK cells and intraepithelial lymphocytes (IELs) were identified as cellular targets of IL-23 in IBD patients. Upon cell-to-cell contact with intestinal inflammatory macrophages NKp46(+) NK cells from patients with CD were activated via IL-23 and subsequently produced IFN-gamma suggesting that NK cells may produce proinflammatory cytokines in response to IL-23 stimulation [88]. Moreover, IL-23 stimulation was shown to promote IEL and NK cell activation and cytotoxicity in IBD patients [77] indicating a broad range of IL-23 target cells in chronic intestinal inflammation.

### 6.4. -Clinical targeting of IL-12/IL-23 p40 and IL-23 p19 in IBD

Based on the above studies suggesting a crucial role of IL-23 in IBD, strategies aiming at suppression of IL-23 function are of key interest (Fig. 3). Initial studies in CD patients were conducted with anti-p40 antibodies such as ABT874 or ustekinumab [89–91]. A pilot study in patients with active CD suggested clinical efficacy of ABT874 treatment, as a significant induction of response and remission rates were noted as compared to placebo therapy [89]. Such p40 neutralization suppressed local IL-12 and IL-23 levels simultaneously and reduced levels of proinflammatory cytokines in CD mucosa [82,89]. Subsequent studies using ustekinumab revealed that patients with moderate-to-severe CD had an increased rate of response to induction therapy with ustekinumab as compared placebo-treated patients. Furthermore, CD patients with an initial response to ustekinumab therapy showed significantly increased rates of response and remission with ustekinumab maintenance therapy [90,91]. Ustekinumab therapy was also effective in anti-TNF refractory patients as well as in patients with psoriasiform skin lesions or alopecia under anti-TNF therapy. In the latter context, Tillack et al. [92] treated CD patients with severe psoriasiform lesions and dermal Th1/Th17 cell infiltrates with ustekinumab and demonstrated remarkable effects of such therapy with suppression of skin lesions. Collectively, these results demonstrated that ustekinumab therapy is effective for treatment of active CD and anti-TNF-induced skin lesions. Initial results from phase 2 studies in UC suggested additional efficacy of ustekinumab therapy in this disease and subsequent phase 3 trials are under way (https://clinicaltrials.gov/ct2/show/NCT02407236).

Based on the clinical efficacy of IL-23 specific blockers in psoriasis, more recent studies evaluated the effects of IL-23 p19 blockade in CD [93,94]. A 12-week pilot phase 2 study demonstrated that the p19 blocker risankizumab is more effective than placebo for inducing clinical remission in patients with active CD [95]. Transcriptome-wide RNA-Seq profiling of mucosal samples at week 12 showed that risankizumab treatment suppresses the expression of various genes associated with the IL-23/IL-17 axis, Th1 immune pathways, innate immunity, and tissue turnover [96]. Extended induction treatment with risankizumab was also effective in increasing clinical response and remission rates in CD at week 26 [97]. In addition to risankizumab, a phase 2a trial studied the effects of another p19 blocker, denoted MEDI2070, in CD patients who had failed treatment with TNF blockers. This study demonstrated significant clinical improvement in CD patients 8 and 24 weeks after induction of therapy with MEDI2070 as compared to placebo therapy [98]. Therefore, selective blockade of IL-23 p19 emerges as attractive therapeutic approach in CD. Further studies on p19 blockade in both CD and UC patients are currently being conducted (e.g. with the p19 neutralizing antibodies risankizumab, brazikumab, mirikizumab, or guselkumab) and will define the future utility of anti-IL-23 therapy in IBD patients.

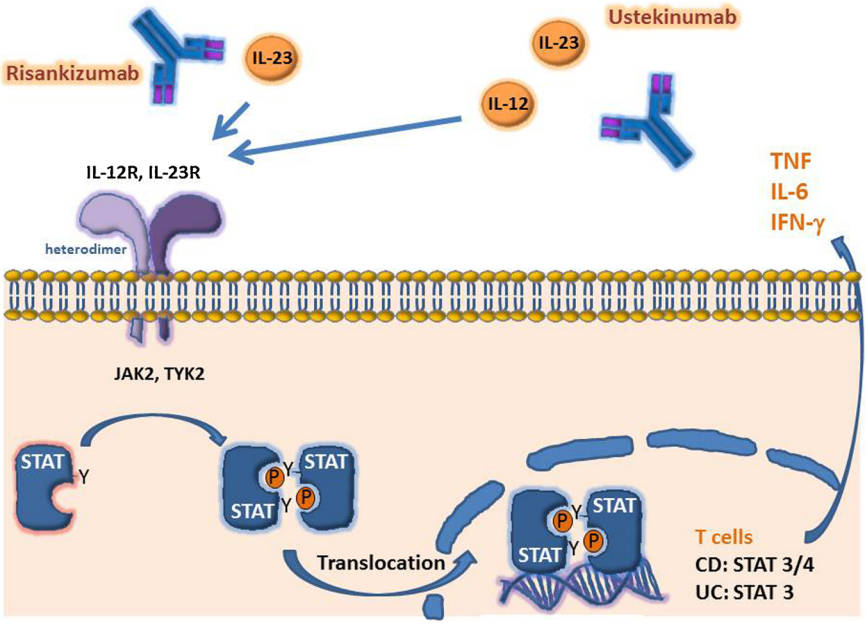


**Fig. 3.** Specific blockers of IL-12/IL-23 p40 (e.g. ustekinumab) and IL-23 p19 (e.g. risankizumab) have been used in patients with CD. These antibodies prevent binding of IL-12 and/or IL-23 to their specific receptors and subsequent activation of Jak2 and Tyk2 in immune cells. This finally leads to blockade of STAT activation and impaired production of proinflammatory cytokines. Modified according to ref. [19].

## 7. Outlook and summary

The above findings unequivocally demonstrate a pivotal role of the cytokine IL-23 in the pathogenesis of IBD and colitis-associated colon cancer. Genetic studies and functional assessment in murine model systems have indicated a crucial role of this cytokine in immunoregulation. Additionally, studies using patient cells have underlined the relevance of IL-23 targeting for suppression of immune cell activation and production of proinflammatory cytokines- Based on these findings, targeting of IL-23 emerges as important concept for suppression of gut inflammation and inflammation-associated tumors in IBD. Indeed, neutralizing antibodies against IL-12/IL-23 p40 (ustekinumab) have been approved for therapy in CD and clinical trials on IL-23 p19 specific blockers in IBD are ongoing. Thus, therapeutic strategies aiming at IL-23 blockade may be of key relevance for future therapy of IBD patients.

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