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Chapter 5

Interleukin 23 in IBD Pathogenesis

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Abstract

Interleukin-23 **(**IL-23) is a cytokine that belongs to the IL-12 cytokine family that is produced mainly by antigen-presenting cells. IL-23 receptor is expressed by various innate and adaptive immune cells, including group 3 innate lymphoid cells (ILC3), neutrophils, γδ T cells, Th17 and natural killer T (NKT) cells. IL-23 regulates various functions of the responding cells critical for host protective responses but is also implicated in many chronic inflammatory diseases including inflammatory bowel diseases (IBD). IL-23 receptor signaling components and downstream effector cytokines IL-17A/F, interferon-gamma (IFN-γ), IL-22, granulocyte macrophage colony–stimulating factor (GMCSF) have been shown to impact IBD-like disease development in various animal models; therapeutic approaches targeting the IL-23 pathway in IBD are in clinical trials. In this chapter, we attempt to review the literature on IL-23–mediated IBD pathogenesis. We did this by gathering the current information about the individual IL-23–producing and IL-23–responsive cells as to how they contribute to IBD pathology through various inflammatory mediators.

Keywords: IL-23, p19, Th17, ILC3

1. Introduction

1.1. IL-23 cytokine

Interleukin-23 (IL-23) is a heterodimeric cytokine that belongs to the IL-12 family cytokines and shares both ligand and receptor subunits with IL-12. IL-23 heterodimer is made up of p19 (IL-23A) and the shared beta chain, p40 (IL12β) subunit which also dimerizes with IL-12p35 and makes up IL-12 cytokine. Due to the shared use of p40, studies performed via the manipulation of p40 prior to the discovery of IL-23 suggested causality between many chronic inflammatory conditions and the IL-12/Th1 axis. With the genetic and immunologic

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studies that targeted individual subunits of IL-12 and IL-23 in mice, a critical causal role for IL-23 in inflammatory bowel disease (IBD) pathogenesis has been established.

1.2. General features of IL-23 protein structure

Human p19 is a four-α-helix protein with 70% similarity with its mouse ortholog. It is encoded by its gene located on chromosome 12q13.2 which is composed of four exons and three introns. p19 protein contains five cysteine residues and several O-glycosylation but no N-glycosylation sites. Human p40 gene, however, is located on chromosome 11q1.3. It is made up of eight exons and seven introns. p40 has homology with soluble class I cytokine receptor chains such as IL-6Rα, and it is composed of three domains (D1-3). p40 is N-glycosylated and can form homodimers. p19 protein by itself does not have any known biological role. Both p40 and p19 has to be produced within the same cell for the generation of biologically active IL-23 heterodimers [1]. The heterodimeric interaction between the p19 and p40 subunits is stabilized by a disulfide bond between p19 residue Cys54 and p40 Cys177 [2].

1.3. Cellular sources of IL-23

IL-23 is expressed and secreted by professional antigen-presenting cells (APCs), chiefly dendritic cells, macrophages and monocytes. Epithelial cells were also shown to contribute to IL-23 production. These include keratinocytes [3], intestinal epithelial cells [4] and glomerular podocytes (epithelial cells in the Bowman's capsule especially during nephrotoxic serum (NTS) nephritis (NTN)) [5]. Furthermore, human fibroblast-like synoviocytes (*ex vivo* and *in vivo*) and human colon subepithelial myofibroblasts were shown to produce IL-23p19 upon IL-1β and TNF-α all of which suggest that non-hematopoietic sources may also contribute to IL-23 production to some extent, given the right stimulation [6, 7].

Different subsets of DCs exist, defined by their developmental origin, tissue location and surface markers [8, 9]. Stimulation with select ligands induces IL-23 production by $CD11c^+$ conventional DCs, pDCs or *ex vivo*-generated BMDC (mice) to varying degrees. The exact source of IL-23 *in vivo* among DC subsets during steady state, infection or chronic inflammation has been queried in various reports and, it appears, may be context dependent. Conventional DCs (cDCs) rely on transcription factor Zbtb46 and include $CD8^+$, $CD4^+$, $CD4^-CD8^-$ subsets in the lymphoid organs, and Langerhans cells in the skin, and interstitial single positive $CD103^+$ or $CD11b^+$ DCs in the connective tissues; $CD11b^+CD103^+$, $CD11b^-CD103^+$, $CD11b^+CD103^-$ as well as DN DC subsets are present in the gut [10]. $CD11b^+$ $CD103^+$ DCs were shown to be dependent on Notch2 and IRF4, and during *Citrobacter rodentium* infection, this subset was reported to be the primary source of IL-23 [10–12]. $CD11b^-$ fraction of $CD103^+$ DCs, which relies on Batf3 was shown to be dispensable for *C. rodentium* immunity [12]. Others also reported $CD11b^+CD103^+$ population as the main IL-23 source upon exposure to TLR5 ligand flagellin [13]. In the lung, $CD11b^+$ but not $CD103^+$ DCs were reported to be the major IL-23 source [10].

Siddiqui et al. showed that, in the context of intestinal inflammation (during T-cell transfer colitis and anti-CD40-induced colitis), E-$cadherin^+$ $CD11b^+$ DCs increase, and these cells are potent IL-23 producers. Despite the expression of CD103 by E-$cadherin^+$ DCs in the steady

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state, during inflammation, the investigators reported loss of CD103 expression, and inflammatory E-cadherin^{+}CD11b^{+} DCs were proposed to develop from Gr-1^{+} monocyte precursors [14].

Besides the reports implicating CD103^{+} DCs' role in IL-23 production, another study by Longman et al., however, reported that CX3CR1^{+} phagocytes not CD103^{+} DCs are the main IL-23 producer in mice [15]. Also in humans, they showed that CX3CR1^{+}CD14^{+} monocyte/macrophages, rather than CD103^{+} DCs, produced more IL-23 upon various Toll-like receptors (TLR) ligands. These are in line with previous reports which showed elevated macrophages (CD14^{+} CD68^{+} also CD205^{+}) with increased IL-23 production in the intestines of IBD patients [16]. Similarly, in *Helicobacter hepaticus*/anti-IL-10R model of murine colitis, CD103^{+} DCs were shown to be dispensable and produced low amounts of IL-23; the major source of IL-23 was MHCII^{+} Ly6C^{+} monocytes, CXCR1High F4/80^{+} macrophages and CX3CR1intLy6C^{low} macrophages/DC population [17]. Thus, in summary, the results regarding the source of IL-23 are divergent; information regarding IL-23 production by different APC subsets in the human intestine is incomplete (**Figure 1**).

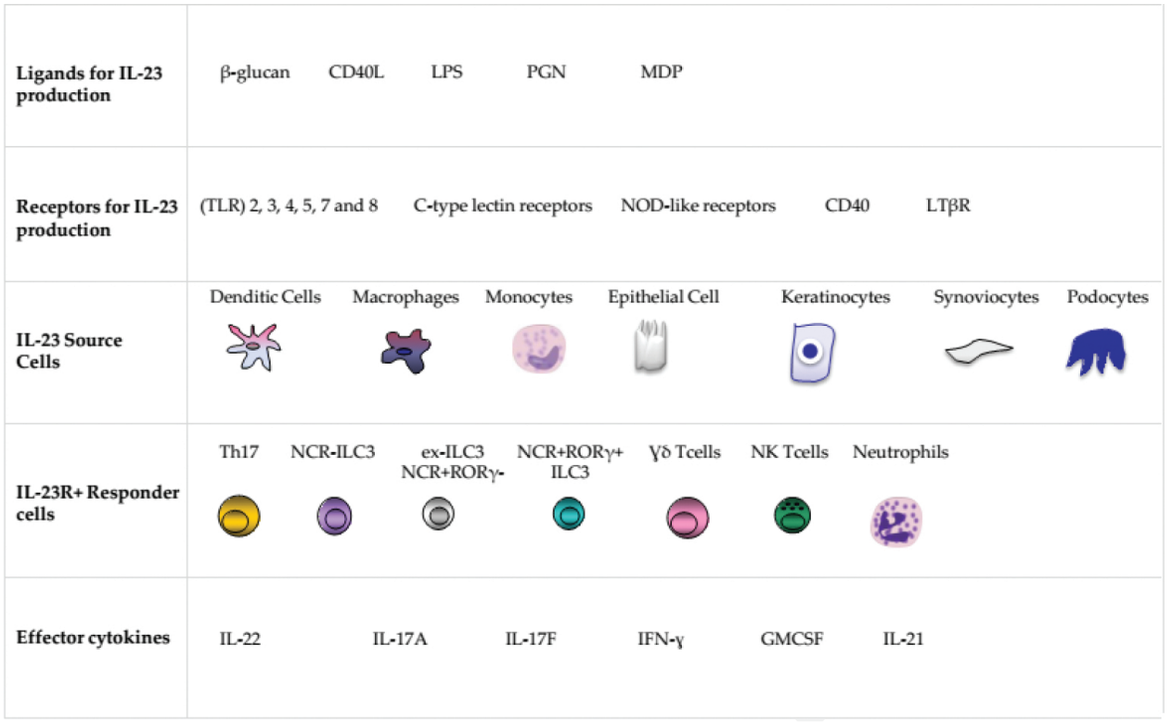


Figure 1. IL-23 inducers, producers and responders.

1.4. IL-23 stimulatory ligands

Microbiota (and pathogen-associated molecular patterns [PAMPs]) play an essential role in IL-23 production. As such, while IL-23 is constitutively expressed in the terminal ileum of SPF-housed mice, its expression is drastically reduced in the germ-free animals [18]. Pattern recognition receptors (PRR) link extracellular signals to p19 and p40 production [19,

20]. Stimulation of C-type lectin receptors, select Toll-like receptors (TLR), and CD40 by their corresponding ligands leads to IL-23 production [21]. β-glucan stimulation of APCs through C-type lectin receptor dectin-1 activates p19, p40 and p35 production (both IL-12 and IL-23) [22]. The ligand used here is curdlan, which is a pure β-glucan. β-glucan when combined with R848 (TLR7/8 ligand) or Pam2C (TLR2/6 ligand) also further increases IL-23 production [23]. TLR2 stimulation with peptidoglycan (PGN) alone, a gram-positive bacterial cell wall component, also induces preferential IL-23 production over IL-12 by DCs. LPS, a TLR4 ligand, can also induce IL-23p19 production, though not as potent as TLR2 ligand PGN [24]. The involvement of TLR4 in IL-23 production was shown using WT and LPS-deficient bacterial strains [25]. Bacterial nucleotide oligomerization domain 2 (NOD2)-ligand muramyl dipetide (MDP) can synergize with TLR2, TLR3, TLR4 ligands (PGN, dsRNA, LPS, respectively) and induces IL-23 production [26]. MDP can also synergize with TLR7/8 ligand R848 to promote IL-23 production [23]. TLR5 ligand flagellin also promotes IL-23 production [13]. It must be noted that DC type used in the abovementioned studies (BMDC, moDC or $CD11c^+$) is important and may result in differential degrees of IL-23 expression in response to abovementioned ligands.

CD40L stimulation of intestinal DCs preferentially stimulates IL-23 production and this induction is much higher compared with moDCs or splenic DCs [27]. Thus, not only microbial signals, but also those coming from T cells can regulate IL-23 production.

Prostaglandin E2 (PGE2), by engaging the G-protein coupled receptors E prostanoid 2 and EP4, also stimulates IL-23 production [28]. Similarly, extracellular nucleotides can signal through purinergic P2Y receptor for IL-23 production [29].

Non-hematopoietic cells also can express IL-23p19. IL-1β and TNF-α stimulation induces IL-23p19 production by synoviocytes [6]. LPS stimulation of TLR4 or ligation of agonistic antibody to LTβR in the colon epithelial cell line stimulates IL-23 production [4]. Similarly, colon epithelial cells, *in situ*, were shown to produce IL-23 in an LTβR-dependent fashion.

1.5. IL-23 gene expression

IL-23 expression is induced through various MAPKs including p38, JNK and ERK [30], as well as NFκB. The p40 gene expression is regulated at the transcriptional level by binding of NFκB, CCAAT/enhancer-binding protein (C/EBP), ets-2, PU.1, IRF1, IRF2, IRF5, IRF8 and activator protein 1 (AP-1) to the promoter region of p40 [31–34] upon stimulation with various ligands. The murine and human p19 promoter was also shown to contain three NFκB binding sites [30]. Two of these binding sites have been shown to be involved in TLR-mediated activation of p19 transcription. Smad3, AP-1 and activating transcription factor-2 (ATF-2) transcription factors were also shown to bind p19 promoter and positively regulate IL-23p19 expression. There are two binding sites for 2 interferon regulatory factor (IRF) genes, IRF3 and IRF7 in both human and murine p19 promoters. IRF3 was reported to be a positive regulator of p19 expression, and thus, its absence was shown to lead to the downregulation of p19 [35].

1.6. IL-23 responsive cells

IL-23 receptor is expressed by both innate and adaptive immune cells. Group 3 ILCs (ILC3), dendritic cells, macrophages/monocytes, γδ T cells, and more recently, neutrophils were among the innate cells that were shown to respond to IL-23. Among IL-23R$^+$ adaptive immune cells are Th17, Th22 and some iNKT cells [36].

1.6.1. Th17 cells

The most studied IL-23 responsive cells are Th17 cells. IL-23 is needed for the maintenance/maturation and expansion of Th17 cells in humans and mice and is dispensable for their initial differentiation from naïve CD4$^+$ T cells. The maintenance of Th17 identity relies on IL-23-mediated induction of *Rorc, Il23r* and *Il17* expression [19]. Th17 cells also require IL-23 to fully acquire a pathogenic character [37]. In fact, several laboratories showed that Th17 cells are very weak inducers of EAE, a mouse model of human MS, unless they are generated in the presence of IL-23 or they express IL-23R. IL-23 exposure programs Th17 cells transcriptionally to have a unique effector cytokine profile compared to nonpathogenic Th17 cells which are not exposed to IL-23. Unlike nonpathogenic Th17 cells, which express only IL-17, IL-23-activated pathogenic Th17 cells express IFN-γ and GMCSF in addition to the IL-17. Various lines of evidence suggest that Th17 cells, and hence IL-23R signaling, is critical for the development of chronic inflammatory conditions such as Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis (RA) and systemic lupus erythematous (SLE) in addition to MS.

1.6.2. Group 3 ILCs

Rorγt$^+$ Group 3 innate lymphoid cells (ILC3s) are a heterogeneous population of cells which have an irreplaceable function in protective immunity against extracellular pathogens in the gastrointestinal mucosa. ILC3s have also been recently implicated in the pathogenesis of inflammatory bowel diseases (IBD) [38–40]. ILC3s express IL-23R and depend on IL-23 for their production of various effector cytokines including IL-22, IFN-γ and IL-17, which take part in the abovementioned processes.

1.6.3. γδ T cells

A fraction of γδ T cells ubiquitously express IL-23R and produce IL-22, IL-21 and IL-17 upon IL-23 stimulation [41]. Skin and mucosal surfaces, particularly intestinal intraepithelial compartment, contain more γδ T cells than other microenvironments. These cells are involved in protective immunity against various pathogens. Studies in mouse models of various chronic inflammatory diseases revealed that γδ T cells may take part in the pathogenesis of IBD, psoriasis, MS and rheumatoid arthritis (RA) via their effector cytokines [41].

1.6.4. Antigen-presenting cells

Data regarding expression of IL-23R by APCs are scarce but do exist. Rorγt was reported to be expressed by CD45$^+$CD11b$^+$ cells, but these cells were found to be CD11c$^-$Gr1$^-$ initially. However, this study focused more on LTi cells not APCs. Sakhina Begum-Haque reported the

presence of Rorγt$^+$ DCs in the context of EAE in the CNS [42]. More recently, Karthaus et al. profiled nuclear receptor expression in murine DCs from various tissues and reported expression of RORγ in pLN and SPLN-resident DCs, and some expression was even observed in BMDC [43]. MLN-resident DCs expressed much higher RORγ message. Conventional DCs expressed more mRNA message than pDCs. Protein levels, however, were not quantified in this work. Short Rorc isoform Rorγt was also not examined. In line with these studies, we reported GFP$^+$ CD11b$^+$ myeloid cells in our IL-23R GFP reporter mice [36]. A better characterization at the protein and functional level of IL-23R and Rorγt is needed to decipher the role of IL-23R in APC function and chronic inflammation.

1.6.5. Neutrophils

Neutrophils in both humans and mice were shown to express IL-23R, Rorγt, IL-17A and IL-22 and respond to IL-23. Due to their prompt recruitment to the sites of infection and abundance, they can limit the infections [44] and the damage associated with chronic inflammation [45].

1.6.6. NKT and other cells

A fraction of NK1.1$^-$ invariant Natural killer T cells (iNKT) express Rorγt, IL-23R and, in response to IL-23, produce IL-17 and IL-22. Rorγt$^+$ iNKT cells are present in the peripheral lymph nodes. IL-23R signaling appears to be important for maintaining the number of such iNKT cells in humans [46]. How IBD pathology is regulated via IL-23-dependent response of iNKT is unclear [47, 48].

A group of CD3$^+$ CD4$^-$CD8$^-$ Rag-dependent T cells were also reported to express IL-23R [49]. Such cells have been shown to increase in number in an IL-23-dependent manner during systemic lupus erythematosus and ankylosing spondylitis murine models.

1.7. IL-23 receptor signaling and down-stream inflammatory mediators

IL-23 signals through its heterodimeric receptor (IL-23R) that is composed of two subunits: IL-12Rβ1, which is shared by IL-12 receptor complex, and IL-23R, which is the unique subunit. The p19 subunit of IL-23 heterodimer interacts with IL-23R, whereas the p40 subunit interacts with IL-12Rβ1 chain. In both humans and mice, IL-23R locus is positioned proximal to IL-12Rβ2 on chromosomes 1 and 6, respectively, and thus is believed to evolve through a gene duplication process [50]. IL-23R is conserved among amniotes and the unique IL-23R subunit protein is made up of 629 and 659 amino acids in humans and mice, respectively. Mouse and human IL-23R has 84% similarity. IL-23R sequence is also highly similar to IL-12Rβ2 and gp130.

IL-23 receptor signals through JAK kinases and STAT transcription factors. IL-23 binding of IL-23R activates of Jak2 and Tyk2, which then phosphorylate the receptor, creating docking sites for the recruitment of STAT proteins. STAT1, 3, 4, 5 are subsequently phosphorylated by activated Jak2 and Tyk2 kinases. The major transcription factor activated by IL-23 stimulation is STAT3. Pathways activated upon IL-23 binding to its receptor include the P38 MAPK pathway, PI3K-Akt and NFκ-B pathway [51–53]. IL-23 signaling activates transcription of

various effector cytokine genes including IL-17A, IL-17F, IL-22 and IFN-γ whose roles in IBD will be reviewed in the sections below.

1.8. IL-23 receptor signaling is involved in IBD in murine models and human studies

Various lines of evidence from murine studies built a pathogenic role for IL-23 signaling in IBD pathogenesis. Using *p19*$^{-/-}$, *p35*$^{-/-}$ and *p40*$^{-/-}$ mice and neutralizing antibodies against p19, p35 and p40, IL-23p19, but not IL-12p35, was demonstrated to be necessary for the development of spontaneous colitis in IL-10$^{-/-}$ mice [54]. Similarly, innate colitis induced by *H. hepaticus* in both Rag$^{-/-}$ or Rag sufficient hosts [55, 56] as well as adaptive T-cell colitis induced in Rag$^{-/-}$ mice via transfer of CD45RB^{high} naïve T cells [54–56] or CD45RB^{low} IL-10$^{-/-}$ memory T cells [54] were all dependent on IL-23p19 but not p35. Moreover, p19 KO mice were shown to be resistant to development of chemically induced colitis via DSS treatment [57]; conversely, IL-23p19 overexpression in mice resulted in enteropathy [58]. Similar to its ligand, IL-23 receptor is required for the development of adoptive naïve CD4^{+} T-cell–induced colitis [59], chemically induced DSS-driven colitis in the presence of adaptive immune cells [57] and innate cell-driven colitis induced via anti-CD40 treatment [60] in mice.

Data obtained from the studies with human IBD patients regarding the ligand as well as IL-23 receptor strongly suggest a role for this pathway in IBD development. In this regard, IL-23 was found to be elevated in the intestinal tissue of IBD patients [16]. Similarly, IL-23R mRNA was upregulated in individual lymphocytes (NK^{+}, CD4^{+}, CD8^{+} cells) obtained from both lamina propria and peripheral blood of CD and UC patients [61, 62]. Sophisticated genome wide association studies revealed IL-23R and downstream signaling molecules JAK2, TYK2, STAT3 variants as risk or resistance factors for CD and UC [63, 64]. Some of the identified variants have been studied. rs11209026 (or R381Q) SNP was discovered as a protective variant for CD [63] and UC [65] in Jewish and non-Jewish cohorts which was later shown to be a loss of function mutation in IL-23R [66, 67]. Arg-381 is located in the cytoplasmic domain of IL-23R protein and is well conserved among species, whereas Gln-381 allele is less frequent [63]. A later study demonstrated that CD8^{+} and memory CD4^{+} T cells purified from Gln-381 IL23R allele carriers produced less IL-17 and IL-22 in response to IL-23 stimulation, and that R381Q carriers contain fewer circulating Th17 and Tc17 cells compared to healthy Arg-381 carriers [68]. Peripheral blood mononuclear cells (PBMC) from individuals with R381Q variant also produce less IL-17 in response to the *Borrelia burgdorferi*, a potent inducer of Th17 responses [69]. Moreover, R381Q IL-23R transfected cell lines displayed reduced STAT3 phosphorylation compared with control IL-23R. These reports collectively provide a mechanistic explanation for the resistance to CD and UC of R381Q SNP allele. Other protective variants against Crohn's include p.Arg86Gln, p.Gly149Arg and p.Val362Ile [70]. The last two also protect from UC. Mechanistically how they affect IL-23R signaling remains unknown. p.Gly149Arg affects a highly conserved extracellular domain of IL-23R, whereas p.Arg86Gln and p.Val362Ile are variants in the poorly conserved domains [71]. These SNPs are believed to reduce IL-23R activity, but experimentally this has yet to be shown.

Risk variants of IL-23R for CD were also described [63]. They are thought to be gain of function mutations. rs10889677 is one such variant with a transversion in the 3′ UTR of IL-23R where

an A in the wild-type allele is mutated to C. This mutation was shown to abolish a regulatory pathway directed by miRNA Let-7e and Let-7f, which consequently resulted in elevated IL-23R mRNA and protein production in human PBMC and $CD4^+$ T cells [72].

Other SNPs in SAT3 (rs381676, rs744166 and rs11871801), in JAK2 (rs10758669), and in TYK2 have been described. However, mechanisms of action of these variants with regard to their impact on IL-23R signaling requires further study [73, 74].

2. IL-23-producing cells in IBD pathogenesis

Antigen-presenting cells are the primary source of IL-23. Thus, mutations in any of the genes responsible in the IL-23 production pathway by APCs would potentially have consequences for IBD pathogenesis. Indeed, examples of such defects in the literature exist. An example of a link between PRR and dysregulated IL-23 production was observed in individuals with NOD2 variant 1007fsinsC [75]. As described above, NOD2 is a cytosolic PRR that detects bacterial cell wall component, and three variants of this receptor were found in 40% of CD patients in western countries [76]. Recently, NOD2 was shown to crosstalk with TLR2 pathway to regulate IL-23 expression by dendritic cells via mobilizing miRNAs. miR-29 expression was shown to be augmented by this crosstalk, which directly targets IL-12p40 mRNA and indirectly IL-23p19. DCs with homozygous or heterozygote NOD2 variant 1007fsinsC from CD patients thus have defective miR-29, and consequently augmented IL-23 expression [75].

Susceptibility and protective variants of CARD9 have been discovered [77, 78]. CARD9 works downstream of β-glucan receptor dectin-1 and regulates IL-23 production. It is, however, unclear whether these variants are loss or gain of function mutations, but it is likely that these variants may lead to dysregulated IL-23 production by APC.

In some mouse IBD models, APCs were manipulated to determine their impact on pathogenesis. In DSS-induced chemical colitis, depletion of $CD11c^+$ DCs via DT injections in CD11c DTR mice during disease confers protection, whereas depletion before disease exacerbates the pathology [79–81]. Direct depletion of DCs during T-cell–induced colitis has not been performed although IL-23 production has been traced back to these cells in various IL-23-dependent colitis models and IL-23 neutralization or genetic deletion systems have been utilized along with targeting of various costimulatory molecules expressed by DCs. Nevertheless, transfer of E-cadherin$^+$ BMDCs which express IL-23 exacerbates T-cell–induced colitis [14].

Deletion of monocytes via CCR2 gene targeting or anti-CCR2 antibodies also confers protection from DSS-induced colitis [82, 83].

The importance of APC-derived IL-23 in murine colitis models based on infection has been documented by selective targeting of DCs, macrophages and monocytes [15, 17, 84], all pointing to the significance of APC-derived IL-23.

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3. IL-23 responsive cells in IBD pathogenesis

In this section, "how IL-23 responsive cells drive or prevent IBD pathology" will be discussed. Although IL-23R-expressing cells are manifold, effector cytokines produced upon IL-23 signaling are similar or identical by these innate and adaptive immune cells. The current literature regarding how each IL-23-dependent cytokine coming exclusively from a defined IL-23R$^+$ cell impact IBD pathology will be reviewed. A summary of the IL-23R positive cells are shown in **Figure 2**.

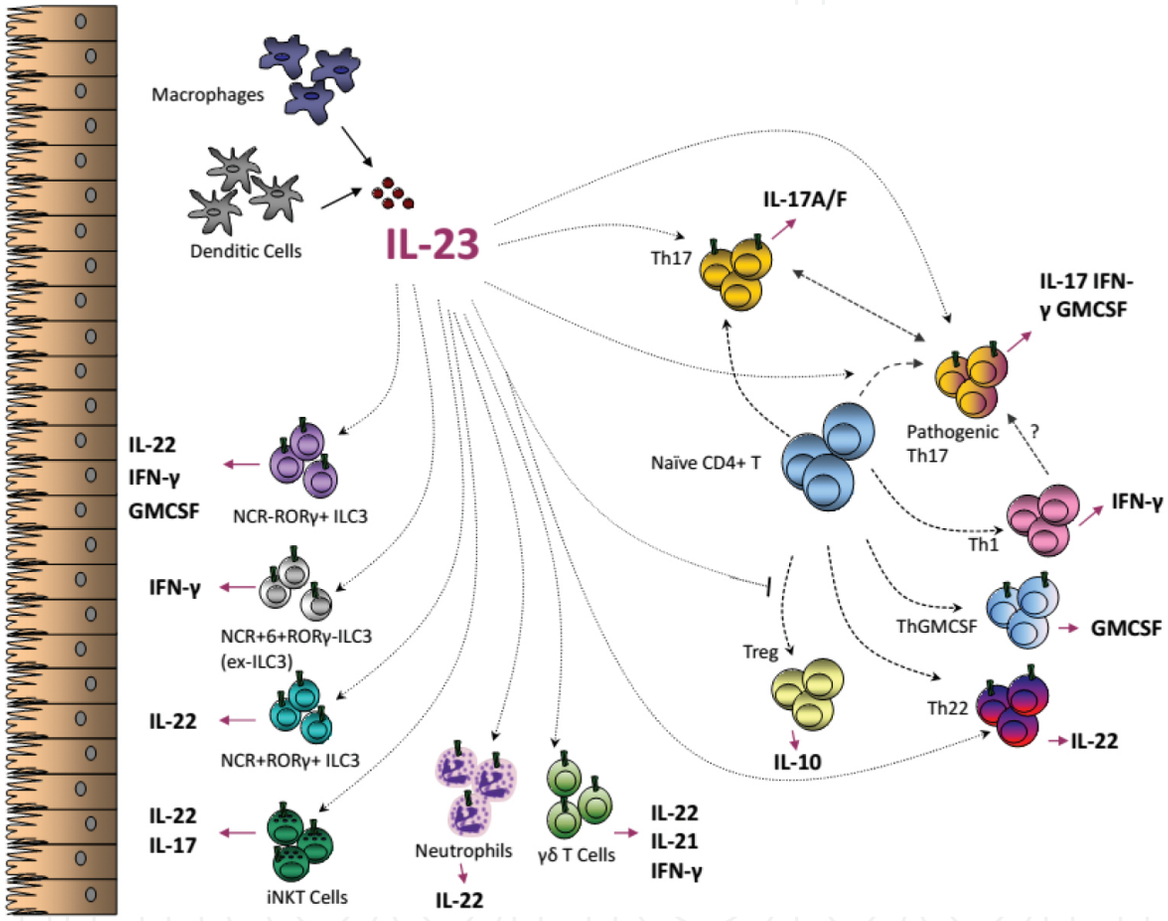


Figure 2. Summary of action of IL-23 on its target cells. IL-23 acts on both innate and adaptive immune cells to promote inflammation during IBD.

3.1. Th17 cells in IBD

3.1.1. IL-17A and F

IL-17 A and F are closely related (50% homology) Th17 signature cytokines that are produced in an IL-23-dependent manner. IL-17A and IL-17F are made of homodimers, however, IL-17A/F heterodimers also form. All of the combinations are recognized by the same heterodimeric

receptor composed of IL-17RA and IL-17RC subunits [19]. Both cytokines were expressed at high levels in the intestines of CD patients [62, 85–87]. Because these cytokines stimulate production of various inflammatory mediators by epithelial or endothelial cells that recruit neutrophils, monocytes and dendritic cells their involvement as pathogenic molecules were studied in IBD context [88, 89]. IL-17A neutralization in DSS model resulted in exacerbation of colitis with higher $CD4^+$ T-cell infiltrates and $CD11b^+$ granulocyte-monocyte infiltrates [90]. IL-17KO mice recapitulated this phenotype [91]. Similar to the chemically induced colitis, adaptive colitis induced by naïve $CD4^+$ T cells also developed more aggressively when *il17*$^{-/-}$ or *il17r*$^{-/-}$ T cells transferred as compared with WT T cells [92]. This protective role of IL-17 in murine models has been confirmed in Crohn's disease patients. Monoclonal anti-IL-17A secukinumab treatment exacerbated the disease, and adverse effects (high incidences of fungal infection) have been reported [93]. Recently, it was shown that IL-17 is critical for epithelial homeostasis and that the absence of IL-17A during colitis induced by DSS treatment further decreases epithelial integrity and barrier function, resulting in bacterial translocation across the intestinal epithelial barrier [94]. The same phenomenon of IL-17-dependent regulation of epithelial barrier function was reported by Maxwell et al. in a colitis model which was induced in *Abcb1a*-deficient mice upon *Helicobacter bilis* infection [95] which may provide a mechanistic explanation to protective role of IL-17A/F.

In some models of murine IBD, IL-17A and F demonstrated a pathogenic character. In this regard, IL-17FKO mice developed milder DSS-induced colitis compared with WT mice [91]. IL-17A neutralization also improved colitis in a T-cell transfer model in which colitis was induced by IL-17F$^{-/-}$ $CD4^+CD25^-$ T cells (Naïve + memory) [96]. Furthermore, Yen et al. had demonstrated a pathogenic role for IL-17A in $CD4^+$ T-cell transfer colitis induced by IL-10$^{-/-}$ T cells [54]. Lastly, deletion of IL-17RA, receptor for both IL17 and F (but also for IL-17C), or blocking of signaling via IL-17RA IgG in WT mice conferred protection from in TNBS-induced colitis [97].

3.1.2. IFN-γ

IFN-γ is a Th1 cytokine. However, Th17 cells and ILC3s also produce it when stimulated with IL-23. IL-17A expression by T cells is not required for naïve T-cell–driven colitis; in fact, its neutralization in IBD patients does not ameliorate the disease as described above. However, Th17 cells are needed for the pathogenesis of IBD in several murine models as RORγT [87], STAT3 [98], IL-23 [99], and IL-23R [59] manipulation by genetic and biochemical means alters the disease course. These data point to the involvement of other Th17-derived cytokines in colitogenesis. In fact, in naïve T-cell transfer-induced adaptive cell–driven coltitis, anti-CD40 or *Hepaticus*-induced innate colitis models, IL-23-dependent IFN-γ produced by either Th17 or innate ILC3 cells was shown to play a pathogenic role [38, 100]. IFN-γ in this context was shown to regulate myeloid inflammatory cell recruitment (neutrophils, monocytes and eosinophils) to the tissue [60, 101, 102]. In both $CD4^+$ T-cell transfer and *H. hepaticus*-driven murine adaptive models of IBD, Th17 cells that produce IFN-γ^+IL-$17A^+$ together have been described. These double producer cells were eliminated when donor T cells lack IL-23R in the T-cell–transfer colitis model, and colitis scores are improved [103]. IFN-γ^+IL-$17A^+$ double

producers increase in colitic mouse intestine. Independently-performed fate map studies have shown that IFN-γ^+IL-17A$^+$ double producers can further turn RORγT expression off and gradually turn into "alternative" Th1 cells through a process promoted by IL-23 and IL-12 [59, 104, 105]. It is unclear as yet what the relative contribution of Th17/Th1 double producers or alternative Th1 cells or the conventional Th1 cells to IBD pathogenesis are and if it applies to humans.

Besides acting as an inflammatory cytokine, IFN-γ was also shown to regulate IEC survival proliferation through Wnt inhibitor Dkk, which ultimately negatively impacts intestinal epithelial barrier function [106, 107]. Whether epithelial integrity is regulated by IFN-γ of Th17, or ILC3 origin is also unclear.

3.1.3. GMCSF

Granulocyte macrophage colony-stimulating factor (GMCSF) is a hematopoietic growth factor produced by various immune cells such as activated T and B cells, monocytes/macrophages, neutrophils, eosinophils and ILC3s, as well as other sources such as endothelial cells, fibroblasts epithelial cells, mesothelial cells, chondrocytes, Paneth cells and tumor cells [108]. It was shown that GMCSF is produced by Th17 cells in a Rorγt and IL-23-dependent fashion [109, 110]. More importantly, independent studies revealed that GMCSF is required for classical EAE development in mice, especially by activating microglia or mobilizing inflammatory myeloid lineages to the inflammation site [109, 110]. Studies from Fiona Powrie's lab more recently showed that IL-23-dependent production of GMCSF also contributes to the pathogenesis of colitis in naïve CD4$^+$ T-cell transfer- and *Hepaticus*-induced models of murine IBD [111, 112]. In both models, GMCSF was shown to promote eosinophil recruitment and activation in the colon which was needed for pathogenesis. On the other hand, work including with human cells proposed that a distinct lineage of Th cells is programmed to produce only GMCSF and that they constitute the major fraction GMCSF$^+$ Th cells (Though GMCSF$^+$IFN-γ^+ or GMCSF$^+$IL-17A$^+$ cells are also reported) [113]. STAT5 and IL-7 or IL-2 may be important in differentiation or activation of GMCSF$^+$ cells [114, 115]. It is noteworthy that STAT5$^{-/-}$ CD4 T cells are still able to induce colitis [114]. Thus, though GMCSF may have a role in IBD development, how much of that comes through IL-23-dependent pathway or from Th17 cells is unclear and more cell-specific deletion of GMCSF is needed to address this question.

3.1.4. IL-22

IL-22 is an alpha-helical cytokine which belongs to IL-10 family cytokine. Th17, Th22 and $\gamma\delta$ T cells [19], neutrophils [45] and ILC3s produce IL-22 cytokine in response to IL-23 stimulation [116]. IL-22 signals through a heterodimeric cytokine composed of the specific IL-22R1 and IL-10Rβ subunits. Although IL-22 is mostly produced by cells of the hematopoietic lineage, IL-22 receptor is expressed by the non-hematopoietic compartment which includes epithelial cells in the skin, lung and intestines, liver and kidney [117]. IL-22 is needed in the mucosal surfaces for the containment of microbial flora at an arms distance of epithelia. IL-22 stimulates production of various antimicrobial proteins and peptides (Reg3β and γ, β-defensins, S100A7-9 etc.) as well chemokines and cytokines (CXCL1$^-$, 5, 9, IL-6, G-CSF) [116]. Thus, it is

also crucial for host defense against various pathogens including *C. rodentium* [118]. IL-22 promotes mucus production by goblet cells; acts as a growth factor and stimulates epithelial regeneration [118, 119].

IL-22 levels are elevated in the mucosal tissue of both UC and CD patients [120]. As with other Th17- specific cytokines, both protective and colitogenic roles for IL-22 have been described in murine IBD models. Sugimoto et al. were the first to demonstrate that IL-22 could improve murine IBD pathology. They observed a reduction in IL-22 levels after the disease onset in their spontaneous colitis murine model compared with control animals which developed disease due to a T-cell receptor defect (*Tcra*$^{-/-}$mouse) and went after IL-22 [121]. Using this model and DSS-induced colitis, these investigators showed that IL-22 overexpression improved colitis, and its neutralization via IL-22BP (the soluble receptor) or antibody, delayed recovery from colitis. Although the exact source of IL-22 in this work remained less defined due to the possible innate sources (γδ T cells, ILC3, neutrophils), during naïve CD4^{+} T-cell transfer-induced colitis, IL-22 coming from exclusively Th17 cells were shown to be protective. This was shown by the transfer of IL-22$^{-/-}$ naïve CD4^{+} T-cell transfer into *Rag*$^{-/-}$ mice which developed exacerbated colitis compared to that of WT T cells [122]. ILC3 also contribute to intestinal IL-22 production, as such IL-23R$^{-/-}$ Rag1$^{-/-}$ mice develop exacerbated colitis upon naïve CD4^{+} T-cell transfer compared with control Rag1$^{-/-}$ hosts. IL-23R deficient Rag1KO mice had far less IL-22 in their intestines than control Rag1KO mice even after naïve T-cell transfer, showing that indeed ILC3 contribution to IL-22 is significant [60]. So, regardless of the cellular source, reduction in IL-22 levels impacted IBD development/recovery in naïve T-cell–induced colitis. IL-22-mediated protection from colon inflammation was demonstrated by targeting molecules responsible for the induction of IL-22 in different contexts. When AhR signaling was activated via its ligand Ficz, which increased IL-22 production, less colitis developed in TNBS, DSS and CD4^{+} naïve T-cell–induced mice model; Ficz-dependent protection was reversed by neutralization of IL-22 [123, 124]. In all these models, IL-22 was believed to promote epithelial barrier regeneration. Conversely in its absence, epithelial barrier was breached and could not be repaired [122]. IL-22 receptor signaling activates STAT3; research shows that deletion of STAT3 in IL-22 responsive epithelial cells impairs IL-22-mediated intestinal epithelial repair which was demonstrated in a DSS-induced model [125]. This study revealed an important role for IL-22-induced mucin in IL-22-mediated protection from colitis.

IL-22 was also shown to drive colitis in noninfectious and infection-induced T-cell–dependent colitis models [126, 127]. Kamanaka et al. developed a T-cell–dependent colitis model by adoptive transfer of IL-10 unresponsive IL-10dn^{-} CD45RB^{low} CD25^{-} CD4^{+} memory T cells into *Rag*$^{-/-}$ hosts. The colitis developed in this model was IL-22-dependent (exclusively of TH17/Th22 origin), as such IL-22$^{-/-}$ CD45RB^{low} CD25^{-} CD4^{+} memory T cells did not induce colitis compared with IL-22. It is noteworthy that colitis in this model, unlike the naïve T-cell transfer model, does not cause ulcers, but rather is characterized by mucosal thickening and hyperplasia consistent with proliferative potential of IL-22 [127]. *Toxoplasma gondii* infection-induced colitis in B6 mice has also been shown to be IL-22 driven (through its effects on MMP-2), thus IL-22 deletion ameliorated colitis in this context [128].

3.2. ILC3, γδ T and NKT cells in IL-23R-mediated pathology

3.2.1. Group3 ILCs

Group 3 ILCs (ILC3) are Rorγ$^+$ innate cells that respond to IL-23 and are enriched in mucosal surfaces [129]. Although very rare in the circulation, in the intestinal lamina propria, Rorγ$^+$ ILC3s are enriched and constitute up to 8% of lymphocytes and ~70% of ILCs in the murine intestinal LP [39]. ILC3s include fetal LTi cells and adult ILC3s [130]. Various adult ILC3s were described in humans and in mice based on the expression of natural cytotoxicity receptors and cytokine production. These include (1) IL-22 producing NCR$^+$ ILC3 [131] which are also called ILC22, NK22, NKR-LTi or NCR22 [132]; (2) NCR$^-$IL-17A$^+$IFN-γ$^+$ double producing ILC3 [38] and (3) NCR$^-$IL-17A$^+$ ILC3s [133, 134] in mice [135]. Fetal and adult ILC3 were shown to differ in their CCR6 expression. Fetal LTi cells express higher CCR6, whereas adult ILC3s appear to be CCR6 low and accumulate after birth in a microbiota-dependent fashion. CCR6$^-$ adult ILC3s were also reported to rely on AhR and ligands acquired through diet [135]. All the ILC3 cells depend on Rorγt for their development and express IL-23R and produce Th17 cytokines in response to the IL-23, although the combination of cytokines differ with the microbial signal and ILC3 type.

Regardless of our incomplete understanding of their ontogeny, ILC3s have been shown to take part in the pathogenesis of IBD-like diseases in many murine models in the past 5 years. More importantly, not only Th17 cells but also CD3$^-$ ILC3s were reportedly elevated in the intestinal tissue of both UC and CD patients; they also contributed to elevated IL-22, IL-17A/F and IL-26 levels in tissue of IBD patients [136].

3.2.1.1. ILC3-derived IL-17 and IFN-γ

Although IL-17A neutralization trials failed at achieving a clinical benefit to IBD patients, IL-17A, particularly of ILC3 origin, has been shown to promote IBD-like pathogenesis in murine models. This was shown to be the case in *H. hepaticus*-induced colitis in Rag$^{-/-}$ mice, shown by Buonocore et al. in their landmark paper [38, 55, 56]. In this innate model, IL-17A$^+$ IFN-γ$^+$ ILC3 numbers elevated and neutralization of either cytokine alone or together ameliorated colitis. Additionally, deletion of ILC3 by crossing Rag$^{-/-}$ mice to Rorc$^{-/-}$ animals or ILC3 depletion via anti-Thy1 antibodies make them resistant to colitis induced by *H. hepaticus*. Pathogenicity of IL-17A was also reported in another innate colitis model, the *Tbx21*$^{-/-}$*Rag2*$^{-/-}$ (TRUC) mice. TRUC mice develop spontaneous colitis in a microbe-dependent fashion (which has recently been shown to be *H. Typhlonius*-dependent) [137]. Interestingly, colitis in this model is TNF-α-dependent until the age of 12 weeks after which blockade of TNF-α is ineffective. Through neutralization of IL-23 or IL-17A or blockade of IL-7R signaling, it was shown that ILC3s have been shown to drive colitis in this model via IL-17A. Both TNF-α and IL-6 appear to enhance the disease by enhancing IL-23 production or its signaling [133, 134].

In both *H. Hepaticus*-induced colitis and anti-CD40-induced colitis models (both of which are IL-23 mediated) ILC3-derived IFN-γ drives pathogenesis, and as such, IFN-γ neutralization in these models ameliorated colitis [27, 38, 100]. ILC3s indeed produce IFN-γ when stimulated with IL-23 [60]. Similar to Th17 cells, ILC3 cells have been reported to be plastic cells. Vonar-

bourg et al.'s studies revealed that that RORγT^{+}NKp46^{-} ILC3s (NCR^{-}ILC3), upon exposure to IL-12 and IL-15, upregulate NK cell marker NKp46 giving rise to NCR^{+}ILC3 *in vivo*. These cells subsequently downregulate RORγT and assume a Th1 or NK such as phenotype and called RORγt-NKR LTi. (currently considered as ILC1) [100]. These ex-ILC3s were shown to produce IFN-γ and were argued to be the major source of IFN-γ and the driver of colitis in the anti-CD40-induced colitis model. The plasticity of ILC3s has also been described in humans [138, 139]. In the presence of IL-12 and IL-2, human CD3^{-}CD127^{+}c-kit^{+} NKp44^{+} ILC3s downregulate Roγt and IL-23R; upregulate T-bet and then produce IFN-γ. These ex-ILC3s are categorized as non-NK ILC1 [138]. More recently, the ILC3-to ILC1 conversion has been shown to be a reversible process regulated by different subsets of antigen-presenting cell, presumably depending on the microbes or other external signals [139]. Elevated percentages of ILC1 have been reported in Crohn's disease-inflamed intestine [140], as well as in humanized mice treated with DSS [138]. However, causality with the disease, or whether their contribution is significant for pathogenesis in humans is also unclear given the scarcity of their number [136].

3.2.1.2. ILC3-derived IL-22 in IBD

ILC3s also produce IL-22 in response to the IL-23. Both pathogenic [60, 102] and protective [57, 141, 142] roles have been described for IL-22 that is coming from exclusively ILC3s. Deletion of ILC3s by crossing *Rag*$^{-/-}$ mice to *Rorc*$^{-/-}$ renders double KO mice more susceptible to DSS-induced colitis and also delays the recovery [57, 141]. Similarly, IL-22-deficient B6 mice or IL-23R$^{-/-}$ *Rag*$^{-/-}$ mice develop more severe intestinal damage in response to the DSS challenge which are reversible by recombinant IL-22-Fc injections [57]. IL-22 is needed for the healing of epithelia upon DSS-induced damage. However, too much of it in certain context may also promote colitis characterized by hyperplasia and mucosal thickening and myeloid inflammatory cell recruitment [119, 125]. We and others have shown this pathogenic effect of IL-22 using the innate cell-mediated colitis model induced by anti-CD40 injections. Neutralization of IL-22 in *Rag*$^{-/-}$ mice ameliorated colitis, conversely, restoring IL-22 expression in *IL-23R*$^{-/-}$*Rag*$^{-/-}$animals (which are protected from colitis), brought colitis back [60, 102]. How IL-22 mediates colitis is not entirely clear, but our data suggest that IL-22 may modulate IL-10, IFN-γ levels and neutrophil recruitment [60].

Protective effects of IL-22 may also be due to impact on microbial flora. Recent studies suggested that IL-22 may contribute to protection from IBD by restricting growth of certain genera of bacteria in the steady state [143]. A study by Zenewicz et al. revealed that intestine of *Il-22*$^{-/-}$ mice differs in representation of 14 different genera compared with WT mice and is more susceptible to DSS-induced colitis. More importantly, this susceptibility is transmissible to WT mice through co-housing of WT with *il22* KO mice, which points to functions of IL-22 independent of epithelial regeneration [143]. Supporting this view, another study using *AhR*$^{-/-}$*Rorc*$^{-/+}$ mice demonstrated that reduced IL-22 levels in the murine intestine allows overgrowth of SFB, which consequently promotes Th17 differentiation [144]. Thus *AhR*$^{-/-}$*Rorc*$^{-/+}$ mice develop spontaneous colitis owing to hyper-Th17 responses.

3.2.1.3. ILC3-derived GMCSF in IBD

Both human and mouse ILC3s form IBD patient intestine and murine intestine, respectively, were shown to produce GMCSF in an IL-23-dependent manner [101, 102]. Similar to adaptive cell-induced colitis models, during anti-CD40-induced colitis ILC3 contributed to GMCSF substantially, and its blockade via neutralizing antibodies blocked colitogenesis [101, 102]. GMCSF-dependent recruitment of myeloid effector cells (eosinophils-monocytes) may be the underlining mechanism for the pathogenic effects as described in adaptive cell-induced colitis models [111, 112]. GMCSF, however, was also shown to impact ILC3 motility out of crypto-patches, which may additionally contribute to its pathogenic role during innate cell-induced colitis [101].

3.2.2. γδ T cells

γδ T cells are nonconventional T cells with innate features and comprise 1–5% of lymphocytes in mice and human blood. Their numbers go up to 50% of lymphocytes in skin and mucosal tissues [145]. γδ T cells express Rorγt and IL-23R and are another source of IL-17 and IL-22, which can be produced both in IL-23-dependent and independent manner. In peripheral blood as well the intestines [146–148] of active IBD patients, elevated percentage and absolute number of γδ T cells were reported. Both tissue protective and pro-inflammatory roles in murine IBD models have been described for γδ T cells. In this regard, *Tcrδ*$^{-/-}$ mice developed more severe DSS-induced colitis accompanied by reduced regeneration and epithelial tissue repair [149, 150]. Depletion of γδ T cells also exacerbated TNBS-induced colitis in rats [151]. A recent study showed that this protective effect (of γδ T cells) was mediated through IL-22 and further enhanced by retinoic acid (RA) which induced RA receptor binding to IL-22 promoter [152]. More recently, γδ T cells were shown to be the major IL-17A source during acute DSS-induced colitis. In this model, IL-17 production was reported to be mostly IL-23 independent and regulated epithelial permeability through instructing localization of occluding, a tight junction protein [94].

Studies in some murine IBD models implicated γδ T cells as the contributor to pathology. Colitis in *Tcrα*$^{-/-}$ mice, which resembles to UC and spontaneously develops in a microbiota-dependent fashion, improved up on genetic deletion of γδ T cells [147]. In also a T-cell transfer model, γδ T cells enhanced colitis [153]. *Tcrβδ*$^{-/-}$ mice developed less colitis compared with *Tcrδ*$^{+/+}$ mice upon naïve CD4^{+} T-cell transfer. Cotransfer of IL-17^{+} CCR6^{+} γδ T cells but not CCR6^{-} IFN-γ^{+} γδ T cells with naïve T cells restored colitis in this model through potentiating Th17 and Th1 cells [153]. In another murine spontaneous colitis model which develops due to CD4^{+} T-cell-–specific deletion of phosphoinositide-dependent protein kinase 1 (Pdk1), γδ T cells were shown to be required for colitogenesis [154].

3.2.3. NKT cells

Type I NKT (iNKT) cells are characterized by their invariant T-cell receptor α-chain which is detectable by α-galactosylceramide loaded CD1d tetramers [155]. A population of NK1.1^{-} iNKT cells were shown to express RORγT and IL-23R [47, 48] and produce IL-17. These

RORγT + iNKT cells, when costimulated with IL-23 and IL1β, induce production of large amounts of IL-22 and IL-17 [47, 48]. Some studies documented a reduction in type I iNKT cells in the blood and intestinal tissue of CD and UC patients [156] (see the review for detailed role of iNKT in IBD [155]). Because iNKT cells produce IL-4, IL-13 and can promote Th2-responses, they have been experimentally shown to play a protective role in various murine IBD models including DSS [157, 158], TNBS [159], naïve $CD4^+$ T-cell transfer [160] and *T. gondii* induced [161, 162] models of colitis. However, exactly how IL-23–dependent production of IL-22 or IL-17 by iNKT cells confers protection or impacts IBD pathogenesis has not been fully elucidated.

3.2.4. Neutrophils

Some fractions of murine neutrophils (~20%) express Rorγt and IL-23R; even higher factions of human neutrophils (75%) have been shown to respond to IL-23 and produce IL-17A and IL-22 [163, 164]. A recent study demonstrated that during DSS-induced colitis, neutrophils significantly contribute IL-22 production; as such IL-22 WT neutrophil transfer improves colitis [45]. Neutrophils are recruited to intestine during T-cell transfer colitis and *Hepaticus*-induced colitis as well. Their neutralization in one study did not suggest any pathogenic role in these models [111]. It is unclear how neutrophils would impact intestinal pathology in other innate and T-cell–dependent colitis models.

4. Therapeutic approaches targeting IL-23 signaling in IBD

With the motivation from studies described above and the commonality of IL-23 signaling across a number of autoimmune/chronic inflammatory conditions, several companies have targeted IL-23 signaling pathway components with various means for therapeutic intervention in multiple inflammatory diseases including IBD. Most of these antagonists are monoclonal human or humanized antibodies that target specific (p19) or common (p40) subunits of IL-23 (**Table 1**). Others target downstream effector cytokines or cytokine receptors induced by IL-23 signaling such as IL-17A, IL-17F, IL-22 or IL-17RA. Few of those attempt to block IL-23 signaling and Th17 arm by inhibiting the transcription factors regulating IL-23 or IL-23R production via blockade with apilimod and Rorc inhibitors, respectively. Some of therapeutics are currently in use for conditions other than IBD; others are in the development–discovery stage, and some have been discontinued due to lack of efficacy or adverse effects (review by [165, 166]. **Table 1** gives a summary of the therapies directly targeting IL-23.

Ustekinumab is the only FDA-approved IL-23/IL-12 blocker that is currently used for treatment of psoriasis and psoriatic arthritis. It is a neutralizing fully human monoclonal antibody against the common p40 subunit. Several clinical trials are assessing its effectiveness against a list of autoimmune conditions. Ustekinumab phase III trials for Crohn's disease and ankylosing spondylitis showed promising results [167–169]. Ustekinumab is also being tested for atopic dermatitis and rheumatoid arthritis. Multiple Sclerosis patients, however, did not benefit from Ustekinumab for unknown reasons [170]. Briakinumab is also a p40-specific monoclonal

antibody developed by Abbott, but due to cardiac problems associated with its use, it did not make to the market [171]. Since Ustekinumab blocks both IL-12 and IL-23, the Th17 and Th1 arm of the helper T cells are affected together. IL-23p19-specific monoclonal antibodies which will exclusively target Th17 arm and spare Th1 lineage may be more beneficial for the long-term use. Although both Th1 and Th17 cells are implicated in many autoimmune conditions (Psoriasis, IBD, MS), the Th1 arm of the helper cells are crucial for immunity against intracellular pathogens and tumors, and thus selective targeting of Th17 may help to reduce the risk of certain infections or developing tumors during long-term use of immunosuppression.

Drug	Target	Company	Status	Disease
Ustekinumab	p40 (IL-12p40; IL-23p40) mAb human	Centocor Ortho Biotech and Janssen Research	Approved Approved Phase III Phase I Phase II Phase II Phase II Phase II Discontinued	Plaque psoriasis Psoriatic arthritis Crohn's disease CVID-dependent enteropathy Ankylosing spondylitis; Sarcoidosis atopic dermatitis; rheumatoid arthritis Multiple sclerosis
Briakinumab	p40 (IL-12p40; IL-23p40) mAb human	Abbott	Discontinued Discontinued Discontinued	Psoriasis Crohn's disease Multiple sclerosis
Guselkumab	IL-23 p19 antagonist mAb human	Janssen Research	Phase III	Psoriasis
BI 655066	IL-23 p19 antagonist mAb humanized	BoehringerIngelheim	Phase II	Crohn's disease; psoriasis
Tildrakizumab	IL-23 p19 antagonist mAb human	Schering-Plough/Merck	Phase III	Psoriasis
MP-196	IL-23p19 antagonist mAb	Effimune	–	Autoimmune disease
FM-303	IL-23p19 antagonist mAb	Femta Pharmaceuticals	Discovery	Inflammatory bowel disease
AMG 139	IL-23p19 mAb human	Amgen, AstraZeneca	PhaseII	Crohn's disease; psoriasis
IL-23 Adnectin	IL-23R	Bristol-Myers Squibb	Discovery	Immune disorder
Anti-IL-23 immunotherapy	IL-23R	Peptinov SAS	Discovery	Inflammatory disease
LY3074828	IL-23 p19 antagonist mAb humanized	Eli Lilly	Phase I	Psoriasis
Apilimod (STA-5326)	Blocks NFKB translocation, IL-12, IL-23 production	Synta Pharmaceuticals	Discontinued	Psoriasis; rheumatoid arthritis; common immunodeficiency

Adapted and modified from Tang and Iwakura [165] and Patel and Kuchroo [166].

Table 1. Identified interleukin-23 receptor (IL-23R) antagonists.

Guselkumab, Tildrakizumab, BI655066, AMG 139, MP-196 are monoclonal anti-p19 neutralizing antibodies that are now actively being tested by different companies for psoriasis at different phases (ClinicalTrials.gov). BI 655066 is additionally being tested on CD patients in a phase II trial. With positive results from psoriasis cases, the remaining p19 blockers are very likely to be extended to trials with Crohn's disease patients soon.

In addition to the IL-23 itself, several other downstream effector cytokines of IL-23R signaling pathway are being targeted with monoclonal antibodies to treat autoimmune diseases. Monoclonal antibodies against IL-17A, IL-17F, IL-17RA proved to be very effective treating psoriasis in various trials [166, 172]. However, secukinumab (anti-IL-17A) trial did not benefit CD patients [93], thus due to lack of any improvement with IL-17A neutralization brodaluzumab (IL-17RA antibody) development and trials were terminated [173]. As described in previous sections, recent studies suggest an important role to IL-17A intestinal barrier function which may be essential for the containment of microbiota. Thus, its removal may exacerbate the condition in IBD [94, 95].

IL-22 is another IL-23 regulated cytokine which went through clinical trials (ClinicalTrials.gov). Fezakinumab (ILV-094) is a monoclonal human IL-22 antibody and has been tested in psoriasis and RA with no results being revealed. Due to its involvement in various IBD models, IL-22 antibodies are also a likely candidate to through clinical trials in CD patients.

There are Rorc inhibitors that are being tested in healthy volunteers (VTP-43472 and JTE-151). They inhibit both Rorγ and Rorγt *ex vivo* and *in vivo* results are not yet available [166].

IL-23 receptor signals through JAK2/TYK2 kinases. Several JAK2 inhibitors are in clinical trials for treatment of cancer and autoimmune disease. Ruxolitinib is a JAK1/JAK2 inhibitor approved by FDA for myelofibrosis and is now being tested in RA and psoriasis patients. Baricitinib is another Jak1/Jak2 inhibitor in Phase II clinical trials in RA patients. Lastly, lestaurtinib is a JAK2 inhibitor and is in Phase II trials on psoriasis patients. These molecules (ClinicalTrials.gov) are eventually likely to be tested on IBD patients.

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