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IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases

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The cytokine interleukin-12 (IL-12) was thought to have a central role in T cell–mediated responses in inflammation for more than a decade after it was first identified. Discovery of the cytokine IL-23, which shares a common p40 subunit with IL-12, prompted efforts to clarify the relative contribution of these two cytokines in immune regulation. Ustekinumab, a therapeutic agent targeting both cytokines, was recently approved to treat psoriasis and psoriatic arthritis, and related agents are in clinical testing for a variety of inflammatory disorders. Here we discuss the therapeutic rationale for targeting these cytokines, the unintended consequences for host defense and tumor surveillance and potential ways in which these therapies can be applied to treat additional immune disorders.

IL-12 and IL-23 are produced by inflammatory myeloid cells and influence the development of T_H1 cell and IL-17–producing T helper (T_H17) cell responses, respectively. The rationale for developing IL-12 antagonists was prompted by observations that mice deficient in IL-12p40 are resistant to experimentally induced autoimmune conditions, including paralysis induction after immunization with brain-derived antigens, arthritis inflammation after immunization with a joint antigen, ocular disease after immunization with a retinal antigen and multiple gut disease models. This suggested that IL-12 could be an effective therapeutic target[1–5]. Studies of neutralizing antibodies to IL-12p40 in multiple mouse strains seemed to confirm the importance of therapeutically targeting IL-12 to decrease immune pathology[6,7]. However, mice deficient in the other IL-12 subunit, IL-12p35, showed no protection or showed exacerbated disease in some models[1,2]. Following the recognition, in 2000, that IL-12 and IL-23 share the IL-12p40 subunit but only IL-23 uses the p19 subunit[8], it was determined that mice deficient in IL-23 but not IL-12 are resistant to experimental immune-mediated disease[1–5]. By 2000, the first anti–IL-12p40 therapy targeting IL-12—subsequently recognized to target IL-23 as well—was under evaluation in patients with Crohn's disease[9]. Currently, at least 10 therapeutic agents targeting IL-12, IL-23 or IL-17A are being tested in the clinic for more than 17 immune-mediated diseases (**Table 1**). Here we discuss the preclinical and clinical data validating these therapeutic strategies and the potential consequences of targeting these immune pathways.

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IL-12 and IL-23: related but functionally distinct

In mice and humans, IL-12 is composed of the IL-12p40 subunit linked to the IL-12p35 subunit, and the heterodimer signals through the IL-12 receptor (IL-12R), which comprises the IL-12Rβ1 and IL-12Rβ2 subunits (**Fig. 1**). IL-12 stimulates nonreceptor Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2) activity, leading to phosphorylation of signal transducer and activator of transcription (STAT) family members STAT1, STAT3, STAT5 and, in particular, STAT4 homodimers[10,11]. IL-23 is composed of the IL-23p19 subunit and the IL-12p40 (here called IL-12/23p40) subunit, which signals through IL-23R and IL-12Rβ1 (ref. 8). Like IL-12, IL-23 activates JAK and STAT signaling molecules, but it activates STAT3 predominantly (ref. 12). The difference in mouse IL-12– and IL-23–dependent signaling is due in part to the preferential activation of STAT4 by IL-12 and of STAT3-dependent target genes by IL-23.

IL-12 and IL-23 are secreted by human and mouse dendritic cells and tissue-resident macrophages in response to exogenous or endogenous signals[5,13,14] associated with host defense and wound healing. Whereas IL-12 promotes differentiation of naive CD4 T cells into interferon (IFN)-γ–producing T_H1 cells, IL-23 does not directly promote T_H cell differentiation, owing to the absence of IL-23

receptor (IL-23R) on human and mouse naive T cells[15,16]. The molecular mechanism governing *in vivo* development of IL-23R$^+$ memory T cells in humans is unclear, but in mice, exposure to cytokines including transforming growth factor-β (TGF-β), IL-1 and IL-6 induces expression of retinoic acid receptor–related orphan receptor-γt (RORγt), a lineage-specific transcription factor that promotes expression of *Il23r* and *Il17a*[17]. IL-23R signaling can then induce the phosphorylation and activation of STAT3, which acts to promote transcription of *Il23r* and *Rorc* (encoding RORγ), establishing a positive feedback loop and stabilizing expression of genes controlling T cell activation (including *Rorc* and *Il23r*) and encoding proinflammatory effector molecules (*Il17a*, *Il17f*, *Il22* and *Csf2*)[12,18–21]. Importantly, these T_H cells sense their cytokine microenvironment and can be 'reprogrammed' to produce a multifaceted immune response. This inherent flexibility can translate into optimal immunity, ineffective (tolerogenic) response or immunopathology, depending on the immune stimuli[18,22–24].

Therapeutic rationale

In addition to these preclinical disease model data, familial genetic studies, large-scale genome-wide association studies (GWAS) and next-generation sequencing approaches have highlighted therapeutic indications where IL-23 may contribute to inflammatory disease risk. For example, a psoriasis GWAS reported a protective association for the single-nucleotide polymorphism (SNP) rs11209026 (c.1142G>A; p.Arg381Gln) residing in the IL-23R protein-coding sequence with a modest odds ratio (OR) of 0.67 ($P = 7 \times 10^{-7}$)[25]. A GWAS in ileal Crohn's disease also showed an association with rs11209026 (ref. 26), with the minor glutamine variant protective for Crohn's disease risk with an OR of 0.26–0.45. The protective association of this variant (and other SNPs in linkage disequilibrium with it) in Crohn's disease was also shown in ulcerative colitis[27–41]. The largest meta-analysis of all inflammatory bowel disease GWAS to date (~40,000 cases and ~40,000 controls) indicates that carriage of the glutamine variant gives a modest reduction for disease risk (OR = 0.43, $P = 8 \times 10^{-161}$) (ref. 36). The rs11209026 allele is also associated with protection from ankylosing spondylitis[42,43], psoriatic arthritis[44–47] and graft-versus-host disease[48–51]. Notably, this IL-23R variant has not been reliably associated with other common inflammatory diseases such as rheumatoid arthritis, type 1 diabetes or multiple sclerosis in GWAS powered to detect protective effects similar to those seen in

Table 1 IL-12/23p40, IL-23p19 and IL-17A and IL-17RA antagonists in clinical development

Target	IL-12p40; IL-23p40		IL-123p19						IL-17A; IL-17RA		
	Ustekinumab (CNTO-1275)	Briakinumab (ABT-874)	Tildrakizumab (MK-3222; SCH 900222)	Guselkumab (CNTO-1959)	BI-655066	AMG 139; MEDI-2070	LY3074828	LY2525623	Secukinumab (AIN457)	Ixekizumab (LY2439821)	Brodalumab (AMG 827)
Psoriasis	Approved	Ph3	Ph3	Ph3	Ph2	Ph1	Ph1	Ph1 (terminated)	Approved	Ph3	Ph3
Psoriatic arthritis	Approved			Ph2					Ph3	Ph3	Ph3
Crohn's disease	Ph3	Ph2 (terminated)	Ph1		Ph2	Ph2			Ph2 (terminated)		Ph2 (terminated)
Ankylosing spondylitis	Ph2				Ph2				Ph3	Ph3 (study withdrawn prior to enrollment)	
Rheumatoid arthritis	Ph2			Ph2					Ph3	Ph2	Ph2 (terminated)
Multiple sclerosis	Ph2	Ph2							Ph2		
Graft-versus-host disease	Ph2										
Atopic dermatitis	Ph2										
Hidradenitis suppurativa	Ph2										
Primary biliary cirrhosis	Ph2										
Sarcoidosis	Ph2										
Systemic lupus erythematosus	Ph2										
Behçet's disease; uveitis									Ph3 (terminated)		
Asthma									Ph2		Ph2 (terminated)
Dry eye									Ph2		
Polymyalgia rheumatica									Ph2		
Type 1 diabetes									Ph2 (terminated)		

The highest level of clinical development for each agent in each indication is listed. Trial status was obtained as listed on http://www.clinicaltrials.gov (accessed April 2015). Specific reasons for early trial termination are not consistently provided. Ph3, phase 3; Ph2, phase 2; Ph1, phase 1.

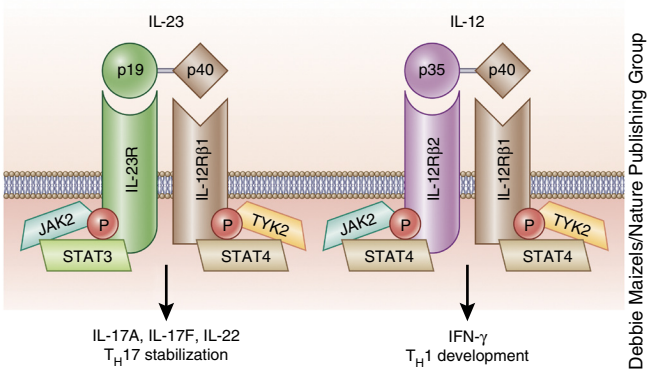

Figure 1 Schematic representation of IL-12 and IL-23, and their receptors and downstream signaling pathways. IL-12 is made up of the IL-12/23p40 and IL-12p35 subunits, and IL-23 comprises IL-23p19 and IL-12/23p40. IL-12 signals through the IL-12Rβ1 and IL-12Rβ2 subunits, and IL-23 signals through IL-12Rβ1 and IL-23R. IL-12 stimulation of JAK2 and TYK2 activity leads to phosphorylation of STAT4 and other STAT molecules. IL-23 also activates the JAK-STAT pathway but acts mainly on STAT3. IL-12 induces the production of IFN-γ, which is required for the development of T_H1 immune response. IL-23 induces IL-17A, IL-17F and/or IL-22 and stabilizes T_H17 cells.

Crohn's disease and psoriasis[52–54]. Although these GWAS findings are compelling, it is important to keep in mind the limitations of such studies; these common loci tend to additively explain only a small proportion of the narrow-sense heritability of disease risk[55]. Whereas some *in vitro* functional studies suggest that the rs11209026 protective allele results in an attenuation of IL-23R signaling[56–60], definitive proof of disease association, mechanism of action and functional significance of the IL-23 pathway can be determined only by testing antagonists in the clinic.

Clinical efficacy of IL-12 and IL-23 antagonists

The inflammatory role of IL-12 revealed in the mid-1990s provided the rationale to develop the human IL-12–neutralizing antibodies ustekinumab (CNTO-1275), briakinumab (ABT-874; J695) and the 'SMART anti-IL-12 antibody'. Ustekinumab and briakinumab were reclassified as anti–IL-12/23p40 antibodies after the discovery of IL-23 in 2000. The SMART anti–IL-12 antibody was designed to recognize the heterodimeric structure of IL-12 p35-p40 and was discontinued in 2003 owing to its inability to target IL-23, which has a major role in autoimmune disease[61]. Both ustekinumab and briakinumab were evaluated in a number of immune-mediated diseases, with psoriasis seeing the most advanced clinical development (**Table 1**).

Psoriasis

Psoriasis is an inflammatory skin condition involving well-defined, red, raised, scaly lesions resulting from excessive growth and aberrant differentiation of keratinocytes. Concentrations of IL-12/23p40 and IL-23p19 mRNA are higher in lesions than in nonlesional and normal skin, whereas IL-12p35 mRNA is present but decreased in lesional skin[62,63]. Cytokines induced by IL-12 (such as IFN-γ) and IL-23 (such as IL-17A, IL-17F and IL-22) are elevated in lesional plaques[63]. Preclinical models have illustrated that IL-23 exposure in murine skin drives the excessive growth and abnormal differentiation of keratinocytes, whereas IL-12 does not promote the same pathology[19,63–69].

The extent and severity of lesions are quantified according to the Psoriasis Area and Severity Index (PASI), and antipsoriatic biological therapies are evaluated on the basis of the frequency of patients with moderate to severe disease who show 75% reduction in baseline PASI score (PASI-75) (**Fig. 2**). Ustekinumab's efficacy and safety was evaluated in two phase 3 studies after subcutaneous dosing of 45 mg or 90 mg at week 0, week 4 and every 12 weeks afterward. The primary endpoint was PASI-75 response at week 12, which ranged between the two studies from 66.7% to 67.1% (for the 45-mg dose group) and from 66.4% to 75.7% (for the 90-mg dose group); the group given placebo showed 3%–4% response[70,71] (**Fig. 2**). Briakinumab's efficacy and safety was evaluated in four phase 3 studies of monthly subcutaneous administration of 200 mg (for the first two doses) and 100 mg thereafter. Week 12 PASI-75 responses ranged from 76.6% to 81.9% across the four studies; responses in the placebo group ranged from 4.5% to 7.4% (refs. 72–75) (**Fig. 2**). Ustekinumab's efficacy and safety profile were acceptable for registration in the United States and Europe for the treatment of patients with moderate to severe psoriasis. Major adverse cardiac events (i.e., myocardial infarction, stroke or cardiovascular death) occurred in a higher number of patients receiving briakinumab compared to those receiving placebo in some phase 3 trials[72]. Briakinumab's registration application was withdrawn pending further analysis and potential additional studies that have not occurred to date[76].

Two IL-23–specific antagonists, tildrakizumab (MK-3222; SCH 900222) and guselkumab (CNTO-1959), have completed phase 2 trials for psoriasis; data from these trials enable cross-study comparison of the efficacy of IL-23–specific agents versus broader IL-12– and IL-23–targeting agents. In a preliminary report, tildrakizumab's efficacy was evaluated after subcutaneous dosing of 5, 25, 100 or 200 mg at weeks 0 and 4 and every 12 weeks onward. The primary endpoint was the week 16 PASI-75 response, which was 66% and 74% for the 100-mg and 200-mg dosage groups, respectively; the placebo group had a 4% response (**Fig. 2**). The clinical benefit was also comparable to the earlier IL-12/23p40 study primary endpoint, wherein the week 12 PASI-75 response was ~60% and ~70% for the 100-mg and 200-mg dosage groups, respectively, with a 4% response to placebo (K. Papp, personal communication). The 100-mg and 200-mg regimens are now under investigation in phase 3 studies. Guselkumab's efficacy was evaluated after subcutaneous dosing of 5, 15, 50, 100 or 200 mg at 8-week intervals or at weeks 0 and 4 and every 12 weeks thereafter. The week 16 PASI-75 responses ranged from 79% to 81% for the three highest dose groups that included both dosing schedules (**Fig. 2**); week 12 PASI-75 data were not reported[77]. The 100-mg dose regimen is currently under investigation in phase 3 studies. A third IL-23–specific antibody, LY2525623, was terminated in phase 2 for several reasons, including complexities in development, but not because of safety concerns (NCT01018810). The IL-23–specific antibodies AMG 139 (MEDI2070), BI-655066 and LY3074828 are in earlier stages of development.

The pathogenicity of IL-23 depends in part on the dysregulated production of IL-17A, IL-17F and IL-22, providing a rationale for targeting these factors for inflammatory disorders. Two IL-17A antagonists (secukinumab (AIN457) and ixekizumab (LY2439821)) and an IL-17RA antagonist (brodalumab (AMG 827)) that blocks IL-17A, IL-17F and other IL-17 family members, are in development. The IL-22 antagonist fezakinumab (ILV-094) has been discontinued[78]. The IL-17A and IL-17RA antagonists have shown antipsoriatic efficacy reaching beyond 80% (PASI-75 response at week 12) with biweekly to monthly dosing intervals in phase 3 studies (**Fig. 2**), and secukinumab was recently approved in Europe and the US for psoriasis[79–86].

Psoriatic arthritis (PsA) is a spondyloarthropathy that develops in ~30% of people with psoriasis. PsA is characterized by distal

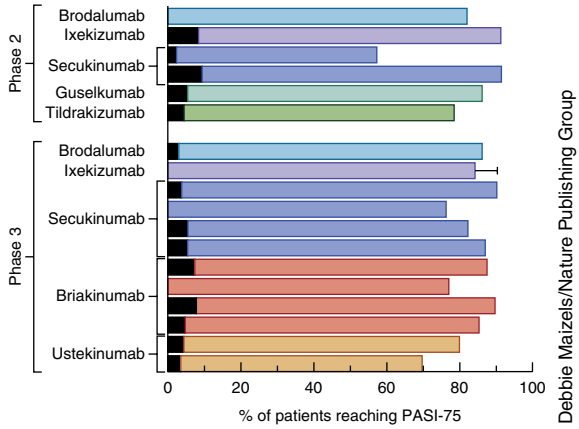

Figure 2 Efficacy of IL-12/23p40, IL-23p19 and IL-17A or IL-17RA antagonists in treating patients with moderate-to-severe psoriasis. IL-23 and IL-23 pathway antagonists demonstrate substantial benefit for a large fraction of patients with moderate to severe psoriasis. Phase 3 results are from week 12; phase 2 results are from week 16 (tildrakizumab and guselkumab) or week 12. The highest reported efficacy for any dose group within the studies' 12–16 week treatment period is plotted. Black bar within each colored histogram indicates the associated placebo group. Ustekinumab's phase 3 results are from PHOENIX-I and PHOENIX-II[70,71]. Briakinumab's phase 3 results are from clinical trials NCT00570986 (ref. 72), NCT00691964 (ref. 73), NCT00679731 (ref. 74) and NCT00710580 (ref. 75). Secukinumab's phase 3 results are from the ERASURE[83], FIXTURE[83], FEATURE[84] and JUNCTURE[84] trials. Ixekizumab's phase 3 results are from UNCOVER-I, UNCOVER-II and UNCOVER-III[85]. Each individual study's efficacy has not been stated but the range of efficacy seen over the three studies has been stated (the graphed bar is the mean and the error bar is the range between the three studies' efficacy).Brodalumab's phase 3 results are from AMAGINE-I[86]. Tildrakizumab's phase 2 results are from NCT01225731, week 16. Guselkumab's phase 2 results are from X-PLORE[77], week 16. Secukinumab's phase 2 results are from NCT00941031 (ref. 80) and NCT01071252 (ref. 81), week 12. Ixekizumab's phase 2 results are from NCT01107457 (ref. 79), week 12. Brodalumab's phase 2, week 12 results are from NCT00975637 (ref. 82), week 12.

interphalangeal joint inflammation, swelling of the fingers and toes, Achilles tendon tendinitis, nail pitting and lower back pain. PsA therapies are evaluated on the basis of the frequency of patients showing a reduction ≥20% in baseline American College of Rheumatology score (ACR20 response). In two phase 3 trials of ustekinumab, the percentage of PsA patients achieving an ACR20 response at week 24 was 20.2%–22.8% with placebo and 42.4%–49.5% with the antibody, leading to its recent approval for treatment of PsA[87]. In two phase 3 PsA trials for secukinumab, week 24 ACR20 response was 15.3–17.3% for patients given a placebo and 50–54% for patients who received the antibody[84]. Similarly, ixekizumab was recently reported to achieve its PsA phase 3 endpoint[88]. In a phase 2 study of brodalumab, the percentage of PsA patients achieving an ACR20 response at week 12 was 18% with placebo and 37%–39% with the antibody[89].

Other inflammatory diseases

Ankylosing spondylitis is another spondyloarthropathy genetically associated with the IL-23 pathway; it is a painful condition involving spinal inflammation that can lead to irreversible spinal fusion. In a small open-label study, 75% of ankylosing spondylitis patients treated with ustekinumab showed ≥20% improvement in their Assessment in Ankylosing Spondylitis (ASAS) score (ASAS-20) at week 24 (ref. 90). Secukinumab in a phase 2 study increased the percentage of ankylosing spondylitis patients achieving ASAS-20 from 24% (treated with placebo) to 59% at week 6 (ref. 91). Additionally, it was recently announced in a press release that secukinumab met its primary endpoint (ASAS-20 at week 16) in two phase 3 ankylosing spondylitis studies[92].

Crohn's disease is an inflammatory bowel disease genetically associated with the IL-23 pathway in which IL-12/23p40, IL-23p19 and IL-17A and IL-17RA antagonists have been evaluated. In a phase 2b study of ustekinimab, a greater percentage of patients with moderate to severe Crohn's disease showed a clinical response (≥100-point decrease in baseline Crohn's Disease Activity Index (CDAI)) to the antibody at week 6 than did those treated with placebo (39.7% and 23.5%, respectively). Importantly, the population enrolled was enriched for patients resistant to tumor necrosis factor (TNF) antagonists, the standard of care[93]. Similarly, a greater percentage of patients with moderate to severe, TNF-resistant Crohn's disease treated with the anti–IL-23p19 antibody MEDI2070 showed a week 8 clinical response than did patients given placebo in a phase 2a study (45.8% and 25.0%, respectively)[94]. Neither secukinumab nor brodalumab provided benefit in Crohn's disease, and both were associated with higher rates of adverse events than was placebo[95,96].

Multiple sclerosis is an immune-mediated disease that has not been genetically associated with the rs11209026 glutamine IL-23R variant in GWAS to date, yet anti–IL-12/23p40 antagonists have been evaluated in phase 2 studies. Patients with relapsing-remitting multiple sclerosis (RRMS) treated with ustekinumab (up to 180 mg monthly) did not show significant changes in the number of new gadolinium-enhanced T1 weighted images of brain lesions as assessed by magnetic resonance imaging at week 23 (ref. 97). RRMS patients treated with different briakinumab dosing regimens showed either a significantly decreased number of gadolinium-enhanced lesions or significantly lower relapse rates at week 24; however, the benefit was not great enough to warrant further development in multiple sclerosis[98]. Secukinumab showed positive results in gadolinium-enhanced T1-weighted imaging of lesions at week 24 in a small phase 2a study[99].

Rheumatoid arthritis and type 1 diabetes are other immune-mediated diseases that the IL-23 pathway has not been genetically associated with and for which no clinical data with IL-12/23p40 antagonists have been published. All three IL-17A and IL-17RA antagonists showed clinical benefit in rheumatoid arthritis[100–102], which may point to IL-23–independent sources of IL-17A–producing cells in the inflamed joint[103,104].

Companion diagnostics to identify patients that would respond optimally to therapy targeting the IL-23 pathway can be beneficial in some situations but not in others. The ease of measuring the magnitude and speed of psoriatic disease reversal combined with the high frequency of responding patients minimizes the need for a companion diagnostic in the psoriasis indication. In contrast, the lower frequency of Crohn's disease patients that show clinical benefit after IL-12/23p40 neutralization, combined with the more invasive procedures needed to quantify mucosal healing of the gut epithelium, support the development of companion diagnostics to enrich for responder patients in clinical trials. Ultimately, the aim is to identify patients who will best benefit from antagonism of the IL-23 pathway. Prospectively identifying ankylosing spondylitis patients who respond to an IL-23 pathway therapy will also be beneficial owing to the slow progressive nature of new bone formation in the inflamed spine and the instrumentation needed to measure bone formation and identify nonresponders to the therapy.

Potential adverse effects of targeting IL-12 and/or IL-23

Treatment of inflammatory disease with any immunosuppressive agent carries the theoretical risk of impaired host defense responses to pathogens and/or decreased tumor surveillance. Emerging data from human loss-of-function variants and mouse preclinical studies have informed the relative risks of targeting IL-12 and/or IL-23.

Considerations related to infectious disease risk

The theoretical risk of compromised immunity are of particular concern owing to immune defects discovered in patients with autosomal recessive deficiencies in IL-12/23p40 and IL-12Rβ1 (refs. 105–107) (**Fig. 3**). Both deficiencies are genetic etiologies of Mendelian susceptibility to mycobacterial disease (MSMD) (genes involved in MSMD are listed at http://www.biobase-international.com), a rare condition in otherwise healthy patients who have a selective infection predisposition to weakly virulent mycobacteria such as Bacillus Calmette-Guerin (BCG) vaccines, nontuberculous environmental mycobacteria and virulent *Mycobacterium tuberculosis* (OMIM 209950)[108–113]. Half of patients with MSMD also have nontyphoidal and, to a lesser extent, typhoidal *Salmonella* infection. Other rare severe infectious diseases have been reported in single or a few patients. The first MSMD genetic etiology involved *IFNGR1* (which encodes the IFN-γ receptor) mutations[114,115], but MSMD-causing mutations have since been reported in seven autosomal and two X-linked genes[116]. The most common MSMD etiology is autosomal recessive IL-12Rβ1 deficiency[105,107,117,118]. All mutations are loss of function, resulting in complete IL-12Rβ1 deficiency in the 170 patients reported to have biallelic mutations, and the deficiency is purely recessive. Patients' leukocytes do not respond to IL-12 or IL-23 and produce low levels of IFN-γ. Less is known about IL-12/23p40 deficiency because only 49 patients from a limited number of ethnic groups have been reported to date[119]; however, all patients show a complete deficiency owing to a lack of protein expression. A related genetic etiology of MSMD is caused by mutations in the gene encoding nuclear factor-κB (NF-κB) essential modulator NEMO that impair T cell– and CD40L-dependent IL-12 induction by phagocytes[120,121].

IL-12Rβ1 deficiency has phenotypes ranging from early death to asymptomatic course until adulthood[122]. IL-12/23p40 and IL-12Rβ1 deficiencies seem to be clinical phenocopies, and the greater severity of IL-12/23p40 deficiency probably reflects the smaller and less diverse patient pool[119]. In both groups, Mycobacterial infections are the most frequent infections[105,112,113,117,118,123–125], and about half of all IL-12Rβ1–deficient patients develop invasive salmonellosis. A significant proportion of patients have mucocutaneous *Candida* infections owing to impaired IL-23–dependent IL-17A immunity[122,126]. The involvement of IL-17A and IL-23 may also be important for *Salmonella* and *Klebsiella* immunity owing to these infections being less common in MSMD with IFN-γ receptor deficiency[119,122,127,128].

Mycobacterial infections in patients with IL-12/23p40 or IL-12Rβ1 deficiency probably result from impaired IL-12–dependent IFN-γ immunity, given the mycobacterial phenotype in patients with inborn IFN-γ signaling defects. Proof of a role for IL-12 in humans would be provided only by the identification of MSMD patients with IL-12p35 or IL-12Rβ2 deficiency. It is possible, alternatively or additionally, that impaired IL-23–dependent IFN-γ immunity contributes to mycobacterial infection. Importantly, patients with IL-12/23p40 and/or IL-12Rβ1 deficiency typically have one episode of mycobacterial disease; BCG disease protects from environmental mycobacterial disease[122]. Nevertheless, IL-12/23p40 and IL-12Rβ1 are essential for immunity against mycobacteria in the course of primary infection but seem to be redundant in the course of secondary infection or from reactivation. In contrast, mucocutaneous candidiasis is probably due to impaired IL-23–dependent IL-17A and IL-17F immunity, given the candidiasis phenotype in patients with inborn defects in IL-17F, IL-17RA, IL-17RC and ACT1 signaling (which are not seen in patients with defects in IFN-γ immunity) and the diminished proportions of IL-17–producing T cells in some patients with deficiencies in IL-12/23p40 or IL-12Rβ1 (refs. 129–132). The infections are chronic, with persistent or recurrent candidiasis, indicating that IL-12/23p40 and IL-12Rβ1 are essential for protective mucocutaneous immunity against *Candida* in the course of primary and secondary infections. Mice lacking IL-12p35, IL-12p19 and IL-12/23p40 when challenged with *Mycobacterium*, *Salmonella* or *Candida* have phenotypes that generally mirror what has been observed in humans (**Table 2**). Overall, studies of IL-12/23p40 and IL-12Rβ1 deficiencies indicate that human IL-12 and IL-23 are redundant in host defense to many pathogens[133].

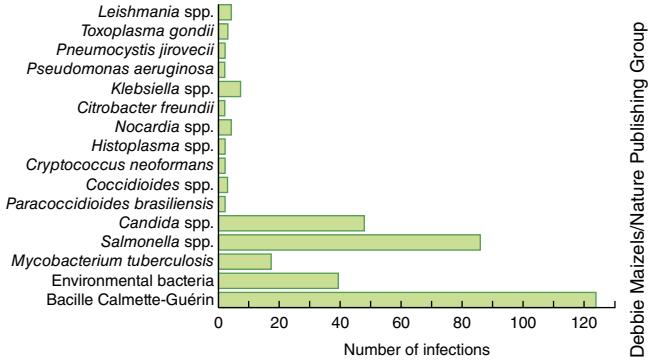

Figure 3 Pathogens that have been identified as causing infections in patients with IL-12/23p40 ($n = 49$) or IL-12Rβ1 ($n = 170$) deficiency. *X* axis indicates the number of patients with each infection. Some patients with IL-12Rβ1 deficiency have multiple infections.

Considerations related to tumor immune surveillance

In mice, antigen-presenting cells such as dendritic cells, monocytes and macrophages produce IL-12, and its downstream mediators are essential for antitumor immunity[11,134]. More specifically, IL-12 acts on both innate and adaptive lymphoid cells such as natural killer (NK) cells and $CD8^+$ cytotoxic T lymphocytes, and these then produce IFN-γ, which has a key role in preventing tumor initiation, growth and metastases[135,136]. IL-12 has also been reported to exert IFN-γ–independent tumor-suppressive activities by activating innate NK cell p46-related protein $(NKp46)^+$ lymphoid tissue inducer cells[137]. IL-12p35–deficient mice are more susceptible to carcinogen-induced skin papilloma formation than are wild-type mice[138], and mice deficient in IL-12/23p40 or IFN-γ that are exposed to the chemical carcinogen methylcholanthrene-A (MCA) have higher tumor incidence and tumor growth than do wild-type controls[139,140]. Notably, naive IL-12/23p40–deficient mice do not have increased tumor development over their normal lifespan[141]; in contrast, IL-12Rβ2–deficient mice that are nonresponsive to IL-12 and IL-35 signaling have a high incidence of lymphoid malignancy[142].

The effects of IL-23 may be more complex (**Fig. 4**). Mice deficient in IL-12/23p40 or IL-23p19 are resistant to carcinogen-induced skin papilloma formation[138], and IL-23p19–deficient mice are strongly protected from developing MCA-induced fibrosarcomas[143]. In contrast

Table 2 The role of murine IL-12 and IL-23 against various pathogens

Pathogen	Genotype	Outcomes after challenge	Refs.
Mycobacterium tuberculosis	*Il12b*$^{-/-}$	Susceptible to mucosal aerosol and systemic challenge.	189–191
	Il12a$^{-/-}$	Susceptible to mucosal aerosol and systemic challenge but less so than *Il12b*$^{-/-}$ mice.	190,191
	Il23a$^{-/-}$	Little difference in phenotype after mucosal aerosol challenge for the first 90 d except loss of IL-17A expression; 90 d after mucosal aerosol challenge, lung granulomata–associated B cell follicle development is compromised and mycobacterial growth control reduced. γδ T cell–derived IL-17A is required after high-dose pulmonary delivery.	192–194
Mycobacterium bovis (BCG)	*Il12b*$^{-/-}$	Susceptible to systemic challenge.	191
	Il12a$^{-/-}$	Susceptible to systemic challenge but less so than *Il12b*$^{-/-}$ mice.	
Salmonella enterica vars. Typhimurium and Enteriditis	*Il12b*$^{-/-}$	Susceptible to challenge, leading to high bacterial loads and early mortality.	195,196
	Il12a$^{-/-}$	IL-12 is critical for NK cell–derived IFN-γ required for protection in low-dose oral-challenge (*S.* Typhimurium).	197
	Il23a$^{-/-}$	In an oral challenge model, IL-23 is required for IL-17 and IL-22 and orchestrates neutrophil influx but also regulates IL-12–mediated epithelial cell death (*S.* Typhimurium).	197,198
Candida albicans	*Il12b*$^{-/-}$	Resistant to systemic but not oral challenge.	199
	Il23a$^{-/-}$	Susceptible to oral challenge and phenocopies IL-17RA–deficient mice; IL-23 and IL-17A are required for critical early neutrophilic response.	200,201
	Il23a$^{-/-}$	Resistant to vulvovaginal model; similar to IL-17RA–deficient and IL-22–deficient mice, where no differences in neutrophil infiltrate, fungal burden or innate alarmins were observed.	202
	Il23a$^{-/-}$	Susceptible to cutaneous challenge with increased fungal burden, reduced IL-17A, reduced epithelial cell hyperplasia and slower healing; responses in IL-12–deficient mice are unchanged.	203

to these tumor-promoting effects, IL-23 may have tumor-suppressing activity in a mouse model of ultraviolet radiation–induced skin cancer or when exogenous IL-23 is administered or overexpressed in mouse and human tumor cells[134]. The IL-12–IL-23 axis also has an important role in controlling the equilibrium phase of cancer immunoediting[144], which has been best characterized in an MCA-induced mouse fibrosarcoma model[145]. IL-23 neutralization using anti–IL-23p19 in mice bearing occult tumors results in the elimination of the residual tumor cells, whereas IL-12/23p40 neutralization enables tumor outgrowth[146]. In contrast to its role in tumor initiation, IL-23 has a relatively modest role in antitumor immunity in mice bearing different established solid tumors, but it is nonetheless relevant in metastases models[143,147]. Thus, the hierarchy of dominance between IL-12's tumor suppression and IL-23's tumor promotion can vary in different cancer types, leading to different outcomes after IL-12/23p40 inhibition.

IL-23R expression on tumor cells has been reported[148,149], suggesting that it may have direct oncogenic potential by activating STAT3, which increases tumor cell proliferation, survival and invasion[150–152] (**Fig. 4**). In mice, IL-23 overexpression is sufficient to induce rapid (3–4 weeks) *de novo* development of intestinal adenomas, with 100% incidence independent of exogenous carcinogens, *Helicobacter* colonization or pre-existing mutations in tumor-suppressor genes[150]. The tumorigenesis is mediated by resident Thy1$^+$IL-23R$^+$ group 3 innate lymphoid cells and occurs before recruitment of conspicuous inflammatory infiltrates[150]. IL-23 can also promote metastasis of human colorectal carcinoma cell lines that have impaired suppressor of cytokine signaling-3 (SOCS3) through activation of STAT5 (ref. 153) or of hepatocellular carcinoma through induction of NF-κB–induced matrix metallopeptidase-9 expression[154] or by promoting the epithelial-mesenchymal transition of esophageal carcinoma cells via the Wnt–β-catenin pathway[155]. Comprehensive examination of human cancers has revealed, in agreement with the role of IL-23 in promoting mouse tumor growth, overexpression (relative to adjacent noncancerous tissue) of IL-23p19 mRNA in the majority of human carcinomas[138,156]. Furthermore, patients with breast, pancreatic and colorectal cancers have higher serum IL-23 concentrations than do healthy individuals[154,157–159].

However, IL-23 can also promote tumor growth indirectly. Although IL-23R is generally not expressed on CD8$^+$ T cells or NK cells[160], and its mechanism of action on these cells has not been fully elucidated, mouse IL-23 can indirectly suppress CD8$^+$ T cell and NK cell function[137,142,146] by eliciting various cytokines and immunomodulatory factors from other cell types[134,161] (**Fig. 4**). For example, in mice and humans, IL-23 is crucial for the maturation and effector function (for example, IL-17A and IL-22 production) of T_H17 cells *in vivo*[162]. Although T_H17 cells and IL-17A suppress tumor growth in some mouse models and in certain human cancers when used in a therapeutic context[163,164], in a surveillance context, IL-17A seems to be pro-tumorigenic (**Fig. 4**). More specifically, IL-17A and IL-23 can act directly on tumor cells. In a mouse model of pancreatic intraepithelial neoplasia (PanIN), IL-17A directly promotes tumor initiation and progression, as IL-17R is expressed on PanIN epithelium[165]. In a mouse model of spontaneous colorectal tumorigenesis driven by loss of the tumor suppressor *Apc* (adenomatous polyposis coli), IL-23 signaling promotes tumor growth, progression and intratumoral IL-17A responses[166]. IL-17A is sometimes involved in IL-23's pro-tumor activity, as blockade of IL-17A or IL-23R produces similar antitumor activity in some models[167]. However, IL-17A–deficient mice often have no tumor phenotype, whereas IL-23–deficient mice do[143,168,169]. Importantly, one cannot surmise T_H17's role in tumor immunity on the basis of IL-17A expression, as many other innate immune cells such as γδ T cells, NKT cells and group 3 innate lymphoid cells express IL-23R and can produce substantial quantities of IL-17A and/or IL-22 (refs. 161,164,170–175) (**Fig. 4**).

Similarly to IL-17A, IL-22 mediates tumor-promoting and tumor-suppressing functions in different mouse models of cancer induced by inflammation or carcinogen[161]. However, clinical data in several cancer types, such as gastric and colorectal cancer, suggest that IL-22 overexpression correlates with worse prognosis and survival[174,175].

Tumor-induced immune suppression is now recognized as a major pathway by which tumors evade immune destruction[176], and it can be mediated through lymphoid and myeloid cells. Over the past five years, T cell checkpoint receptor blockade, particularly in combination together, has achieved remarkable success in the clinic and generated tremendous enthusiasm in the immuno-oncology field[177];

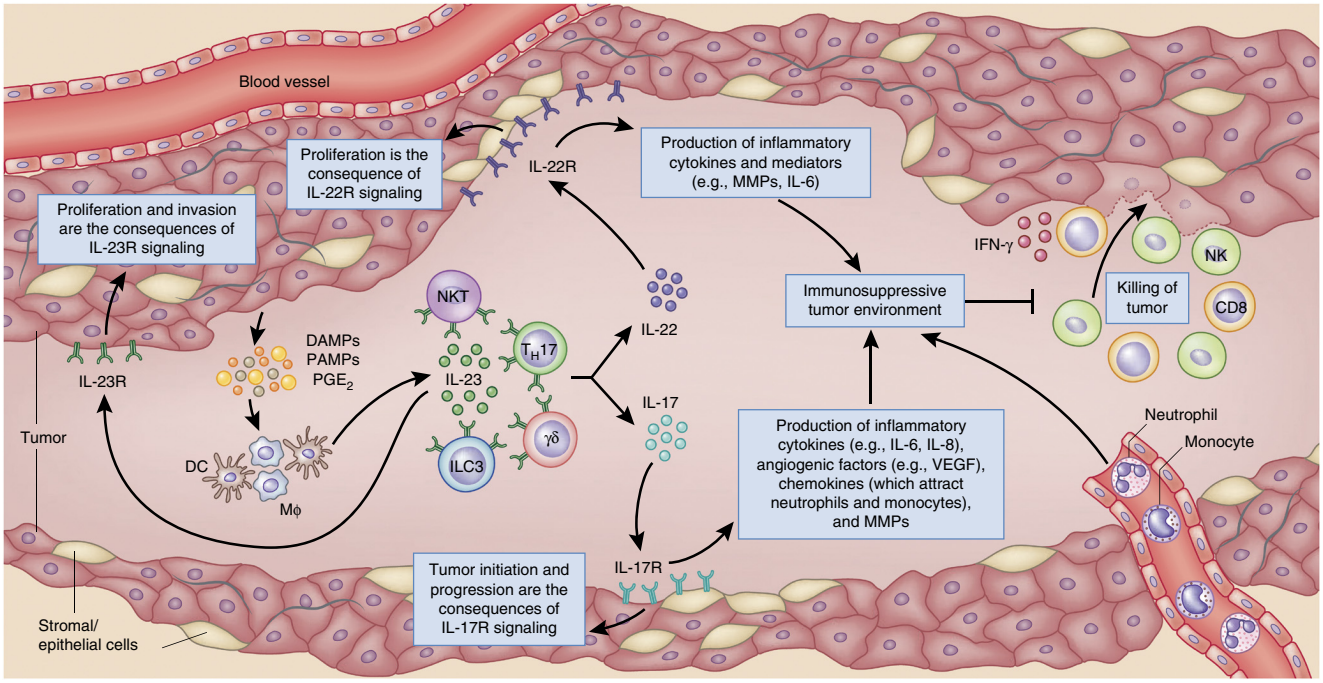

Figure 4 Schematic representation of the mechanisms by which IL-23 indirectly or directly promotes tumorigenesis, growth and metastasis. IL-23 is produced by myeloid cells in response to exogenous or endogenous signals such as damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) or tumor-secreted factors such as prostaglandin E2 (PGE_2). IL-23 can act directly on tumor cells to promote their transformation, proliferation and/or metastasis. In mice, IL-23R is expressed on several innate and adaptive immune cell types, which are found in various proportions in tumors. Stimulation of IL-23R on these immune cells leads to production of cytokines such as IL-17 and/or IL-22, which can have direct proliferative effects on stromal or tumor cells. IL-17 and/or IL-22 also elicit a range of factors from various hematopoietic and nonhematopoietic cells, which can have direct effects on tumor proliferation and metastasis or induce the production of additional inflammatory cytokines, chemokines and mediators such as IL-6, IL-8, matrix metallopeptidases (MMPs) and vascular endothelial growth factor (VEGF), all of which can contribute to the generation of a tumor microenvironment in which CD8 and NK cell effector functions are suppressed. DC, dendritic cell; Mϕ, macrophage.

nevertheless, not all cancer types respond to checkpoint blockade, as they can be quite heterogeneous with respect to lymphoid and myeloid infiltrates. Given that the balance of IL-12 and IL-23 can dictate tumor progression or suppression, targeting this axis may be beneficial[178], particularly in combination with other immunotherapies (for example, immune checkpoint inhibitors, targeted therapies or immunostimulatory cytokines), as has been reported in a number of preclinical models[147,169,179]. Thus, the understanding of IL-23's tumor-promoting or tumor-suppressive function will improve as researchers decipher the functional relevance of different IL-23 responsive cell types at different stages of tumor growth and development.

Clinical toxicities of targeting IL-12 and/or IL-23

Owing to the roles of IL-12 and/or IL-23 in host defense and tumor surveillance, particular attention has been focused on infectious disease–related adverse events after anti–IL-12/23p40 treatment in humans. Meta-analysis of briakinumab's phase 2, phase 3 and open-label extension (OLE) psoriasis databases in 2010 identified 14 cases of candidiasis (including mucocutaneous esophageal and oral candidiasis); no reports of mycobacteria or *Salmonella* were noted. With regard to the roles of IL-12 and/or IL-23 in tumorigenesis, malignancies were observed at a rate of 1.7 events per 100 patient years (PY), and were cancers commonly seen in the general population. Nonmelanoma skin cancers were seen in 1.7% of patients at 1.2 events per 100 PY, with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) having similar frequencies (0.7 events per 100 PY and 0.5 events per 100 PY, respectively). Twenty-seven major adverse cardiovascular events (MACE) events were reported (seven events during phase 3 study M06-890 and 20 events during OLE), leading to 1.33 events per 100 PY during the placebo-controlled portion of the study and 0.57 events per 100 PY overall[180]. The extensive data set for ustekinumab was summarized in a five-year follow-up analysis of phase 3 studies, including OLE[181,182]. Mycobacteria, *Salmonella* and systemic fungal infections were not reported; no information was provided about mucocutaneous candidiasis. Malignancies were observed at 1.1 events per 100 PY for both dose groups. Nonmelanoma skin cancers were seen at 0.64 events per 100 PY in patients treated with 45 mg ustekinumab and 0.44 events per 100 PY for patients treated with 90 mg ustekinumab. The ratio of BCC events to SCC events was 4:1 (40 BCC and 10 SCC). MACE events occurred at 0.56 events per 100 PY and 0.36 events per 100 PY for patients treated with 45 mg and 90 mg ustekinumab, respectively[182].

The rates of opportunistic infection, malignancy and MACE events seem to be higher with briakinumab than with ustekinumab. In addition, BCC occurs more frequently than SCC (generally at a ratio of 4:1) in the general population, and higher rates of SCC may be seen in patients treated with immunosuppressive agents (4:1 BCC:SCC ratio for ustekinumab, 1.4:1 BCC:SCC ratio for briakinumab). The higher signal with briakinumab may be due to briakinumab's more frequent dosing schedule leading to higher drug exposure than with ustekinumab (200 mg monthly initially and then down dosing to 100 mg monthly) versus either 45 mg or 90 mg quarterly) and/or

that briakinumab is a very high-affinity antagonist to IL-12/23p40 (ref. 183). Phase 3 and OLE studies with anti–IL-23 antibodies will be needed to determine whether IL-23–specific antagonism provides an improved safety profile over ustekinumab. Approximately ten inhibitors targeting IL-23 or IL-17A from multiple companies are being tested currently[184] (**Table 1**). The emerging clinical results show that targeting IL-23 and IL-17A has tremendous medical benefit—especially for psoriasis and ankylosing spondylitis.

Concluding remarks

Clinical testing of IL-23 and IL-17A inhibitors have confirmed the initial hypotheses that IL-23–T_H17 pathways are indispensable in promoting immune-mediated diseases, and agents targeting these pathways work particularly well in specific disease settings. However, it is not clear why IL-17A and IL-17RA antagonists work well for psoriasis but exacerbate Crohn's disease[95,96]. It appears that different classes of inhibitor targeting IL-23 and IL-17 pathways may have unique nonoverlapping attributes in different clinical settings. Investigators are still learning where the overlap occurs and what the differences are between targeting IL-23 and targeting other related pathway cytokines. For example, mouse innate lymphoid cells constitutively produce gut protective IL-17A and IL-22 in an IL-23–independent manner. The constitutive IL-17A and IL-22 expression levels generated in response to commensal gut organisms seem to be crucial for maintenance of epithelial barrier function[185] and tight junction formation (D.J.C., unpublished observation). However, high levels of IL-17A and IL-22 induced by IL-23 can be pathogenic during tissue injury responses in the presence of additional inflammatory cytokines such as IL-1, IL-6, GM-CSF and TNF. Therefore, targeting IL-23 via anti–IL-23p19 will partially suppress IL-17A and reduce inflammation, whereas anti–IL-17A therapy will neutralize all protective IL-17A.

The immune system's function is to maintain balance in the face of insult from external pathogens and accumulation of genetic errors leading to cancer. Disruption of this balance toward immune-exuberance can lead to autoimmunity and immunopathology after infection, whereas inadequate immunity can allow pathogen evasion and breakdown in tumor surveillance. The common thread that connects autoimmunity, infection and cancer is inflammation, and the drivers of inflammation are intercellular messengers that enable cross-talk between immune cells and surrounding stromal tissues. We have underscored the importance of innate cell-produced IL-12 and IL-23 as intermediaries that act on T cells and NK cells to promote inflammation and highlighted that IL-12 and IL-23 have overlapping cellular immune functions. Whereas IL-12 is important in driving STAT1- and STAT4-mediated immune surveillance against specific intracellular pathogens and immunity against neoplasm, IL-23 promotes STAT3-dependent antifungal immunity and drives 'sterile' wound-healing responses in psoriatic lesions, which have a gene signature similar to that of many autoinflammatory conditions[186,187]. Strikingly, this signature of uncontrolled wound-healing response is also observed in many cancers[188]. Although there is insufficient clinical data to determine the long-term safety of IL-23 inhibitors, preclinical models suggest that IL-23 paradoxically promotes tumorigenesis by enhancing skin and mucosal tissue inflammation associated with immune evasion mechanisms.

As the roles of IL-12 and IL-23 were elucidated in preclinical models, there was concern that inhibiting these factors could lead to profound immune suppression. Is it better to target factors capable of regulating a broad range of immune function and may leave patients unprotected against pathogens and cancers or to aim for a restricted pathway that may have limited efficacy for treatment of immune disorders? Although the efficacy and safety profiles of IL-12/23p40, IL-23p19 and IL-17A and IL-17RA therapies become clearer with each clinical trial, the decisions to progress these targets were made many years in advance, on the basis of limited data. Animal studies are important for elucidating the cellular and molecular mechanisms, but clinical testing is required to determine whether a specific disease mechanism also operates in humans. Immunological research is at an inflection point, where the basic concepts of molecular and cellular immunology are being translated into effective therapies for diseases that were considered intractable only a few years ago. Despite the challenges, efforts to translate basic disease mechanisms to the clinic are finally paying off. Although much work remains to be done, the fundamental question of which immune target will benefit which patient population is now being clarified. We optimistically await the answers that will change the lives of patients with serious immune-mediate conditions.

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COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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