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IL-23/IL-17A Dysfunction Phenotypes Inform Possible Clinical Effects from Anti-IL-17A Therapies

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Biologics that neutralize specific cytokines have improved outcomes for several immune-mediated disorders but may also increase risks for particular side effects. This article postulates potential immunologic consequences of inhibiting components of the IL-23/T-helper cell 17 pathway–the target of next-generation biologics for treating psoriasis–based on clinical phenotypes of inherent or acquired deficiencies in this pathway. Generally, downstream deficiencies (e.g., IL-17A, IL-17F) are associated with fewer disorders compared with upstream deficiencies, suggesting that selectively blocking downstream targets may result in a narrower range of side effects. However, safety of these specific inhibitions must be established in long-term studies.

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INTRODUCTION

Imbalances in cytokine levels have been implicated in the pathogenesis of a variety of diseases (O'Shea *et al.*, 2002). For disorders in which cytokines are upregulated, such as psoriasis and rheumatoid arthritis, biologic agents that neutralize specific cytokines have improved treatment outcomes while decreasing side effects (Kim and Solomon, 2010; Focosi *et al.*, 2011). Such drugs act therapeutically by modulating abnormal immune responses caused by aberrant cytokine levels. An unintended consequence, however, is that these therapies may also inhibit normal host defenses that utilize the targeted cytokine (Kim and Solomon, 2010; Chu, 2013).

Clinical improvements observed in patients with psoriasis and rheumatoid arthritis treated with tumor necrosis factor-α inhibitors have inspired researchers to study novel cytokine targets with the goal of maximizing therapeutic efficacy while minimizing side effects (Nwe *et al.*, 2013). Targeting these cytokines may alleviate safety concerns resulting from upstream cytokine inhibition and inhibition at multiple points in the inflammatory cascade (Bongartz *et al.*, 2006; Leombruno *et al.*, 2009). As understanding of the pathogenesis of inflammatory and immune-mediated diseases has improved, cytokines involved in the IL-23/T-helper cell (Th)17 pathway have been identified as key modulators of adaptive immune responses associated with the initiation, progression, and maintenance phases of these diseases (Blauvelt, 2008; Kellner, 2013; Qu *et al.*, 2013). Therefore, there is a strong rationale for targeting cytokines in this pathway (Figure 1a).

Because antimicrobial peptides partially triggered by the IL-23/Th17 pathway are involved in mucocutaneous defense against bacterial and fungal pathogens, therapeutic targeting of this cytokine may increase susceptibility to these infections (Waite and Skokos, 2012; Bedoya *et al.*, 2013; Kellner, 2013). Hence, this article will review the role of the IL-23/Th17 pathway in the pathogenesis of immune-mediated disorders and explore potential immunologic consequences of inhibiting members of this pathway. The principal method for understanding the immunologic consequences of disrupting the IL-23/Th17 pathway will be to examine clinical phenotypes associated with pathway deficiencies, which may occur because of genetic mutations affecting the production or activation of a specific cytokine or its receptor or because of the production of autoantibodies against endogenous cytokines.

ROLE OF THE IL-23/TH17 PATHWAY IN THE PATHOGENESIS OF PSORIASIS AND OTHER IMMUNE-MEDIATED DISEASES

In patients with psoriasis, Th17 cells are elevated in cutaneous lesions and blood, as are the messenger RNA and protein levels of IL-23, IL-17A, IL-17F, IL-22, and IL-21 (Di Cesare *et al.*, 2009; Kagami *et al.*, 2010; Michalak-Stoma *et al.*, 2011; Yilmaz *et al.*, 2012; Nwe *et al.*, 2013). These findings suggest that Th17 cells and associated cytokines are important pathogenic mediators of psoriasis (Hueber *et al.*, 2010). The IL-23/Th17 pathway model postulates that, in response to a specific trigger, specific cells produce tumor necrosis factor-α, IL-1β, IFN-α, and IL-6 in susceptible individuals (Lynde *et al.*, 2014). These cytokines stimulate myeloid dendritic cells to produce IL-23, which promotes Th17 cell differentiation, proliferation, and maintenance (Rizzo *et al.*, 2011; Lynde *et al.*, 2014). Th17 cells migrate to the skin and become activated via the signal transduction protein signal transducer

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Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; CARD9, caspase recruitment domain-containing protein 9; CMC, chronic mucocutaneous candidiasis; HIES, Hyperimmunoglobulin E syndrome; MSMD, Mendelian susceptibility to mycobacterial disease; NTS, Nontyphoidal Salmonella*; Th, T-helper cell*

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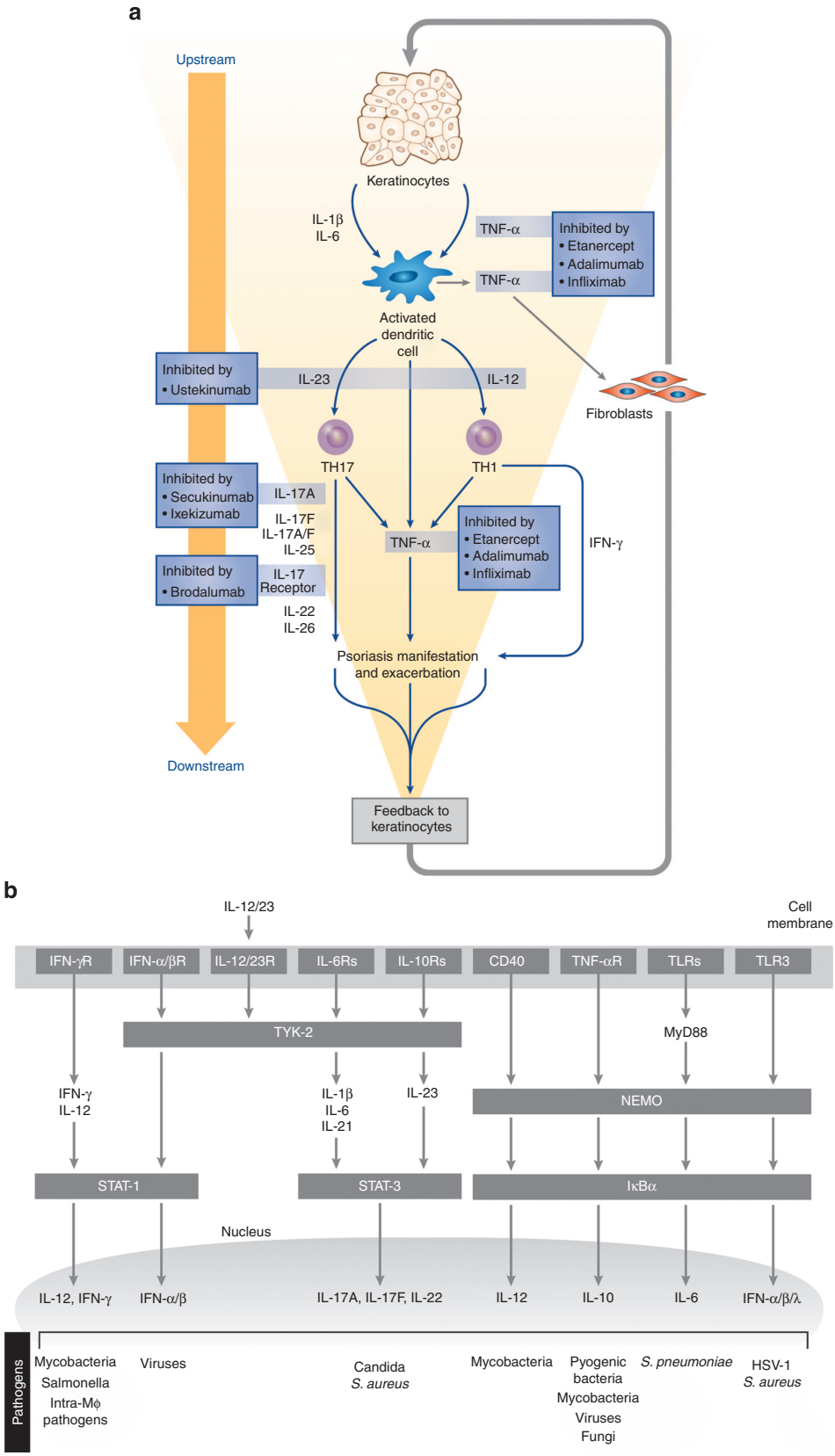

Figure 1. Role of cytokines in psoriasis pathophysiology and immune defense against infections. (**a**) Pathophysiology of psoriasis, with indications for the relative positions of key cytokines and their inhibitors. (**b**) Signaling pathways associated with specific increases in susceptibility to pathogens. HSV, herpes simplex virus; NEMO, NF-kappaB essential modulator; STAT, signal transducer and activator of transcription; TIR, Toll-like receptor/IL-1 receptor; TNF-R, tumor necrosis factor receptor; TYK, tyrosine kinase (Bustamante *et al.*, 2008). Adapted from Bustamante *et al.*, 2008, with permission from Elsevier.

Table 1. Phenotypes of human immune–related disorders associated with the IL-23/Th17 pathway

Clinical presentation	Known defects associated with disease	Effects on IL-17, IL-23, and closely related cytokines
MSMD	*IL12RB1* mutation	Impaired IFN-γ-mediated immunity
	IL12B mutation	
	IFNGR1 mutation	
	STAT1 mutation	
	IL-12/23p40 deficiency	
	IL-12Rβ1 deficiency	
Tuberculosis infection	*IL12RB1* mutation	Reduced production of IFN-γ
Salmonella infection	IL-23R deficiency	Depletion of Th17 cells and IL-17A/F results in reduced immunoprotective effects
	IL-12/23p40 deficiency	
	IL-12Rβ1 deficiency	
CMC disease (associated with *C. albicans* infection)	IL-17RA deficiency	Reduced production of IL-17A, IL-17F, IL-22, and IFN-γ weaken epithelial mucosal barriers
	IL-17F deficiency	
	STAT1 GOF mutation	
	CARD9 mutation	
	Dectin-1 LOF mutation	
APECED (APS-1)	*AIRE* mutation	High levels of autoantibodies to IL-17F, IL-22, and IL-17A
HIES (Job's syndrome)	*STAT3* mutation (AD)	Reduced differentiation of Th17 cells and production of IL-17A
	DOCK8 mutation (AR)	

Abbreviations: AD, autosomal dominant; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; APS-1, autoimmune polyendocrinopathy syndrome type 1; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; GOF, gain-of-function; HIES, hyper-IgE syndrome; LOF, loss-of-function; MSMD, Mendelian susceptibility to mycobacterial disease; Th, T-helper cell.

and activator of transcription 3 (STAT3) to produce IL-17A, IL-17F, and IL-22, along with several chemokines. In addition, IL-17-, IL-21-, and IL-22-producing CD8+ T cells have been observed in psoriatic plaques and implicated in the pathogenesis of psoriasis (Ortega *et al.*, 2009; Res *et al.*, 2010). Together, these cytokines and chemokines drive chronic inflammation associated with psoriatic lesion formation, including keratinocyte activation and hyperproliferation. Activated keratinocytes, in turn, produce many of the same pro-inflammatory mediators that initiate the psoriasis cascade, thereby creating a self-perpetuating cycle that leads to persistence of psoriatic plaques (Di Cesare *et al.*, 2009; Harper *et al.*, 2009; Gaffen, 2011; Girolomoni *et al.*, 2012; Nwe *et al.*, 2013).

PHENOTYPIC PRESENTATION OF CYTOKINE OR RECEPTOR DEFICIENCIES IN THE IL-23/TH17 PATHWAY

Several unique defects have been identified in genes that encode for components of the IL-23/Th17 pathway. These genetic mutations result in a number of rare, complex human diseases associated with either cytokine or receptor deficiencies or with autoantibody production. Common consequences of these disorders are increased susceptibility to pathogens due to changes in host defense. Table 1 provides a summary of findings on human diseases associated with defects in IL-23/Th17 function; descriptions of the phenotypic presentations of these diseases follow.

Mendelian susceptibility to mycobacterial disease (MSMD)

Mendelian susceptibility to mycobacterial disease is a rare syndrome with clinical symptoms resulting from infection with mildly virulent bacteria (Fieschi *et al.*, 2003 and 2004). Although early descriptions of MSMD suggested that infection susceptibility was usually limited to *Mycobacterium* and *Salmonella* (Fieschi and Casanova, 2003; Fieschi *et al.*, 2003 and 2004), more recent studies have shown that *Candida* infections are not uncommon (~25% of patients), and *Klebsiella pneumonia* infection, paracoccidioidomycosis, and leishmaniasis have also been reported (Ouederni *et al.*, 2014; Ramirez-Alejo *et al.*, 2014). Most *Candida* infections in this population are isolated oropharyngeal candidiasis, and risk of systemic infection is low (Fieschi and Casanova, 2003; Ouederni *et al.*, 2014). Patients with MSMD do not exhibit increased susceptibility to common viral pathogens, suggesting that their immune system is not broadly compromised (Fieschi and Casanova, 2003). However, the prognosis for MSMD varies, ranging from complete recovery to premature mortality (Ramirez-Alejo *et al.*, 2014).

To date, nine mutations have been associated with MSMD; the clinical phenotypes of MSMD can vary depending on the nature of the underlying genetic mutation (Bustamante *et al.*, 2008; Ouederni *et al.*, 2014; Ramirez-Alejo *et al.*, 2014). Mutations in *IL12RB1*, which encodes a common subunit of the IL-12 and IL-23 receptor, can cause profound defects in

IL-12 and IL-23 signaling (van de Vosse *et al.*, 2013) and are the most common cause of MSMD (Bustamante *et al.*, 2008; Ouederni *et al.*, 2014). Patients with IL-12Rβ1 or IL-12/23p40 deficiencies are more susceptible to salmonellosis and mild forms of candidiasis compared with patients with MSMD caused by other mutations (Bustamante *et al.*, 2008; Ouederni *et al.*, 2014). *IFNGR1, IFNGR2*, and *STAT1* mutations directly affect IFN-γ-mediated immune responses, and the level of impairment in IFN-γ function is correlated with clinical phenotype (i.e., patients with only partially impaired IFN-γ responses have milder disease; Bustamante *et al.*, 2008; Boisson-Dupuis *et al.*, 2012). The *STAT1* mutations observed in patients with MSMD are autosomal-dominant loss of function and are associated with generally mild disease (Boisson-Dupuis *et al.*, 2012).

Tuberculosis

Mutations in *IL12RB1* are also associated with increased susceptibility to tuberculosis in humans (Altare *et al.*, 1998; Akahoshi *et al.*, 2003; Al-Muhsen and Casanova, 2008; de Beaucoudrey *et al.*, 2010). It has been hypothesized that these *IL12RB1* polymorphisms may reduce receptor responsiveness to IL-12 (and possibly IL-23), thereby disrupting IFN-γ-mediated immunity (Akahoshi *et al.*, 2003). Animal models have also shown that TLR2-deficient mice infected with *M. tuberculosis* TLR2 have significantly decreased Th17 cell counts, IL-17 expression, and IL-23p19 expression (Teixeira-Coelho *et al.*, 2011). Similarly, polymorphisms in *TLR2* and TLR2-signaling molecules have been associated with increased susceptibility to tuberculosis infection in humans (Teixeira-Coelho *et al.*, 2011). Observed IL-17A deficiencies are probably of limited importance in host defense against tuberculosis infection, as IL-22 has been shown to be the key Th17 effector cytokine in pulmonary host defense mechanisms (Aujla *et al.*, 2008), and depletion of IL-17A-producing $CD4^+$ T cells has been shown to have little to no effect on disease progression during primary *M. tuberculosis* infection (Khader *et al.*, 2005).

Salmonella

Nontyphoidal *Salmonella* (NTS) infections can cause localized, albeit potentially severe, gastroenteritis in immunocompetent individuals. However, when immunocompromised individuals are exposed to NTS, the pathogen can spread beyond the intestines to the bloodstream, resulting in a life-threatening condition known as NTS bacteremia (Raffatellu *et al.*, 2008; Godinez *et al.*, 2011). Studies in humans have linked IL-12/IL-23-component deficiencies to increased susceptibility to severe extra-intestinal NTS infection; however, it was not specified which genes were affected in these patients (MacLennan *et al.*, 2004). The protective role of these cytokines against *Salmonella* appears to be independent of the IFN-γ immune response (MacLennan *et al.*, 2004). Rather, it is suggested that the IL-23/Th17 pathway has a key role in mucosal inflammatory responses to NTS infection (Godinez *et al.*, 2011).

Chronic mucocutaneous candidiasis (CMC)

Severe acquired immunodeficiencies (e.g., uncontrolled HIV or Severe Combined Immunodeficiency) or genetic defects in the IL-23/Th17 pathway can increase patients' susceptibility to a number of syndromes that are all associated with chronic or recurrent mucosal or skin infections with *Candida albicans* (Table 1; Puel *et al.*, 2010b; Hanna and Etzioni, 2011; Huppler *et al.*, 2012). These syndromes are collectively referred to as CMC (Hanna and Etzioni, 2011). CMC manifests as superficial lesions on the skin, nails, and mucosal surfaces that often respond poorly to antifungal therapy (Puel *et al.*, 2010b; Hanna and Etzioni, 2011). Clinical presentations and severities of CMC are variable, even between family members with the same genetic mutations (Cárdenes *et al.*, 2010; Boisson-Dupuis *et al.*, 2012; Lilic, 2012). Subtypes of CMC include the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED), autosomal-dominant CMC with or without thyroid disease, and isolated CMC disease (van de Veerdonk *et al.*, 2011). Across the subtypes of CMC, IL-22 has been identified as a dominant cytokine in providing protective immunity against candidiasis (De Luca *et al.*, 2010; Kisand *et al.*, 2010). IL-17A and IL-17F are also natural defenders against CMC, but studies have suggested that these cytokines may be less critical compared with IL-22 in mucosal host–defense mechanisms (De Luca *et al.*, 2010; Kisand *et al.*, 2010 and 2011).

Another key modulator of human mucosal antifungal defense is the β-glucan receptor, dectin-1. In a study of family members affected by chronic vulvovaginal candidiasis or onychomycosis, Ferwerda and colleagues identified stop-codon mutations in *dectin-1* that were associated with reduced production of IL-17, tumor necrosis factor-α, and IL-6 (Ferwerda *et al.*, 2009). However, neutrophil function is preserved in patients with dectin-1 deficiencies, resulting in protection against invasive fungal infections (Ferwerda *et al.*, 2009).

Cytokine autoantibodies linked to APECED. APECED, also known as autoimmune polyendocrinopathy syndrome type 1, is a rare inherited disorder characterized by hypoparathyroidism, adrenocortical failure (Addison's disease), and severe CMC that is localized to mucosal membranes (Kisand *et al.*, 2011; Huppler *et al.*, 2012). Although almost all patients with APECED have CMC, they rarely display increased susceptibility to other infections (Puel *et al.*, 2010b; Hanna and Etzioni, 2011; Huppler *et al.*, 2012; Puel *et al.*, 2012). Autosomal-recessive mutations in the autoimmune regulator (*AIRE*) gene result in high levels of autoantibodies against IFN-α, IL-17F, IL-22 and to a lesser extent IL-17A (Kisand *et al.*, 2010; Puel *et al.*, 2010a and b; Huppler *et al.*, 2012; Kluger *et al.*, 2012).

Autosomal-dominant CMC with or without thyroid involvement. Autosomal-dominant CMC has been observed in patients with gain-of-function mutations in *STAT1* (Liu *et al.*, 2011; van de Veerdonk *et al.*, 2011; Boisson-Dupuis *et al.*, 2012; Huppler *et al.*, 2012). These mutations increase STAT1-dependent cellular responses to IFN-α/β, IFN-γ, and IL-27 and to cytokines that predominantly activate STAT3. Increased STAT1 activation in response to the STAT3-dependent IL-17 inducers IL-6 and IL-21 hinders development of T cells that produce IL-17A, IL-17F, and

IL-22 (Liu *et al.*, 2011; van de Veerdonk *et al.*, 2011; Cypowyj *et al.*, 2012; Huppler *et al.*, 2012). Several different *STAT1* gain-of-function missense mutations also have been identified, but the link between the type of mutation and clinical presentation is not well defined. However, complete STAT1 deficiency is thought to be associated with more severe infectious phenotypes (Boisson-Dupuis *et al.*, 2012).

Isolated CMC. Isolated CMC is commonly referred to as CMC disease (Cypowyj *et al.*, 2012). CMC disease without any other known phenotype has been observed in patients with a complete autosomal-recessive deficiency in the receptor IL-17RA (due to mutations in the *IL17RA* gene) or autosomal-dominant mutations in *IL17F* (Cypowyj *et al.*, 2012; Puel *et al.*, 2011). Genetic mutations in *IL-17RA* result in a lack of cellular response to IL-17A, IL-17F, IL-17A/IL-17F, IL-17C, and IL-17E (also known as IL-25; Cypowyj *et al.*, 2012; Puel *et al.*, 2011).

Caspase recruitment domain-containing protein 9 (CARD9) is a signal transducer found in the cytosol of myeloid cells that is required for induction of Th17 cells (Huppler *et al.*, 2012; Drewniak *et al.*, 2013). Isolated CMC has also been observed in patients with autosomal-recessive *CARD9* mutations. The CMC phenotype in CARD9-deficient patients tends to be more severe, and cases of invasive CNS and brain candidiasis have been reported (Puel *et al.*, 2010b; Huppler *et al.*, 2012; Drewniak *et al.*, 2013; Sillevis Smitt and Kuijpers, 2013; Wang *et al.*, 2014). Some studies have suggested that susceptibility to CMC in CARD9-deficient individuals results from impaired dectin-1 signaling (Hanna and Etzioni, 2011). However, recent studies have shown that neutrophil-killing defects may be responsible for allowing more invasive forms of CMC to progress (Drewniak *et al.*, 2013).

Hyperimmunoglobulin E syndrome

The Hyperimmunoglobulin E syndrome (HIES, Job's syndrome) is a rare primary immunodeficiency that can result in severe atopic dermatitis, pneumatocele formation, connective tissue and skeletal abnormalities, and recurrent skin and lung infections (Hanna and Etzioni, 2011; Szczawinska-Poplonyk *et al.*, 2011). Cutaneous and pulmonary staphylococcal infections and CMC are also observed in the majority of patients with HIES (Puel *et al.*, 2010b; Hanna and Etzioni, 2011). In addition, serum IgE levels are markedly elevated to more than 10–100 times normal range (Ma *et al.*, 2008; Hanna and Etzioni, 2011).

Autosomal-dominant HIES is caused by dominant-negative mutations in *STAT3* (Ma *et al.*, 2008; Zelante *et al.*, 2009; Hanna and Etzioni, 2011). These mutations result in decreased expression of regulator retinoid-related orphan receptor γt, which is a transcription factor required for IL-17 expression; thus, IL-17A production is greatly reduced (Ma *et al.*, 2008). Reductions in IL-1β-, IL-6- IL-21-, and IL-23-induced differentiation of naive $CD4^+$ T cells into Th17 cells result in lower Th17 cell counts and contribute to reductions in IL-17 and IL-22 expression (Ma *et al.*, 2008; Schimke *et al.*, 2010; Huppler *et al.*, 2012; Puel *et al.*, 2012). Different *STAT3* mutations are associated with different levels of impairment in IL-17 production and varying disease severity. For example, IL-17 production was found to be completely absent in patients with R382W or V463del *STAT3* mutations, whereas patients with *STAT3* linker domain mutations produced measureable amounts of IL-17 and had milder disease (van de Veerdonk *et al.*, 2010).

Another distinct disorder, autosomal-recessive HIES, has been observed in patients with deficiencies in dedicator of cytokinesis 8, which results in impaired T-cell activation and memory (Schimke *et al.*, 2010; Huppler *et al.*, 2012; Lilic, 2012). In addition, dedicator of cytokinesis 8 regulates actin, which may explain the skeletal abnormalities observed in patients with HIES (Szczawinska-Poplonyk *et al.*, 2011). Isolated cases of autosomal-recessive HIES have also been observed in patients with TYK2 deficiencies, suggesting that defects in Janus kinase signaling may also be associated with certain forms of HIES (Minegishi and Karasuyama, 2009; Schimke *et al.*, 2010; Lilic, 2012). Such deficiencies are further upstream in the IL-23/Th17 pathway, as Janus kinases phosphorylate STATs (Minegishi and Karasuyama, 2009). The clinical features of autosomal-recessive HIES are similar to autosomal-dominant HIES, but patients with the recessive form may be more susceptible to severe fungal and viral infections, as well as asthma, food allergies, and malignancies (Szczawinska-Poplonyk *et al.*, 2011; Huppler *et al.*, 2012). Patients with *DOCK8* mutations are less likely to present with certain cutaneous symptoms, such as newborn eczematous eruptions, which are more common in patients with autosomal-dominant HIES caused by *STAT3* mutations (Sillevis Smitt and Kuijpers, 2013).

DISCUSSION

Several diseases can manifest as a result of inherent or acquired deficiencies in cytokines or their receptors. Examination of the clinical phenotypes from these diseases may provide insights into potential side effects for therapies that target these cytokines. Several important caveats should be noted: importantly, anticytokine therapy is not expected to mimic cytokine-signaling pathway mutations, in which the development of these diseases is likely to be affected by lifelong (and sometimes complete) depletion in cytokine levels. Thus, the genetic diseases discussed herein are not expected to mirror what would be observed during biologic therapy for immune-mediated disorders. Furthermore, current anticytokine therapy does not impair production of the targeted cytokine and thus does not result in complete and, more importantly, permanent loss of function. These distinctions are critical because the extent of functional deficiencies in rare diseases identified here corresponds to the extent of the clinical phenotypes (van de Veerdonk *et al.*, 2010). For example, in patients with HIES, partial IL-17 deficiency is associated with a milder clinical phenotype compared with complete IL-17 deficiency (van de Veerdonk *et al.*, 2010). Similarly, in most of the genetic disorders discussed, many different cytokines are altered simultaneously and thus are highly dissimilar to single-cytokine depletion mediated by a biologic.

Long-term favorable clinical outcomes are possible for many patients with genetic deficiencies in the IL-23/Th17 pathway because of redundancies in host–defense mechanisms and

because deficiencies in a single cytokine or its receptor generally do not lead to widespread disease susceptibility (Fieschi *et al.*, 2003; Godinez *et al.*, 2011). For example, although early studies postulated that IL-12 production by phagocytes and antigen-presenting cells was a key component of both innate resistance and adaptive immune responses (Trinchieri, 1995), Fieschi and colleagues later found that deficiencies in IL-12 or its receptor do not increase susceptibility to a wide range of infections (Fieschi and Casanova, 2003; Fieschi *et al.*, 2003). Instead, consequences of these deficiencies are usually limited to MSMD, whereas defenses against other microorganisms remain intact, and risk for serious systemic infection remains low (Fieschi and Casanova, 2003; Fieschi *et al.*, 2003). Similarly, studies examining susceptibility to NTS bacteremia have concluded that, although IL-17A has a key role in protecting ileal mucosa, isolated deficiencies in this cytokine are unlikely to result in substantially increased risk for systemic *Salmonella* infection because the antimicrobial functions of IL-17A, IL-1β, and tumor necrosis factor-α are redundant such that all of these cytokines can induce expression of neutrophil chemoattractants in epithelial cells (Godinez *et al.*, 2011). It is more likely that broadly compromised host defenses are a result of immunodeficiencies further upstream that affect multiple inflammatory and immune response pathways.

Predictably, data suggest that deficiencies in cytokines and receptors further downstream in the IL-23/Th17 pathway are associated with fewer disorders than deficiencies in upstream components of the pathway. For example, dysregulation of *IL12RB1*, which encodes a common subunit of the IL-12 and IL-23 receptor, is associated with increased susceptibility to a range of infections, including MSMD, *Salmonella*, and tuberculosis, whereas the potential consequences of more downstream IL-17 deficiencies are generally limited to superficial skin and mucosal fungal infections. These observations are consistent with the involvement of upstream cytokines in pleotropic processes, including the regulation of other cytokines, whereas downstream cytokines are generally effectors of specific target tissue responses. Deficiencies in signaling pathways used by several cytokines also tend to be associated with a higher number of associated disorders. As shown in Figure 1b, upstream cytokines are more broadly involved in defense mechanisms against a range of bacterial, fungal, and opportunistic infections compared with downstream cytokines (Bustamante *et al.*, 2008; Di Cesare *et al.*, 2009; Furst, 2010; Chu, 2013). In contrast, human deficiencies in receptors for downstream cytokines, most notably in the IL-17 family (IL-17A through F), tend to manifest as increased susceptibility to a few specific types of infection, including mucocutaneous candidiasis and cutaneous *Staphylococcal* infections alone (Gaffen, 2011; Cypowyj *et al.*, 2012; Patel *et al.*, 2013). The role of IL-17 cytokines in host defense against most other common pathogens is largely redundant; for example, both IL-17A and IL-17F are needed for mucocutaneous immunity against *C. albicans* (Girolomoni *et al.*, 2012; van den Berg and McInnes, 2013), and no mutations in IL-17A resulting in generalized immunodeficiency have been identified to date (Cypowyj *et al.*, 2012; Patel *et al.*, 2013).

Overall, this paper has explored how patients inherently deficient in certain components of the IL-23/Th17 pathway may—and may not—be analogous to patients receiving agents that are also designed to target this pathway. Understanding the consequences of this inhibition may thus inform future long-term collection and analyses of data related to potential infectious complications of these agents.

CONFLICT OF INTEREST

Dr Blauvelt has served as a scientific consultant and clinical study investigator for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Janssen Ortho Biotech, Eli Lilly & Co., Merck, Novartis, Pfizer, and Sandoz. Dr Lebwohl has served as a consultant or investigator for Abbott, Amgen, Anacor Pharmaceuticals, Inc., BioLineRX, Ltd., Celgene Corporation, Coronado Biosciences, Dermipsor, Eli Lilly & Co., Galderma, GlaxoSmithKline-Stiefel, Janssen Ortho Biotech, LEO Pharmaceuticals, Maruho Co., Ltd., Meda Pharmaceuticals, Novartis, Pfizer, Ranbaxy, and Valeant. Dr Bissonnette has served as a consultant, investigator, or speaker for, or received grants from, AbbVie, Amgen, Apopharma, Astellas, Celgene Corporation, Eli Lilly & Co., Galderma, GSK-Stiefel, Incyte, Janssen Ortho Biotech, Leo, Merck, Novartis, Pfizer, and Tribute.

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