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## REVIEW

# Interleukin 23 receptor: Expression and regulation in immune cells

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The importance of IL-23 and its specific receptor, IL-23R, in the pathogenesis of several chronic inflammatory diseases has been established, but the underlying pathological mechanisms are not fully understood. This review focuses on IL-23R expression and regulation in immune cells.

**Keywords:** Chronic inflammatory diseases · Gene regulation · Interleukin-23 (IL-23) · Interleukin-23 receptor (IL-23R) · Transcription factors

## Introduction

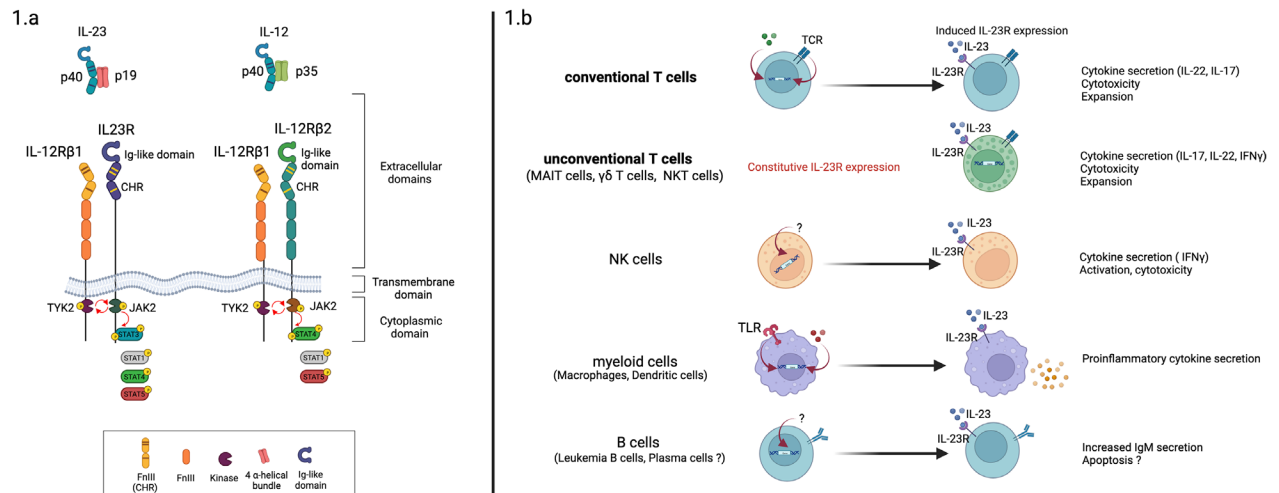
IL-23 was identified in 2000 based on the homology of its IL-23p19 subunit to IL-12p35 [1]. Early data indicated that IL-23 enhanced IFN- $\gamma$  production by memory CD4<sup>+</sup> T cells; however, it was later shown that IL-23 also induced IL-17 production by these cells [2]. The observation that IL-23p19 knock-out mice but not IL-12p40 knock-out mice were protected from brain autoimmune inflammation, in the EAE model [3], provided the first evidence that IL-23 was a key player in inflammatory diseases. Genome-wide association studies subsequently demonstrated an important role of the IL-23 signaling pathway in the pathogenesis of several chronic inflammatory diseases, including Crohn's disease [4], axial spondyloarthritis [5], and psoriasis (Pso) [6]. IL-23 therefore appeared to be an excellent pharmacological target for inflammatory diseases, a notion that has been validated in the clinics by the successful treatment of Pso, psoriatic arthritis, and Crohn's disease with IL-23 blockers [7, 8]. IL-23 signals via a heterodimeric receptor (in this review: IL-23R) composed of a specific subunit, IL23R, and the IL12R $\beta$ 1 subunit, which is shared with the IL-12 receptor [9]. IL-23 signaling has been studied in particular in the context of Th17 cell differentiation and function, but more recent data have demonstrated high frequencies of IL-23R-positive "innate-like" T-cell populations, in particular, mucosal-associated invariant T cells and  $\gamma\delta$  T cells [10]. Very recent data have demon-

strated the important role of IL-23 signaling in infectious conditions. Patients with autosomal recessive IL-23R deficiency display Mendelian susceptibility to mycobacterial disease due to impaired IFN- $\gamma$  production and, less frequently, to chronic mucocutaneous candidiasis due to impaired IL-17A/F production [11]. Here, we focus on two questions: what are the immune cells that express the IL23R and how is IL23R expression acquired.

## The IL-23R: Structure and signaling

IL-23 is a heterodimeric cytokine formed by two disulfide-bound subunits: p19 (encoded by *IL23A*) and p40 (encoded by *IL12B*) [1]. The latter subunit is shared with another inflammatory cytokine, IL-12 [12, 13]. IL-23 and IL-12 receptors also share a common chain: IL-12R $\beta$ 1 pairs with the IL23R chain to form the IL-23 receptor complex (IL-23R) that confers responsiveness to IL-23, or with IL-12R $\beta$ 2 to form the IL-12 receptor complex [14]. Only human IL-23 exhibits affinity for the human IL-23R [9] and the interaction of both p40 with IL-12R $\beta$ 1 and p19 is required for competent signaling of IL-23R [15, 16]. Recently, the crystal structure of the human IL-23R has been solved. Bloch et al proposed a sequential assembly mechanism of the receptor complex in which the IL23R chain first binds to IL-23p19 subunit exclusively via its N-terminal domain. This induces a conformational change of the IL-23 heterodimer that enables the p40 subunit to bind to IL-12R $\beta$ 1 with high affinity and to recruit the complex [17]. IL-12R $\beta$ 1 and IL23R lack intrinsic kinase activity

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**Figure 1.** IL-23R structure and expression on immune cell subsets. (a) Schematic representation of the IL-23 receptor complex and the IL-12 receptor complex. Abbreviations: Ig-like domain, immunoglobulin-like domain; CHR, cytokine-binding homology region; FnIII, Fibronectin III. (b) Expression of IL-23R in the main immune cell populations. Most studies have focused on T-cell populations. Created with BioRender.com

and signal through the recruitment of JAK tyrosine kinases. IL-12Rβ1 recruits TYK2, whereas IL23R interacts with JAK2 and the latter association is indispensable for IL-23 signaling [18, 19] (Fig. 1). The activation of Tyk2 and Jak2 by IL-23R promotes mainly STAT3, but also STAT1, STAT4 and STAT5 phosphorylation [9]. In contrast, IL-12Rβ2-mediated signaling promotes predominantly STAT4 phosphorylation [20], but can also induce STAT1 and STAT5 phosphorylation [21]. IL-23 receptor complex signaling has been extensively reviewed in [16].

### The *IL23R* locus

In humans, the *IL23R* gene is located on chromosome 1 and is directly adjacent to the *IL12RB2* gene. IL-12 stimulation was shown to induce *IL23R* expression [22], raising interesting questions about the coordinated versus exclusive regulation of these two genes in differentiating T-helper cells. Several *IL23R* isoforms may be produced by alternative splicing, resulting in premature termination and frameshifts that can generate receptors lacking the signaling components, or isolated ectodomains with the potential to act as decoy receptors [23–25]. The functional significance of these isoforms is unclear, although several have been detected in human NK and T cells, and some are preferentially expressed in lung carcinoma cells [23].

### Functional effect of coding genetic variants

A large number of genetic variants have been described at the *IL23R* locus (see [26] for an extensive review). The single nucleotide polymorphism rs11209026 is the best characterized functionally. This single nucleotide polymorphism has been associated with protection against the development of several CIDs, including CD, axSpA, Pso, and psoriatic arthritis [4, 27–32]. The

minor allele G to A variant introduces an amino acid change (Arg381Gln) in the intracellular domain of the IL-23R, in the proximity of the JAK2 kinase binding site. Human T cells carrying the minor allele show reduced IL-23-dependent STAT3 phosphorylation and IL-17 production, and subjects carrying this variant have decreased frequencies of circulating Th17 or IL-23R<sup>+</sup> T cells [33–35]. Coffre et al. found that CD4<sup>+</sup> T cells from SpA patients carrying the minor allele express lower levels of genes associated with both Th1 and Th17 differentiation and function, including *IL17*, *RORC*, *IFNG*, *IL12RB2*, and *IL23R* itself, supporting the protective role of this genetic variant [36].

Reduced STAT3 activation was also observed with two other protective coding variants (G149R, V362I) when expressed in Hela cells. In this case, reduced functionality of the variants could also be linked to reduced IL23R protein maturation and stability [37].

### Immune cell subsets expressing the IL-23R

To fully understand the role of IL-23 in protective immunity and in disease, it is important to identify the cells that are responsive to this cytokine. Many of these studies have been performed in mouse models. IL-23R was identified in 2002 [9] and has been mostly studied in the context of Th17 cells [2]. However, the important role of IL-23 in complex CID may suggest a broader role of this cytokine and more recently the attention has shifted to other immune cells, including innate-like T lymphocytes.

#### *IL-23R* in conventional T cells

Parham et al. [9] in 2002 described the presence of *IL23R* transcripts in T helper 1 cell clones. IL-23 became a focus of attention when it was shown to promote a distinct subset of murine

T-helper cells producing IL-17 [2]. IL-23 supports the expansion and survival of established murine Th17 cells [38] and Th17 clones express higher levels of IL-23R transcripts and IL-12R $\beta$ 1 than Th1 cells [39]. IL-23 can upregulate its own receptor in TCR-stimulated human CD4<sup>+</sup> T cells and increase IL-22 secretion but is not required for IL-17A production from stimulated memory CD4<sup>+</sup> T cells [40].

Although murine double-positive thymocytes express constitutively *IL23r*, conventional T cells in the periphery show IL-23R expression only upon activation [41, 42].

IL-6 plays a major role in *IL23r* induction in mouse CD4<sup>+</sup> T cells [43]. In particular, IL-6 and TGF- $\beta$ 3 induce development of highly pathogenic Th17 cells, with increased expression of *IL23r* and *IL22* [44]. IL-23 signaling in murine CD4<sup>+</sup> T cells induces Blimp-1, which enhances transcription of pathogenic factors [45]. IL-23R expression is important for disease development in several mouse models, including autoimmune encephalitis [46] and adjuvant-induced arthritis [47].

In vitro, differentiation of naïve CD4<sup>+</sup> T cells with IL-12 and IL-21 also induces high levels of IL-23R, which confers pathogenicity to Th1-like cells during intestinal inflammation [48]. IL-23 also expanded IL-17-producing tissue-resident memory CD4<sup>+</sup> T cells (TRM17) in the skin of mice infected with *C. albicans*. IL-23 blockade in mice and in psoriasis patients leads to depletion of skin TRM17 cells [49].

T-follicular helper cells (Tfh) isolated from an EAE mouse model also expressed IL-23R and IL-17 after restimulation in vitro [38]. IL-23 signaling induced a Tfh-IL-17 phenotype and promoted AID-mediated class-switch recombination [50].

A subset of regulatory T cells that expresses the transcription factor ROR $\gamma$ t may also be responsive to IL-23 [51], although IL-23 signaling in this population may have different outcomes in different experimental settings, suggesting the need for further investigation. Murine intestinal Treg express higher levels of *IL23r* than Treg in other tissues [52], and expression of ROR $\gamma$ t and IL-23R depends on the microbiota strain [53, 54]. In a colitis model, IL-23R signaling decreases Treg frequency in the gut and impairs their suppressive functions [52, 55], possibly because of reduced expression of Foxp3 [56]. However, Yang et al. [51] described the enhanced suppressive activity of the Foxp3<sup>+</sup>ROR $\gamma$ t<sup>+</sup> T-cell population in a colitis model, a difference that may depend on the different donor strains used for the transfer. IL-23 signaling also had a positive effect on Treg expansion in skin disease models, where IL-23 induced accumulation of Treg cells that express ROR $\gamma$ t and IL-17, and treatment with anti-IL-23p19 reduced the number of skin Th17-like-Tregs [57].

CD4<sup>+</sup> FOXP3<sup>+</sup> T cells expressing *IL23R* along with *RORC* and *IL17F* were also detected in a Th17-like T-regulatory cell cluster in humans by single-cell RNA profiling [58].

IL-23 may also affect the function of type 1 regulatory T cells in inflammatory bowel disease patients, decreasing their IL-10 production [59].

Similar to CD4<sup>+</sup> T cells, IL-23R expression can be induced in murine naïve CD8<sup>+</sup> T cells by IL-6 and TGF- $\beta$  [60]. In mice, CD8<sup>+</sup> T cells constitute about 10% of eGFP-IL23R<sup>+</sup> cells in the spleen

[61], and IL-23 supports the production of IFN $\gamma$ /IL-17 in CD8<sup>+</sup> T cells [60].

Human memory CD161<sup>+</sup> CD8<sup>+</sup> T cells also respond to IL-23 [62]. *IL23R*<sup>+</sup> IL-17A<sup>+</sup> CD8<sup>+</sup>  $\alpha\beta$  T cells are enriched in synovial fluid from psoriatic arthritis patients, suggesting that these cells may support chronic inflammation [63]. Similarly to what was observed for Th1 cells, enrichment of T-bet<sup>+</sup>IL-23R<sup>+</sup> CD8<sup>+</sup> T cells was observed in the intestine and blood of Graft-versus-Host Disease patients [64].

### IL-23R in innate-like T cells

Mucosal-associated invariant T cells (MAIT) constitutively express the IL-23R in both mice and humans, where it can be already detected in cord blood MAIT cells [65]. Up to 85% of lung MAIT cells expressed IL-23R in naïve reporter mice [66]. *IL23r* expression is further increased by TCR stimulation and addition of cytokines, such as IL-12, IL-18, and IL-15 [67]. In mouse models, the expression of either T-bet or ROR $\gamma$ t distinguishes MAIT1 from MAIT17 cells, the latter preferentially expressing *IL23r* [68]. IL-23 signaling can also expand a MAIT-17/1 phenotype [66]. These distinct subsets cannot be identified in humans, where *IL23R* constitutes a “core” gene for all MAIT cells [69–71]. The expression of *IL23R* is higher in human tissue-resident (mucosal, lung, skin, liver and entheses) MAIT cells [10, 66], [72–74]. The enrichment of IL-23R expressing MAIT cells in synovial fluid from psoriatic arthritis and rheumatoid arthritis patients [75] and in peripheral blood of spondyloarthritis patients [10] suggests a role for IL-23R<sup>+</sup> MAIT cells in the pathogenesis of CID.

It has been shown that both murine and human  $\gamma\delta$  T cells constitutively express IL-23R [76, 77]. The expression of *IL23r* in murine  $\gamma\delta$  T cells has been extensively studied.  $\gamma\delta$  T cells constitute the major IL-23R-expressing subset in lymphoid organs of naïve mice [61, 78] and produce IL-17 in response to IL-23 stimulation [76, 79, 80]. Spleen  $\gamma\delta$  T cells from naïve mice show low expression of *IL23r* mRNA and protein, but express IL-23R after antigen stimulation in vivo and have immunosuppressive activity on Th17 cells [81]. Murine IL-23R<sup>+</sup>/IL-1R<sup>+</sup> $\gamma\delta$  T cells were found to display a focused TCR repertoire, supporting a role for antigen recognition in the expansion of this subset [53]. In the mouse, IL-23 responsive  $\gamma\delta$  T cells belong mainly to the V $\gamma$ 4<sup>+</sup> and V $\gamma$ 6<sup>+</sup> subsets [82] and may play a role in protection against infections [79, 83].

In humans, IL-23R may be preferentially expressed on V $\gamma$ 9V $\delta$ 2 cells that also express high levels of IFN $\gamma$  and cytotoxic molecules [77]. Human IL23R<sup>+</sup>  $\gamma\delta$  T cells may also play a role in inflammatory disease. Enteseal IL23R<sup>+</sup>  $\gamma\delta$  T cells express high levels of *IL23R* transcripts [84], and IL-23R<sup>+</sup> cells are enriched in the joints of spondylarthritis patients [85]. IL-23R<sup>+</sup>  $\gamma\delta$  T cells were also increased in children with primary nephrotic syndrome [86]. Like their murine counterpart, human  $\gamma\delta$  T cells were shown to produce IL-17 and IL-22 in response to IL-23 stimulation [85].

More recently, a T-cell population co-expressing  $\gamma\delta$  and  $\alpha\beta$  receptors were described in mice and humans. These cells expressed high levels of IL-23R and displayed a hyperinflammatory phenotype in response to IL-23 [87].

Murine and human NKT are other populations that express the IL-23R and can produce IL-17 (and IL-21) in response to IL-23 stimulation [62, 85, 88]. In humans, a small fraction of NKT cells express IL-23R in peripheral blood. However, IL-23R<sup>+</sup> NKT cells are enriched in the synovial fluid of patients with spondylarthritis [85]. IL-23 synergizes with IL-18 to promote IFN $\gamma$  production in human NKT cells and to stimulate the proliferation of NKT and NK cells [89].

### IL-23R in other innate lymphoid cells

Innate lymphoid cells (ILC) are mostly tissue-resident lymphoid cells that lack an antigen-specific receptor. ILCs were also found to express *Rorc* and *Il23r* and to be involved in the development of innate colitis [69, 90–92]. ILCs can be assigned to different subsets (ILC1, ILC2, and ILC3) that mirror the Th1, Th2, and Th17 subsets of conventional T cells. The IL-23R is mainly expressed in the ILC3 subset, both in mice [69, 70] and in humans [93, 94], although IL-23 enhanced the differentiation and growth of both human ILC1 and ILC3 [95].

ILC3 cells in synovial tissue of spondylarthritis patients express *RORC* and *IL23R* and respond to IL-23 by expressing *IL22* and *CSF2*, but not *IL17A* [93].

### IL-23R in NK cells

*IL23R* transcripts were first detected in human NK clones and cell lines by Parham et al. [9]. IL-23 treatment was shown to induce human NK activation and secretion of IFN $\gamma$  [96].

### IL-23R in B cells

B cells constitute about 10% of eGFP-IL-23R<sup>+</sup> cells in mouse spleen [61], but the role of IL-23 in this population has been poorly studied.

Primary B cells from healthy humans do not express IL-23R, which is upregulated in acute lymphoblastic leukemia B cells [97]. IL-23 signaling in acute lymphoblastic leukemia B-cells induced apoptosis and inhibited proliferation, exerting antileukemic activity [97]. Expression of the IL23R chain, in the absence of IL-12Rb1, was also reported in chronic lymphocytic leukemia B cells, and correlated with tumor progression [98]. The role of IL-23 signaling in normal B-cell function is poorly investigated. Cell surface staining for IL-23R was also detected on plasma cells from healthy donors, which responded to IL-23 by increasing IgM secretion [99].

### IL-23R in myeloid cells

Very little is known about IL-23R expression and function in myeloid cells. Parham et al. [9] found that human monocytes and dendritic cells (DC) express negligible levels of *IL23R*, however murine bone-marrow-derived (but not peritoneal) macrophages stimulated with LPS and IL-10 expressed *Il23r* in the absence of detectable *Il12rb1*, which could be induced by IFN $\gamma$  stimulation. Inflammatory macrophages isolated from brains of mice with EAE, but not from healthy mice, expressed *Il23r* [3], and in a house dust mite model of airway inflammation, IL-23R positive cells in the lung were mainly macrophages and CD11<sup>+</sup> dendritic cells [100]. These data suggest that IL-23R in myeloid cells may be expressed only in particular conditions, consistent with the lack of expression by unstimulated human myeloid cells reported in databases [101, 102]. Surface expression of IL-23R was described for human monocyte-derived macrophages, which responded to IL-23 treatment with increased secretion of proinflammatory cytokines [103, 104]. Mycobacterial infection also increased the expression of IL-23R and IL-23 in human and murine macrophages [105].

Low levels of *IL23R* mRNA have been reported in human dendritic cells [9] and IL-23R levels were elevated in monocyte-derived DC from patients with HBV-related liver failure [106]. IL-23 was described to have adjuvant effects on DC priming ability [107]; however, IL-23 signaling in DCs has not been further investigated.

Similarly, activated granulocytes have been reported to express IL-23R in inflammatory murine models of colitis or aspergillosis [108, 109], but confirmation of the role of IL-23 in these cells is lacking.

A challenge for the characterization of IL-23R expression is the scarcity of reliable anti-IL23R antibodies and the fact that IL-23R is expressed only at low frequencies in most resting cells.

### Transcriptional regulation of IL-23R

The transcriptional mechanisms regulating IL-23R expression have been mainly addressed in the context of murine Th17 cell differentiation (Table 1, Fig. 2).

Transcription factors of the AP1 family play an important role in Th17 determination and in *Il23r* transcription. In particular, JunB binds cooperatively with BATF and IRF4 to an AP1-IRF composite motif [110, 111], which is also observed at the *Il23r* locus [112]. BATF binding may be determinant to start *Il23r* expression, as it was shown to occur also at sites of closed chromatin, and was proposed to act as a pioneer factor in inducing chromatin remodeling by recruiting the boundary transcription factor CTCF [113]. Further mechanistic studies will be required to precisely define the role of this pathway in inducing IL-23R expression.

Several of the Th17-inducing transcription factors may also affect *Il23r* transcription indirectly, for example by acting on the expression of Rorty, which also binds to the *Il23r* locus and regulates its activation [114, 115]. Other factors, such as T-bet,



**Table 1.** Transcription factors that bind to the murine and human loci encoding IL-23R.

Factor	Description	Technique	Reference
Murine			
Irf4	ChIP seq analysis on murine naïve CD4 <sup>+</sup> cells differentiated under Th17 polarizing condition demonstrates binding of Irf4, Batf, and JunB to the AICEs motifs present in the promoter and intron 3 of the <i>Il23r</i> locus.	ChIP-seq	[110]
Batf		Knock-out	
JunB		EMSA	
Irf4	Binding of Batf, Irf4, and Junb at <i>Il23r</i> promoter, intron 3, 6, and 7 was detected by ChIP seq in Th17 differentiating cells.	ChIP-seq	[127]
Batf			
JunB			
Roryt	Roryt binds to the <i>Il23r</i> promoter and to introns 3 and 6 in Th17 cells. Foxp3 binding was observed in iTregs at intron 6 of <i>Il23r</i> .	ChIP-seq	[115]
Foxp3			
p300	Binding of JunB and p300 to the promoter and the introns 3, 6, and 7 of the <i>Il23r</i> locus.	ChIP-seq	[128]
JunB			
Blimp1	ChIP seq was performed in IL-17.EGFP <sup>+</sup> cells differentiated in the presence of TGFb, IL-6, and IL-23. Blimp1 binds <i>Il23r</i> intron 3, together with Stat3, p300 and Rorgt. Stat3 binds at several regions in the <i>Il23r</i> locus.	ChIP-seq	[45]
Stat3			
p300			
Roryt	HiF1alpha binds the <i>Il23r</i> promoter together with Rorgt and p300 in CD4 <sup>+</sup> cells activated under the Th17 skewing condition.	ChIP-PCR	[129]
Hif1α			
Roryt			
p300	Naive CD4 <sup>+</sup> T cells were sorted from CD4 <sup>Cre</sup> RBPJ <sup>flox/flox</sup> mice and differentiated under the Th17 polarizing condition. In Th17 cells, Rbpj binds the <i>Il23r</i> promoter, to a site (1100 bp upstream of the TSS) distinct from those bound by other factors indicated in this table.	ChIP-PCR	[130]
Rbpj			
Batf	Batf was shown to bind the <i>Il23r</i> locus (promoter and introns 2,3 and 6 in Th17 cells) and to pioneer the opening of the chromatin. Batf-induced binding of Ctcf, Ets1, and Med12 to the <i>Il23r</i> locus.	ChIP-seq	[113]
Ctcf		Knock-out	
Ets1			
Med12			
Rora	ChIP-seq experiments revealed Rorgt binding at the <i>Il23r</i> promoter, intron 3 and 6, and Rora binding to the <i>Il23r</i> promoter and intron 3 in Th17 cells.	ChIP-seq	[114]
Roryt		Knock-out	
Tbet	Direct binding of T-bet to the <i>Il23r</i> promoter was shown in splenocytes from Va2.3/Vb8.2 TCR-transgenic mice activated with myelin basic protein peptide. The binding induces decrease in <i>Il23r</i> expression.	ChIP-PCR	[116]
		Knock-down	
Tbet	T-bet binding was also observed at <i>Il23r</i> third intron in a transfer model of colitis and negatively regulates its expression.		[117]
Tbet	T-bet binds to <i>Il23r</i> locus (introns 3 and 6) in murine Th1 cells.		[118]
Stat3		ChIP-seq	[121]
Clock	Binding of Clock at the <i>Il23r</i> promoter in splenic γ/δ <sup>+</sup> T cells isolated from wild-type mice.	ChIP-PCR	[131]
Human			
FOSL1/ FOSL2 BATF	Colocalization of FOSL1/FOSL2 and BATF binding at the <i>IL23R</i> promoter in Th17 cells induced from Naïve isolated Cord blood CD4 cells.	ChIP-seq	[120]
BRD4	BRD4 binds to the <i>IL23R</i> locus in CD4 <sup>+</sup> T cells activated through the TCR. A selective BET inhibitor reduced IL-23r expression in vitro and in a graft-versus-host disease model.	ChIP-seq Inhibitor treatment	[132]

may display context-dependent effects on IL-23R expression: Tbet was shown to increase *Il23r* levels in an EAE model by direct binding to the *Il23r* promoter but to repress *Il23r* in Th17 cells in a colitis model [116, 117]. Tbet was reported to bind the

*Il23r* gene also in Th1 cells, without affecting IL23R expression [118].

FOSL proteins play a complex role in the regulation of Th17 differentiation and IL-23R expression. In the mouse, FOSL2



**Figure 2.** Transcription factors binding to the *IL23r* locus. (a) Alignment of the human and murine *IL23R* loci, obtained with the VISTA browser. Regions with >70% identity are marked in color: Conserved noncoding sequences (CNS) in salmon, 5' and 3'-UTR in light blue, and exons in purple. (b) Epigenetic marks tracks were obtained from the GEO database with the following GSM ID: ATACseq, GSM4731624; H3K4me1, GSM4291301; H3K27ac, GSM4291309; and H3K4me3, GSM4291303. (c) Indication of transcription factors bound to the murine and to the human *IL23R* locus obtained from published ChIP data.

controlled the inflammatory response by reducing the expression of proinflammatory cytokines such as *IL17A* and *IL17F*; however, *FOSL2* was also important for Th17 maintenance and survival since it increased *IL23r*, *IL21*, and *IL12rb1* expression [112]. Overexpression of *FOSL1* and *JUNB* together promotes murine Th17 differentiation, increasing the expression of *IL17*, *Rorc*, and *IL21*. Consistently, inhibiting *Fosl1* and *Junb* expression in vivo attenuated disease in an arthritis model [119]. Overexpression of *FOSL1* in  $CD4^+$  T cells from healthy donors led to an increase in *IL-17*-producing cells and *IL-17A* secretion [119]. A recent study in humans showed that *FOSL1*, *FOSL2*, and *BATF* bind at the same site in the *IL23R* locus and at other Th17-associated genes. However, the study described a positive regulatory role of *BATF* but a negative role of *FOSL* proteins, since *FOSL1* and/or *FOSL2* overexpression decreased *IL23R* transcription. The authors suggested that *BATF* and *FOSL* proteins compete for binding to transcriptional partners and target genes [120].

*Stat3* was also shown to directly regulate *IL23r* expression [45, 121]. Jain et al. [45] demonstrated that *IL23r* was downregulated in naive  $CD4^+$  T cells from *STAT3* conditional KO mice, cultured under Th17 polarizing condition. *IL23r* expression was not affected in *STAT1* KO mice.

### Posttranscriptional regulation of *IL23R* expression

*IL23R* expression can be controlled posttranscriptionally by several miRs, adding another layer of complexity to *IL-23R* regulation.

*Let-7f* targets *IL23R* 3'UTR and its overexpression decreases *IL23R* levels in human  $CD4^+$  T and K562 cells. *Let-7f* levels can be regulated by estrogen signaling in humans and in mice. Th17

cells from female asthma patients had lower *let-7f* expression and higher *IL-23R* expression than Th17 from male patients, and *let-7f* inhibition further increased *IL-23R* levels. Administration of estrogen and progesterone to ovariectomized mice decreased *let-7f* levels and increased *IL-23R* and *IL-17* expression [122]. Consistently, Th17 cells from *Esr<sup>-/-</sup>* mice showed increased levels of *let-7f* and reduced *IL-17* and *IL-23R* expression [123]. Overexpression of *let-7g* in activated  $CD4^+$  T cells protected from severe disease in a mouse model of multiple sclerosis, reducing the secretion of proinflammatory cytokines and *IL23r* expression in Th17 cells [124].

*IL23r* 3'UTR is also targeted by miR-34a and miR-34a<sup>-/-</sup> mice show increased levels of *IL-23R* and *IL-17* in the colon following infection with *Citrobacter rodentium* [125].

The inhibitory effect of miR146b-5p on *IL-23R* cell surface expression in chronic lymphocytic leukemia cells is mediated by the downregulation of the *IL-12Rb1* chain of the receptor [126].

## Conclusion and perspectives

In the past decade, our understanding of the role of the *IL-23/IL-23R* pathway in health and disease has greatly advanced, resulting in the implementation of novel therapeutics of great efficacy for immune-mediated inflammatory diseases, such as psoriasis and psoriatic arthritis. However, much remains to be learned about *IL-23* biological activity in health and disease.

The majority of the studies characterizing the *IL-23/IL-23R* pathway have focused on T lymphocytes, and primarily, on conventional  $CD4^+$  T cells. The biological functions of this pathway in other immune cells, such as innate lymphocytes, B cells, and myeloid subsets need to be further explored. The data available

today indicate that most immune cells need to be activated in order to acquire responsiveness to IL-23. The stimuli and the transcriptional pathways that induce the IL-23R in the different cell types are variable, depend on the cell type and the environmental context, and are still poorly characterized. Additionally, future efforts should also focus on understanding the downstream effects of IL-23 signaling in the different cell types, and their role in disease settings.

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**Abbreviations:** DC: dendritic cells · ILC: innate lymphoid cells · MAIT: mucosal-associated invariant T cells · Tfh: T-follicular helper cells

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