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Review

Th17 Cell Pathway in Human Immunity: Lessons from Genetics and Therapeutic Interventions

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The T helper 17 (Th17) cell pathway has been linked by genome-wide association studies to multiple autoimmune diseases. Identification of the genetic causes of primary immunodeficiency diseases revealed that Th17 cells are also critical in host immunity to mucocutaneous candida infections and *Staphylococcus aureus*. Therapeutic interventions with inhibitors of the different components of the pathway such as interleukin-12 (IL-12), IL-23, IL-17A, and IL-17RA have variably beneficial effects in psoriasis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-infectious uveitis, and multiple sclerosis. Thus, whereas Th17 cells are protective against *Candida albicans* and to a lesser degree *Staphylococcus aureus*, they are pathogenic in many autoimmune diseases. Here, we compare and contrast the effects of human genetic mutations of and therapeutic interventions targeted at Th17 cell molecules. We discuss that although there are similarities when Th17 cell pathway molecules are modulated, each molecule has unique non-Th17 cell features that lead to different functional outcomes.

Introduction

Current understanding of the role of the adaptive immune system in autoimmune disease pathogenesis has largely been based on the work of Bob Coffman and Tim Mossman who first proposed three decades ago the existence of two distinct T cell subsets: T helper 1 (Th1) and Th2 cells, based on cytokine phenotype (Mosmann et al., 1986). Upon activation, naive T cells expand and differentiate into effector T cell subsets, producing distinct cytokines and mediating independent effector functions. An over-exuberant response against self antigens of Th1 cells, which produce interferon-γ (IFN-γ) and interleukin-2 (IL-2) and help generate a cellular immune response to intracellular pathogens, was implicated in the induction of autoimmune diseases. However, elimination of Th1 cells or Th1 cytokines did not prevent development of autoimmunity. In fact, the loss of IFN-γ or p35 chain of IL-12, both of which induce Th1 cell responses, made mice more susceptible to development of experimental autoimmune encephalomyelitis (EAE), an autoimmune disease of the central nervous system (CNS), and other autoimmune diseases. This led to the notion that there must be another cell type, other than Th1 cells, that is probably responsible for the induction of autoimmune disease.

Discovery of IL-23, which shares the p40 chain with IL-12, indirectly led to discovery of Th17 cells (Figure 1). Pioneering studies (Cua et al., 2003; Murphy et al., 2003) utilizing IL-12- and IL-23-deficient mice demonstrated that it was loss of IL-23 and not IL-12 that made mice resistant to the development of EAE and collagen-induced arthritis (CIA). The mice deficient in IL-23 lacked the expression of IL-17-producing T cells in the target organ, which led to the suggestion that IL-23 might be critical for the generation of pathogenic IL-17 producing T cells, and loss of Th17 cells is responsible for the resistance to autoimmune diseases in IL-23-deficient mice. However, although IL-17-producing Th17 cells are indeed a novel subset of T cells, IL-23 alone is not responsible for their induction (discussed below).

Indeed, Th17 cells are potent inducers of tissue inflammation and have been implicated in the pathogenesis of many experimental autoimmune diseases and human inflammatory conditions. In fact, IL-17 and Th17 cells have shown to be present at the tissue sites in a number of human autoimmune diseases and have been implicated in the pathogenesis of rheumatoid arthritis, psoriasis, inflammatory bowel disease, and Sjögren's syndrome. The primary function of Th17 cells, however, appears to be regulation of immune responses that lead to the clearance of extracellular pathogens including bacteria and fungi. In addition to inducing tissue inflammation, Th17 cells have been shown to help B cells (Mitsdoerffer et al., 2010) and play a critical role in forming ectopic lymphoid follicles in the target organs (Ota et al., 2011; Peters et al., 2011; Rangel-Moreno et al., 2011). The cytokines (IL-17, IL-22) and cell-surface molecules (Podoplanin; also known as gp38) selectively expressed by Th17 cells play a crucial role in organizing the formation of tertiary lymphoid follicle-like structures in several different tissues including lung, gut, and the CNS of the mice (Ota et al., 2011; Peters et al., 2011; Rangel-Moreno et al., 2011).

IL-17 and IL-17R

Interleukin-17 (IL-17), the hallmark cytokine of Th17 cells, was discovered in 1993 as a novel cytokine cloned from activated cytotoxic T cells and named as CTLA8 (Rouvier et al., 1993). Based on sequence homology, a total of six members of the family were discovered and called IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. IL-17A is most closely related to IL-17F, and both are produced by the same cells upon activation. While IL-17A and IL-17F both can form homodimers, they can also form heterodimers (IL-17A/F). Of all the family

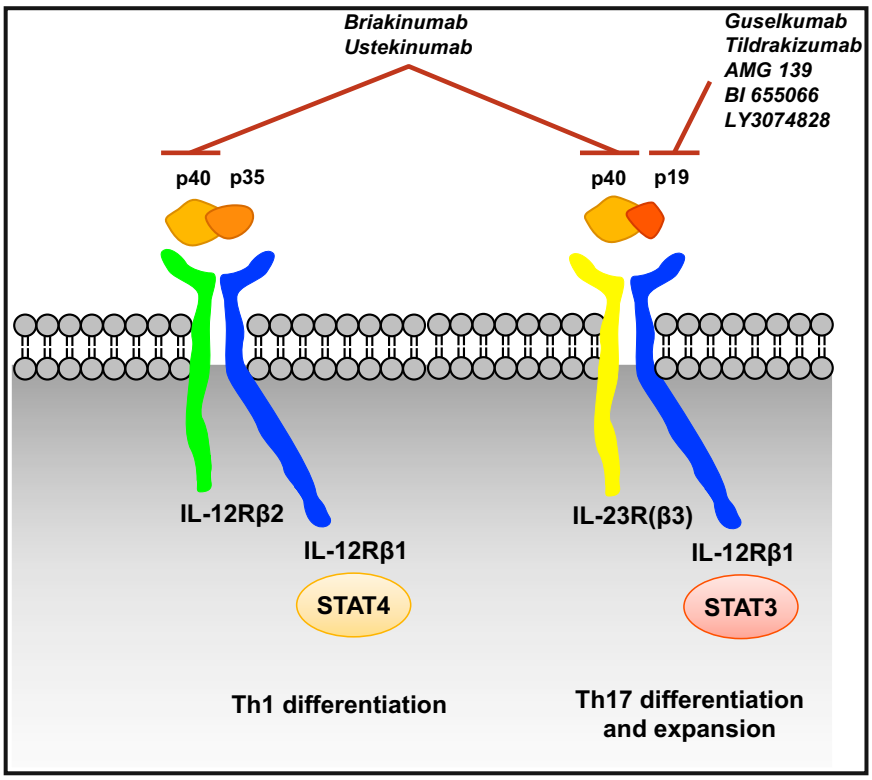

Figure 1. IL-12 and IL-23, Their Receptors, and Key Molecules Involved in Signal Transduction

IL-12 is a heterodimer of the IL-12+23 shared subunit p40 (IL-12p40) and p35 (IL-12p35). IL-23 is a heterodimer of p40 (IL-12p40) and p19 (IL-23p19). The IL-12R is a heterodimer composed of the IL-12+23R shared chain IL-12Rβ1 and IL-12Rβ2. IL-23R is a heterodimer of IL-12Rβ1 and IL-23R. STAT4 is involved in transducing signals through IL-12R and STAT3 for IL-23R. Ustekinumab and briakinumab bind IL-12p40 and block the binding of both IL-12 and IL-23 to their receptors. Guselkumab, tildrakizumab, AMG 139, LY3074828, and BI 655066 bind IL-23p19 and block the binding of IL-23 to IL-23R.

members, IL-17A (also known commonly as IL-17) is most widely studied. IL-17 is produced not only by Th17 cells, but also by a number of cell types including γδ T cells, lymphoid tissue inducer cells (LTi), innate lymphoid cells (ILCs), and natural killer (NK) cells. IL-17A has also been reported to be produced by neutrophils (Ferretti et al., 2003; Taylor et al., 2014), but this is controversial (Huppler et al., 2015). Thus, IL-17A is not identical to Th17 biology.

Soon after the discovery of IL-17 cytokine, the receptor for IL-17 (Figure 2) was identified as a founding member of new family of cytokine receptors (Gaffen, 2009). Based on sequence homology, the IL-17 receptor family has now been identified to have 5 family members, including IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. IL-17RA is ubiquitously expressed on many non-immune cells including epithelial and fibroblastic cells. In epithelial and other parenchymal cells, IL-17R activation induces a panel of proinflammatory cytokines including IL-1, IL-6, tumor necrosis factor (TNF), MMPs, and IL-8 and thus making tissue more amenable to cellular infiltration and tissue inflammation. In addition to its expression on non-immune cells, recent studies show that IL-17RA is also expressed on immune cells including T cells where IL-17 signaling is considered to act as a positive feedback loop and therefore further promote Th17 development or function (Yosef et al., 2013).

IL-17A signals through a heterodimeric complex of IL-17RA and IL-17RC to induce the required proinflammatory cytokine production from responding cells. Like IL-17A, IL-17F also signals through IL-17RA-C but binds with 1%–10% of the affinity. The functional outcome of IL-17A versus IL-17F binding to IL-17 receptor has not been well studied.

While binding of IL-17A and IL-17F to IL-17RA+IL-17RC and IL-17C to IL-17RA+IL-17RE induces pro-inflammatory cytokines and induces autoimmune tissue inflammation, binding of IL-17E to IL-17RA+RB induces Th2 cell-type responses, promotes allergic reactions, and inhibits Th1 and Th17 cell biology. The N-terminal end of the IL-17R has a conserved SEFIR (similar expression of fibroblast growth factor and IL-17R) domain, which is closely related to TIR domain expressed in TLR and IL-1R family members (Gaffen, 2009). IL-17R signaling activates SEFIR domain, which recruits ACT-1 (NF-κB activator 1) and activates downstream NF-κB signaling via TRAF-6 (Wang et al., 2013). Loss of ACT-1 or decoy peptides that block CC-domain in the SEFIR domain also inhibit IL-17 dependent NF-κB activation.

Differentiation of Th17 Cells

Th17 cells were initially characterized by the production of IL-17A, but now have been shown to coproduce a group of cytokines (IL-17A, IL-17F, IL-21, and IL-22), which coordinately act to mediate tissue inflammation. Although initial studies suggested that IL-23 is the differentiation factor for Th17 cells, IL-23 cannot act on the naive T cells to induce Th17 cell differentiation, and Kuchroo and Bettelli proposed that other factors must be required to induce differentiation of naive T cells into Th17 cell because naive T cells do not express IL-23R (Bettelli and Kuchroo, 2005). Indeed, a series of studies showed that Th17 cells differentiate from naive $CD4^+$ T cells in response to TGF-β plus IL-6 (Bettelli et al., 2006; Veldhoen et al., 2006; Weaver et al., 2006) by inducing the expression of ROR-γt, a master transcription factor required for the generation of Th17 cells. An emerging model for the development of Th17 cells includes three overlapping steps: differentiation, amplification, and stabilization. TGF-β+IL-6 induces differentiation; IL-21 produced by developing Th17 cells mediates amplification; and IL-23 expands and stabilizes previously differentiated Th17 cells. In humans and mice, naive T cells can also be differentiated into Th17 cells with IL-1+IL-6+IL-23, without any requirement for TGF-β in the process (Ghoreschi et al., 2010), although

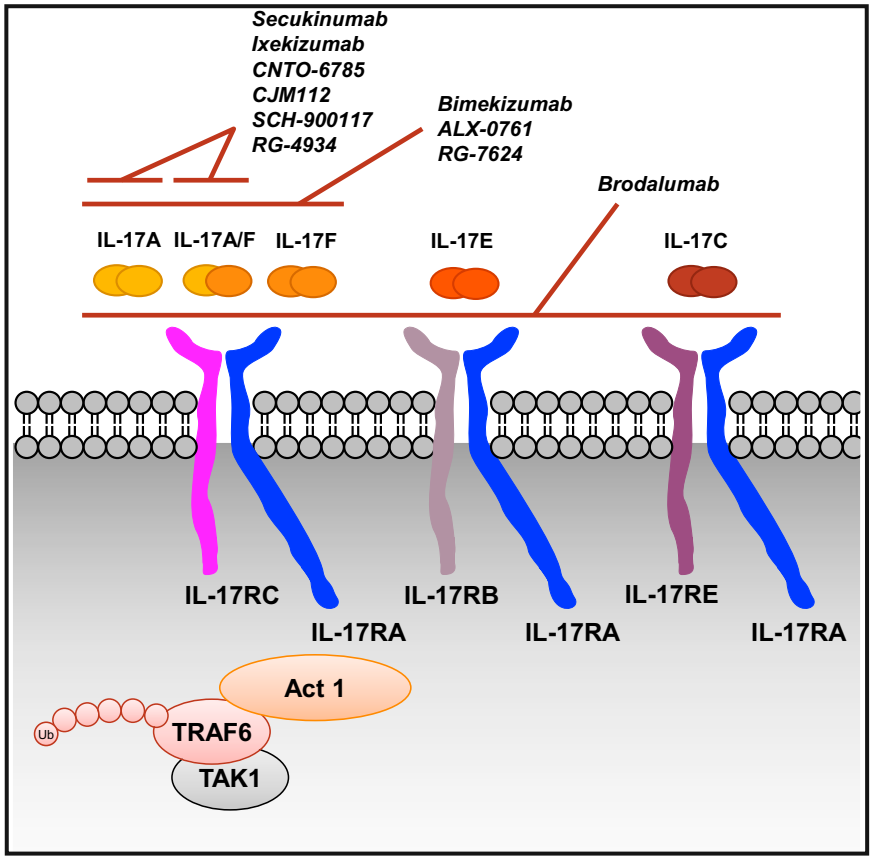

Figure 2. IL-17 Isoforms, Their Receptors, and Key Molecules Involved in Signal Transduction

All of the IL-17 isoforms exist as homodimers, but IL-17A and IL-17F can also form a heterodimer, IL-17A/F. Shown are the receptors for IL-17A, IL-17C, IL-17E, and IL-17F. These receptors are heterodimers of a signal transduction chain, IL-17RA, and a chain that renders more specificity. A heterodimer of IL-17RA and IL-17RC is the receptor for IL-17A, IL-17F, and IL-17A/F. A complex of Act1, TRAF6, and TAK1 is involved in transducing signals through IL-17R. Secukinumab, ixekizumab, CNTO-6785, and CJM112 bind IL-17A and block the binding of both IL-17A and IL-17A/F to their receptor. Bimekizumab, ALX-0761, and RG-7624 bind and neutralize both IL-17A and IL-17F isoforms. Brodalumab binds IL-17RA and blocks the binding of IL-17A, IL-17A/F, IL-17F, IL-17C, and IL-17E to their receptors.

endogenous production of TGF-β was not excluded in these differentiation cultures. These Th17 cells co-expressed both RORγt and T-bet and were highly pathogenic in inducing experimental autoimmune encephalomyelitis (EAE). The two types of Th17 cells induced by TGF-β1+IL-6 or IL-1+IL-6+IL-23 appear to be functionally and transcriptionally distinct, and might have different roles in clearing different types of pathogens. Consistent with this observation, in humans, two different types of Th17 cells have also been described where Th17 cells that produce IL-17 with IFN-γ have specificity for *Candida albicans* and in contrast the Th17 cells that coproduce IL-17 with IL-10 have specificity for *Staphylococcus aureus* (Zielinski et al., 2012). Therefore, Th17 cells might come in different flavors, with ability to clear different types of infections, and this might also translate into whether some Th17 cells are highly pathogenic and others are non-pathogenic in terms of inducing autoimmune disease.

A number of studies have shown that a single nucleotide polymorphism (SNP) in IL-23R is linked to human autoimmune disease; raising the issue of whether IL-23R does something more than just strengthening the phenotype of Th17 cells. Whereas TGF-β+IL-6/IL-21 can induce Th17 differentiation, exposure to IL-23 is critical for evoking pathogenic potential in Th17 cells. Regulatory network analysis, based on protein-protein networks suggests that IL-23 signaling induces SGK-1, which promotes differentiation of pathogenic Th17 cells by inducing phosphorylation of Foxo-1 and unabated expression of IL-23R and pathogenicity of Th17 cells (Wu et al., 2013). Transcriptomic analyses have elucidated transcriptional and regulatory networks that mediate Th17 differentiation and function (Ciofani et al., 2012; Wu et al., 2013; Yosef et al., 2013). Th17 differentiation is accomplished in three different transcriptional waves in 72 hr, and the major regulators form two self-enforcing, mutually antagonistic modules that promote the differentiation of Th17 cells and at the same time inhibit differentiation of other T cell subsets (Yosef et al., 2013).

Th17 Cells in Autoimmune Disease Models

It was initially believed that IFN-γ producing Th1 cells, with specificity for self-antigens are critical for the induction of autoimmunity. This was based on the observation that Th1 cells predominate at the sites of tissue inflammation during autoimmune disease. However, this concept was later refuted, because loss of either IFN-γ or cytokines (IL-12p35) or the receptors that drive Th1 differentiation (IL-12Rβ2) in mice were not resistant but became more susceptible to multiple autoimmune diseases. In sharp contrast, IL-12p40-deficient mice were resistant to multiple autoimmune diseases. This problem was resolved when it was discovered that the p40 chain can pair with another cytokine chain called p19, forming a novel IL-23 heterodimer, and loss of either p19 or p40 chain of IL-23 made mice resistant to multiple autoimmune diseases including EAE, collagen-induced arthritis, autoimmune colitis in IBD models, and experimental autoimmune uveitis. Consistent with these data, loss of IL-17A, IL-17F, or their receptors, alone or in combination, made mice resistant to the development of multiple autoimmune diseases including EAE and CIA. Although IL-23 and IL-17A often have similar effects in animal models of inflammation, they have different effects in the gut. Loss or inhibition of IL-23 results in protection from autoimmune colitis, but loss or inhibition of IL-17A or IL-17RA in different models variably results in no

protection or worsening of disease (Maxwell et al., 2015; O'Connor et al., 2009; Wang et al., 2015). Indeed, IL-17A might have a protective effect by promoting and building epithelial barrier functions (Lee et al., 2015). It should be emphasized that IL-23 does not only act on T cells but also γδT cells and ILCs to induce IL-17 production and all these cells act in a coordinated fashion to mediate autoimmune tissue inflammation, further highlighting the idea that the various molecules and cells involved in the Th17 pathway might have distinct biological effects. These studies highlight that Th17 cells are not the only source of IL-17 but that other cell types including innate cells produce IL-17 and therefore neutralizing IL-17 in vivo might be negating effects of multiple cell types and not only of Th17 cells.

Th17 Cells and Human Disease

In addition to their role in inducing autoimmune disease in experimental models, IL-17 and Th17 cells have been implicated in multiple human autoimmune and infectious diseases. Th17 cells infiltrate at a very high frequency in the affected joints in RA patients and IL-17 activated osteoclasts can induce bone resorption and bone erosion (Miossec et al., 2009). IL-17 has been identified in lesions in multiple sclerosis, psoriasis, Sjögren's syndrome, and inflammatory bowel disease (Fujino et al., 2003; Kotake et al., 1999; Lock et al., 2002; Teunissen et al., 1998). In autoimmune diseases of the CNS, Th17 cells constitute the first wave of pathogenic T cells infiltrating the CNS (Korn et al., 2007), and this might be related to their ability to efficiently breach the blood-brain barrier (Kebir et al., 2007). Th17 cells might promote infiltration of other Th cells (like Th1 cells), macrophages, and neutrophils, which further propagate tissue inflammation and tissue damage. Furthermore, an unbiased whole-genome transcriptomic analysis of the CNS of the MS patients showed that IL-17 is the highest ranking gene expressed in the active plaque compared to the inactive plaques from the same patient (Lock et al., 2002). Additional support for the role of Th17 cells in inducing autoimmune diseases comes from genetic analysis of human autoimmune diseases. A genome-wide association scan for single nucleotide polymorphisms associated with human autoimmune diseases revealed that a specific coding variant of the *IL23R* gene (arginine 381 to glutamine, R381Q, in the cytoplasmic domain of IL-23R) conferred strong protection from Crohn's disease, whereas several variants in the non-coding region of this gene were associated with increased susceptibility to Crohn's disease (Duerr et al., 2006). R381Q has now been shown to have a significant genetic association with multiple other autoimmune diseases including psoriasis, psoriatic arthritis, Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis (AS) (Duerr et al., 2006; Faragó et al., 2008; Hüffmeier et al., 2009; Liu et al., 2008; Rahman et al., 2008). However, the mechanism by which this coding variant of IL-23R regulates autoimmunity has not yet been elucidated.

Identification, largely by reverse genetics, of mutations of components of the Th17 pathway has revealed an essential role for Th17 immunity in protection against certain types of fungal and bacterial infections, with a recurring theme that the effected individuals develop unrelenting chronic mucocutaneous candidiasis (CMC) infections (Table 1). Mutations in IL-12Rβ1, the signal transduction chain of both IL-12 and IL-23 receptors affecting both Th1 and Th17, leads to susceptibility to mycobacteria, candidia, klebsiella, nocardia, and salmonella infections (de Beaucoudrey et al., 2008; de Beaucoudrey et al., 2010; Prando et al., 2013). Similarly, mutations in retinoic acid receptor related orphan receptor C (RORC), the human version of mouse RORγ (not only γT), which regulates not only Th17 development but also IFN-γ production by several cell types, leads to impaired immunity to Candida and mycobacteria (Okada et al., 2015). Multiple different mutations in STAT-3, which cause autosomal-dominant hyper immunoglobulin E (IgE) syndrome, lead to recurrent infections with *Staphylococcus aureus* and *Candida albicans*. The mutations in the DNA binding, SRC homology, and transactivating domains of STAT-3 result in almost complete loss of Th17 differentiation, supporting the crucial role of STAT-3 in Th17 differentiation and underscoring the value of Th17 immunity in clearing fungal infections (Al Khatib et al., 2009; de Beaucoudrey et al., 2008; Ma et al., 2008; Milner et al., 2008), albeit the role of hypomorphic STAT-3 signaling in stromal cells remains to be determined. A gain of function mutation in the STAT-1 coil-coil domain resulted in skewing toward Th1 away from Th17, and these patients also develop CMC infection (Liu et al., 2011). Because Th17 cells are critical for development of anti-fungal immunity, it was found that the hyphal form of *Candida albicans* and its derivatives (Zymosan and b-glucan), both of which are Dectin-1 agonists, induced IL-23 from human DCs. Consistent with this observation, patients with a stop-codon mutation (Tyr238X) in dectin-1 were found to have a defect in the production of IL-17 and Th17 cells and developed CMC (Carvalho et al., 2012; Plantinga et al., 2009). Similarly, CMC is the primary infection observed in the patients with autoimmune polyendocrinopathy syndrome-1, and these patients were observed to have circulating neutralizing antibodies against IL-17A, IL-17F, and IL-22 (Kisand et al., 2010; Puel et al., 2010). Patients with CMC have been found to have defects in IL-17F and IL-17RA, but not in IL-17A, indicating that IL-17F or IL-17A/F is important in protecting against CMC (Puel et al., 2011). The CMC associated with IL-17RA deficiency is complete, and that with IL-17F is partial, indicating that IL-17A and IL-17F are essential but partially redundant for immunity against *Candida albicans*. Downstream of the IL-17 receptor, defects in the signal transduction molecule Act1, which is primary for IL-17R signaling but also modulates other receptors such as CD40L and BAFFR, results in not only CMC but also in staphylococcal infections (Boisson et al., 2013). Collectively, these data suggest that Th17 cells have a critical role in immunity to mucocutaneous *Candida albicans* and *Staphylococcus aureus*.

Therapeutic Interventions in Psoriasis

Rather than an historical perspective, we will take a pathways approach to deciphering what therapeutic interventions in the Th17 pathway have taught us about human immunology and disease, focusing on psoriasis as a model autoimmune disease and then expanding on the roles of IL-17A and Th17 in other diseases where the immune system has strong effects. While generalizations can be drawn about an important role for Th17 in the pathogenesis of various autoimmune diseases, one fundamental finding is that each component of the Th17 pathway has different effects, be they subtle or significant.

Of the molecules involved in human Th17 differentiation and expansion, STAT3, IL-23, IL-23R, and RORC2 have relative

Table 1. Genetic Defects in the Th17 Pathway Leading to Primary Immunodeficiency Diseases

Gene[a]	Inheritance[b]	Protein WT (mut.)[c]	Domain[d]	Regulation	Infection risk	Disease[e]	Reference
ACT1		ACT-1 (T536I)	SEFIR	Th17, impairs the fibroblast response to IL-17	*Candida albicans*, *Staphylococcus aureus*	CMC	(Boisson et al., 2013)
AIRE	AR (G228W = AD)	AIRE (G228W), > 50 others	DNABD and/or multimerization domain SAND	Neutralizing autoantibodies against IL-17A, IL-17F, IL-22	*Candida albicans*, *Staphylococcus aureus*	CMC, APS-1/APECED/Whitaker syndrome, hypoparathyroidism, adrenocortical failure, dental enamel dysplasia, nail dystrophy, alopecia, ovarian failure, vitiligo, diabetes mellitus, testicular failure, hypothyroidism	(Björses et al., 2000)
CARD9	AR	CARD (G72S, R373P)	CARD and coiled-coil	Th17 differentiation	*Candida dubliniensis*	Meningoencephalitis, mucocutaeneous candidiasis, AS, CD, UC	(Drewniak et al., 2013)
DECTIN1		DECTIN-1 (Y238X)	Carbohydrate recognition	Th17	*Candida albicans*	CMC	(Carvalho et al., 2012; Plantinga et al., 2009)
IL12B	AR	IL-12R, 9 mutations	Signal transduction chain	Reduction of Th1, Th17 cells	Mycobacteria, candidia, klebsiella, nocardia, salmonella	MSMD, Bacille Calmette-Guérin disease	(Prando et al., 2013)
IL12RB1	AR	IL-12Rb1, > 100 mutations	Peptide leader sequence, extracellular, transmembrane, intra-cellular cytoplasmic	Reduction of Th1, Th17 cells	Mycobacteria, candidia, klebsiella, nocardia, salmonella	MSMD, Bacille Calmette-Guérin disease	(de Beaucoudrey et al., 2010; Ouederni et al., 2014)
IL17F	AD	IL-17F (S65L)	cytokine-to-receptor binding	Blocks IL17F and IL17A/F signaling	*Candida albicans*, *Staphylococcus aureus*	CMC	(Puel et al., 2011)
IL17RA	AR	IL-17RA (Q284X)	Truncation in extracellular domain	Loss of IL-17R function	*Candida albicans*, *Staphylococcus aureus*	CMC	(Puel et al., 2011)
IL17RC		IL-17RC		Loss of IL-17RC function	*Candida albicans*, *Staphylococcus aureus*	CMC	(Ma et al., 2008)
STAT1		STAT-1	Coil-coil domain	Th17 cell reduction	*Candida albicans*	CMC	(Liu et al., 2011; van de Veerdonk et al., 2011)
STAT3	AD	STAT-3 (V432M), (R382Q), (H437P), (Q644P)	DNABD, SH2, transactivation domain	Th17 differentiation, heterozygous loss-of-function mutation	*Staphylococcus aureus*, *Candida albicans*, fungal infections, viral infections	Autosomal-dominant hyper IgE syndrome (HIES) or Job's syndrome	(Ma et al., 2008; Plantinga et al., 2009)
TYK2	AR	TYK-2		Loss of IL-23 signaling, Th17 maintenance	*Staphylococcus aureus*, *Candida albicans*	Autosomal-dominant hyper IgE syndrome (Job's syndrome)	(Minegishi et al., 2006)

Abbreviations are as follows: RA, rheumatoid arthritis; CD, Crohn's disease; BD, Behcet's disease.

[a]*ACT1*, Actin 1 gene; AIRE, autoimmune regulator; CARD9, caspase recruitment domain-containing protein 9; DECTIN1, dendritic-cell-associated C-type lectin-1.

[b]AD, autosomal dominant; AR, autosomal recessive.

[c]STAT, signal transducer and activator of transcription; mAb, monoclonal antibody; LMW, Low molecular weight compound.

[d]SEFIR, similar expression to fibroblasts growth factor and IL-17R; SAND, Sp100, AIRE, NucP41/75, and DEAF-1; DNABD, DNA binding domain; SH2, src homology 2 domain.

[e]CMC, Chronic mucocutaeneous candidiasis; signal transducer and activator of transcription; APS-1, Autoimmune polyendocrine syndrome type 1; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, UC, ulcerative colitis; MSMD, mendelian susceptibility to mycobacterial disease.

specificity for Th17 compared to other immunological pathways and are potentially suitable for therapeutic intervention. Thus far, there have been no STAT3- or IL-23R-specific therapeutic interventions.

Two antibodies to IL-12p40 (ustekinumab and briakinumab), which neutralize both IL-12 and IL-23 and have effects on both Th1 and Th17 as well as other cell types expressing the IL-12 and IL-23 receptors, have been widely studied (Figure 1). Both have shown good efficacy in psoriasis (Gordon et al., 2012; Kimball et al., 2008; Leonardi et al., 2008; Papp et al., 2008), with approximately 75% of patients achieving a 75% reduction in the psoriasis activity and severity index (PASI 75). While ustekinumab is registered and available for use, large clinical studies with briakinumab had an imbalance of major adverse cardiac events (MACE) that led to its discontinuation (Gordon et al., 2012). The reason why briakinumab and not ustekinumab had MACE events is not clear because they both specifically target the same molecule. However, data regarding levels of pathway inhibition of the two antibodies are sparse. Post-marketing surveillance studies have revealed no significant effects of ustekinumab on MACE or non-NMSC (non-melanoma skin cancer) malignancies (Papp et al., 2015). Although there have been reports of NMSC with ustekinumab use, the significance is not yet clear. Similar to many immunologic interventions, there is a slight increase in infections but no increase in the rate of serious infections compared to placebo. These clinical results suggest that the Th1 and/or Th17 pathways are important for the pathogenesis of psoriasis.

Studies with the p19 subunit of IL-23 (IL-23p19), which is more specific than IL-12p40 for Th17 differentiation and expansion, have provided the mechanistic insight that Th17 is the relevant pathway for psoriasis. Several anti-IL-23p19 mAbs (guselkumab, tildrakizumab, BI-655066, AMG139, and LY3074828) are currently in clinical testing. Results from Phase 2 (early clinical studies with limited numbers of patients) have shown excellent efficacy in psoriasis (Gordon et al., 2015; Kopp et al., 2015; Krueger et al., 2015). Although it is early in clinical testing, the results are only with limited numbers of patients, and the dosing regimens of anti-IL23p19 mAbs have not yet been optimized, there appears to be better efficacy in psoriasis by inhibiting IL-23 alone versus both IL-12 and IL-23. If confirmed, this would suggest that Th1 and Th17 are counterregulatory. The results of a recently completed head to head study of BI-655066 with ustekinumab (ClinicalTrials.gov Identifier NCT02054481) are eagerly awaited. Thus, the Th17 pathway is important for the pathogenesis of psoriasis.

Currently, two low molecular weight oral compounds (VTP-43472 and JTE-151) targeting the Th17 master regulator RORC2 are in Ph1 trials in healthy volunteers. Although preliminary data indicate that VTP-43472 suppresses IL-17A production in ex vivo stimulation studies under conditions promoting Th17 development, little other information is available. Because such compounds will target both RORC variants 1 and 2 (RORγ and RORγt in rodents) and are not specific for only RORC2, data on their effects on various immune and non-immune pathways are eagerly awaited. Thus far, the data in humans point to a similar role for RORC as in rodents, albeit longer term and more detailed data on larger numbers of treated patients and long-term carcinogenicity studies in rodents will be needed to understand the differences between pharmacologic inhibition and genetic deficiency and whether thymic lymphomas will occur with prolonged RORC suppression as they do with genetic RORγ deficiency in rodents (Jetten, 2009).

Although IL-17A is the hallmark cytokine of Th17 cells, they also produce IL-17F and IL-22, and all three cytokines have been hypothesized in animal models to be effector cytokines leading both to protection from infections and damage in autoimmunity. Clinical studies targeting these cytokines or their receptors are providing numerous data suggesting that IL-17A is a primary effector cytokine leading to the clinical manifestations of most but not all autoimmune diseases where Th17 has a role.

Listed in Table 2 are nine known molecules that target either IL-17A or IL-17A+IL-17F that are being or have been clinically tested (Figure 2). Although there are subtle differences between these molecules in parameters such as immunogenicity, potency, pharmacokinetics, dosing regimens, and side effect profiles, the findings and their implications for the understanding of human immunology are quite similar. Thus, we will focus on the one molecule where the first and most data exist (secukinumab) and supplement with data from ixekizumab for confirmation. Large Phase 3 clinical studies with both secukinumab and ixekizumab have shown a remarkable efficacy of IL-17A inhibition in psoriasis with ~90% of patients achieving a PASI 75 and ~40% achieving a PASI 100 response with complete clearing of skin lesions (Griffiths et al., 2015; Langley et al., 2014; Thaçi et al., 2015). Indeed, head-to-head studies of secukinumab with ustekinumab showed significantly higher efficacy of IL-17A inhibition compared to IL-12+23 blockade (see below). In smaller studies evaluating disease pathogenesis by histologic and molecular analysis, IL-17A inhibition results not only in improvements in keratinocyte hyperplasia and acanthosis by blocking IL-17A effects on skin stromal cells, but also a dramatic reduction in skin Th17 cells themselves, their products including IL-17A, IL-17F, IL-21, and IL-22, and factors that drive Th17 including IL-23, thus leading to the hypothesis that IL-17A augments a positive feedback loop for Th17 cells (Hueber et al., 2010). Although there were no cases of CMC, low rates of mild to moderate candida infections that resolved on their own or with standard therapy were seen with both secukinumab and ustekinumab (Griffiths et al., 2015; Langley et al., 2014; Thaçi et al., 2015). No cases of tuberculosis reactivation were reported. These data support the notion that IL-17A is a primary effector cytokine of and critical intervention point for Th17 cells.

Whether inhibiting other family members of IL-17 will have additional therapeutic benefit or side effects is being tested by biologic agents that target both IL-17A and IL-17F (RG7624, ALX-0761, and bimekizumab) and that target IL-17RA (brodalumumab). Data are available only for brodalumumab, which has shown excellent efficacy in psoriasis at the same levels as has been seen with secukinumab (Lebwohl et al., 2015). As with targeting IL-17A, mild to moderate candida infections were seen more frequently with brodalumab than placebo. Although there are no mechanistic explanations, and there might not be a causal relationship, brodalumab has been associated with suicidal ideation. Otherwise, there do not appear to be major differences between targeting IL-17A versus multiple IL-17 isoforms in psoriasis.

Targeting of IL-17A or IL-17RA appears to have better effects than targeting IL-12+23. Although it is difficult to compare results from different studies due to study design, patient selection, and other variables, there have been three studies that compared

Table 2. Therapeutic Interventions Affecting the Th17 Pathway

Target	Agent	Company	Phase[a]	Type[b]	Diseases[c]
IL-17A	Secukinumab (Cosentyx®)	Novartis	Marketed	Fully human mAb	Pso, PsA, AS, MS, Asthma, RA, Uveitis
IL-17A	Ixekizumab	Eli Lilly	Phase 3	Humanized mAb	Pso, PsA, RA
IL-17A	CNTO-6785	Johnson & Johnson	Phase 2	Fully human mAb	RA, COPD
IL-17A	CJM112	Novartis	Phase 2	mAb	Pso, HS
IL-17A	SCH-900117	Merck	Discontinued	Fully human mAb	RA
IL-17A	RG-4934	Roche	Discontinued	Fully human mAb	PsA, RA
IL-17A + IL-17F	Bimekizumab	UCB	Phase 2	Humanized mAb	Pso, PsA, RA
IL-17A + IL-17F	RG7624, NI-1401	Roche	Phase 1	Fully human mAb	AID
IL-17A + IL-17F	ALX-0761	Merck Serono, Ablynx	Phase 1	Bispecific half-life-extended nanobody	Pso
IL-17A + TNF-α	COVA322	Johnson & Johnson	Phase 2	Bispecific antibody fusion protein	Pso, PsA, AS, RA
IL-17A + TNF-α	ABT-122	AbbVie	Phase 2	Dual-variable-domain immunoglobulin	RA, PsA
IL-17A + TNF-α	ABBV-257	AbbVie	Phase 1	Dual-variable-domain immunoglobulin	RA
IL-17RA	Brodalumab, AMG 827	Amgen, AstraZeneca	Phase 3	Fully human mAb	Pso, PsA, Asthma
IL-22	Fezakinumab ILV-094	Pfizer	Discontinued	Fully human mAb	Pso, RA
IL-23p19	Guselkumab CNTO-1959	Johnson & Johnson	Phase 3	Fully human mAb	Pso, PsA, RA, PP
IL-23p19	Tildrakizumab, SCH-900222, MK-3222	Merck, Sun Pharma	Phase 3	Fully human mAb	Pso
IL-23p19	BI-655066	Boehringer Ingelheim	Phase 2	Humanized mAb	AS, CD, Pso, Asthma
IL-23p19	AMG 139, MEDI2070	Amgen, AstraZeneca	Phase 2	Fully human mAb	Pso, CD
IL-23p19	LY3074828	Eli Lilly	Phase 1	Humanized mAb	Pso
IL-12p40 + IL-23p40	Ustekinumab (Stelara®)	Johnson & Johnson	Marketed	Fully human mAb	Pso, PsA, RA, CD
IL-12p40 + IL-23p40	Briakinumab, ABT-874	Abbott	Discontinued	Fully human mAb	Pso
RORC	VTP-43472	Vitae Pharmaceuticals	Phase 1	LMW	Pso, MS, RA, BD, Uveitis
RORC	JTE-151	Japan Tobacco	Phase 1	LMW	Allergy, AID

[a]Phase 1 studies are generally for testing the safety and tolerability of new compounds in healthy subjects; Phase 2 studies are early studies that test efficacy and safety on small numbers of patients; Phase 3 studies test efficacy and safety in large number of patients with an aim to gain market authorization.
[b]mAb, monoclonal antibody; LMW, low molecular weight compound pulmonary disease.
[c]Regulatory authorities have approved use for underlined indications in one or more parts of the world; PP, Palmoplantar pustulosis; Pso, psoriasis; PsA, psoriatic arthritis.

IL-17 inhibitors directly with IL-12+23 inhibitors. In the CLEAR study, 44% (148/334) of patients treated with secukinumab versus 28% (95/335) of patients treated with ustekinumab achieved PASI 100 responses (Thaçi et al., 2015). In the AMAGINE 2 and 3 studies, 44% (272/612) and 37% (229/624) of patients treated with brodalumumab versus 22% (65/300) and 19% (58/313) of ustekinumab treated patients achieved PASI 100 (Lebwohl et al., 2015). Of the early clinical studies performed with anti-IL23p19 mAbs, the best interpretable data to date are with guselkumab, which showed an up to 33% PASI 100 response rate (14/42 patients) after 16 weeks of treatment (Gordon et al., 2015). It remains to be seen in larger Phase 3 and head-to-head studies whether inhibiting IL-23 will be as efficacious as inhibiting IL-17 or whether it will be closer to inhibiting IL-12+23.

Antibodies to IL-22 have also been tested in psoriasis. While IL-22 is an effector cytokine produced by Th17 cells, it is also the hallmark cytokine for Th22 cells that do not produce IL-17 and have the aryl hydrocarbon receptor (versus RORC) as their master regulator. A study with fezakinumab in psoriasis was completed in 2010 (NCT00563524) with no final data released and no further development reported, although an investigator-initiated trial in atopic dermatitis is ongoing (NCT01941537).

The data are consistent with the hypothesis that Th1 and Th17 are counterregulatory, and that IL-17A is a primary effector cytokine of Th17 cells, but the caveat remains that IL-17A is not the only effector cytokine produced by Th17 cells and that it is also produced by other cell types.

Th17 Pathway in Other Autoimmune Diseases

IL-17 and Th17 have been implicated in a multitude of diseases other than psoriasis, and clinical trials with pathway inhibitors have revealed results that were both expected and unexpected from the previous knowledge (Table 3).

Crohn's disease has strong genetic associations with Th17 by virtue of SNPs in IL23R. Thus, it is not surprising that IL-12+23 blockade with ustekinumab had some beneficial effects in the

Table 3. Clinical Efficacy of Th17 Pathway Modulators

Disease (severity)	IL-12+23	IL-23	IL-17A	IL-17RA
Psoriasis	++	+++	+++	+++
Psoriatic Arthritis	+	n.t.	++	+
Ankylosing Spondylitis	+	n.t.	++	n.t.
Asthma	n.t.	n.t.	n.a.	-/+
Crohn's disease	++	n.a.	–	–
Multiple Sclerosis	–	n.t.	++	n.t.
Rheumatoid Arthritis	+	–	++	–
Uveitis (non-infectious)	n.t.	n.t.	+	n.t.

n.t., not tested; n.a., data not yet available; –, not effective; +, partially effective; ++, effective; +++, highly effective.

subset of Crohn's patients who were poorly responsive to anti-TNF-α (Sandborn et al., 2012). A trial testing anti-IL-23p19 mAbs BI-655066 (NCT02031276) is ongoing with results available soon, and one with MEDI2070 (NCT02574637) is planned. With the pathway association and efficacy of ustekinumab, it was expected that IL-17 blockade would also be effective for Crohn's. However, anti-IL-17A mAb secukinumab was ineffective in moderate to severe Crohn's disease (Hueber et al., 2012), and development of brodalumab was also terminated due to lack of efficacy in Crohn's (Mozaffari et al., 2015). It might be that IL-17A has a protective role in gut inflammation, and Th17 cells manifest their gut proinflammatory effects via other factors.

One of the earliest biologic activities of IL-17A and links to inflammation were documented in synoviocytes from patients with rheumatoid arthritis (Miossec and Kolls, 2012), and multiple clinical studies have been performed testing different Th17 pathway inhibitors in RA. IL-17A inhibition with secukinumab resulted in modest efficacy in RA patients who had inadequate responses to methotrexate with 54% achieving ACR20 (Felson and LaValley, 2014) and 17% ACR50 responses at week 16 compared with placebo responses of 36% ACR20 and 6% ACR50 (Genovese et al., 2013; Hueber et al., 2010). Similar results were obtained with ixekizumab where there was also moderate efficacy in patients who were inadequate responders to anti-TNF-α therapy (Genovese et al., 2014). Although the data indicate an important biologic role for IL-17A in RA, the efficacy was not considered robust enough to continue clinical development toward registration and both programs have been stopped. The hypothesis that dual inhibition of TNF-α with IL-17 might be more beneficial than either alone is currently being tested with three mAbs (COVA322, ABT-122, and ABBV-257). This combination is likely to be highly effective, and it remains to be seen whether candida or other infections will limit the utility of the combination. Interestingly, blockade of IL-17RA with brodalumab at doses that have been effective in other diseases clearly had no effect in RA patients with inadequate response to methotrexate (Pavelka et al., 2015). These data raise important questions about differential regulation of synovial inflammation by the different IL-17 family members. While IL-17A appears to be proinflammatory in synovium, it is possible that IL-17E (also known as IL-25), which has a role in Th2 responses and a protective effect in EAE, might have a counterregulatory effect in synovial inflammation. A head-to-head study comparing IL-12+23 mAb ustekinumab with IL-23 mAb guselkumab in patients who were MTX inadequate responders showed mild efficacy of ustekinumab with ACR20 responses of 55% at week 28 versus 40% for placebo, but no efficacy for guselkumab with ACR20 responses of 38% and 44% at two different doses (NCT01645280). Thus, in the joint inflammation of RA, IL-17A appears to have a pathogenic role, but other Th17 derived cytokines or IL-17 family members such as IL-17E might have a protective role.

Enthesitis, inflammation at the sites of attachment of tendons or ligaments to bone, is an IL-23 driven process that is pathognomonic for the seronegative spondyloarthropathies, psoriatic arthritis (PsA), and AS (Ritchlin et al., 2014; Sherlock et al., 2012). Indeed, blocking IL-12+23 with ustekinumab for 24 weeks showed overall ACR20 and ACR50 responses of 44% and 20% compared to responses of 20% and 7% with placebo, and ACR20 responses of 36% compared to 15% for placebo in the anti-TNF-α experienced subpopulation (Ritchlin et al., 2014). These data led to approval of ustekinumab use for PsA. Blocking IL-17A with secukinumab for 24 weeks also showed good, and perhaps as is the case for skin manifestation of psoriasis better, efficacy in PsA with ACR20 and ACR50 response rates of 50% and 35% compared to 17% and 7% for placebo (Mease et al., 2015). Blocking multiple IL-17 isoforms for 12 weeks with brodalumab resulted in ACR20 and ACR50 responses of 39% and 14% compared to 18% and 4% for placebo (Mease et al., 2014). Like in RA, it appears that blocking multiple IL-17 members (including IL-17E) has less effect in the joint inflammation of PsA.

For AS, the only Th17 pathway inhibitor that has clinical results in a double-blinded trial thus far is secukinumab, which in a small Phase 2 study showed an ASAS20 (Sieper et al., 2009) response rate of 59% compared to 24% for placebo (Baeten and Kuchroo, 2013). A Phase 3 study with secukinumab has been completed in AS, and results are pending. An open-label study with ustekinumab also showed good results, but they are difficult to compare due to study design and lack of a placebo arm (Poddubnyy et al., 2014). Thus, the Th17 pathway in particular IL-17A is pathogenic in both PsA and AS.

Non-infectious uveitis, like AS, is commonly associated with HLAB27 and has overlapping mechanisms of pathogenesis. After an early open-label study with high-dose 10 mg/Kg intravenous secukinumab showed promising efficacy in active uveitis (Hueber et al., 2010), three trials testing lower dose 300 mg subcutaneous secukinumab in Behcet's and non-Behcet's, non-infectious uveitis suggested beneficial effects of secukinumab but there was no significant effect on the primary endpoints tested (Dick et al., 2013). A subsequent study showed that higher doses of secukinumab are required for efficacy in uveitis with clinical response rates of 33% with 300mg SC, 62% with 10mg/Kg IV, and 73% with 30mg/Kg IV (Letko et al., 2015), possibly due to different levels of tissue distribution. These data are consistent with the notion that dose and tissue distribution matter for a pharmacodynamic effect in therapeutic intervention.

IL-17 has been implicated in contributing to asthma pathogenesis by its ability to attract neutrophils and eosinophils. Brodalumab treatment for 12 weeks did not result in a significant effect on multiple parameters, but might have had some effect in a subset of patients whose disease was considered highly reversible (Busse et al., 2013). Secukinumab has also been tested, but results are not yet available.

EAE is the setting in which Th17 cells were discovered in rodents, but the role of Th17 cells in multiple sclerosis has been controversial. IL-17 was not considered to the pathogenic cytokine in this disease model. IL-12+23 inhibitor ustekinumab showed no efficacy in relapsing remitting multiple sclerosis (RRMS) (Segal et al., 2008). The reason for this is not clear, and it could be related to the doses used, which might not have had adequate tissue exposure to fully suppress Th17 cells, or the often opposite effects of Th1 and Th17 seen in EAE, because IL-12+23 will inhibit generation of both these T cell subsets. On the other hand, the IL-17A inhibitor secukinumab treatment led to a decrease of the mean raw number of cumulative unique active lesions (CCUAL) in patients with RRMS from 19.9 with placebo to 9.4 with secukinumab at 26 weeks, and the mean raw number of cumulative new Gd-T1 lesions decreased from 14.4 with placebo to 6.5 with secukinumab (NCT01051817). Both CCUAL and Gd-T1 are measures of brain and/or spinal cord inflammation as determined by magnetic resonance imaging. Thus, IL-17A has a prominent role in the pathogenesis of RRMS in man.

Concluding Remarks

Discovery of the Th17 cell and identification of its importance in animal models of autoimmunity such as EAE, has led to an explosion in the understanding of human immunology and autoimmunity. Genetics and therapeutic interventions have provided the biggest insights. Genome-wide association studies linked the Th17 pathway by virtue of SNPs in the IL-23R to psoriasis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Identification of the genetic causes of primary immunodeficiency diseases, mostly by reverse genetics testing Th17 pathway genes in immunodeficiency diseases such as chronic mucocutaneous candidiasis, revealed that Th17 cells have a critically important role in host immunity to mucocutaneous candida infections and *Staphylococcus aureus*. While defects in the entire Th17 pathway, IL-17RA/C, and its signal transduction molecule Act1 lead to profoundly impaired immunity and CMC, defects in IL-17F have a partial CMC phenotype indicating that IL-17A and IL-17F have overlapping and redundant functions in immunity to *Candida albicans*. Therapeutic interventions with inhibitors of IL-12+23, IL-23, IL-17A, and IL-17RA all have variably beneficial effects in psoriatic skin inflammation, with the Th17-specific therapies having dramatically better efficacy than those that target both Th1 and Th17. It is possible that Th1 and Th17 cells have counterregulatory roles in psoriatic skin inflammation. Similarly, the IL-17A inhibitor secukinumab has better efficacy than the IL-12+23 inhibitor ustekinumab in psoriatic joint inflammation. However, the IL-17RA inhibitor brodalumab for reasons that are not yet clear but might be due to concurrent inhibition of IL-17E, appears to be inferior to IL-17A inhibitors in all types of joint inflammation tested thus far, including rheumatoid arthritis and psoriatic arthritis. While IL-12+23 inhibition has beneficial effects in Crohn's disease, neither IL-17A nor IL-17RA inhibitors are effective in this disease. Whether this indicates an unlikely lack of Th17 involvement in the disease or more likely a protective role for IL-17A remains to be determined and will be informed by ongoing studies with IL-23 inhibitors. As predicted by genetics and animal models, Th17 pathway inhibition with IL-17A inhibitor secukinumab has excellent effects in HLA-B27 associated diseases ankylosing spondylitis and uveitis. The role of Th17 and/or IL-17A in EAE with extension to multiple sclerosis has been an area of controversy, and data with secukinumab have shown that there is an important role for IL-17A in multiple sclerosis. Therapeutic inhibition has confirmed the role of the Th17 pathway in immunity to mucocutaneous *Candida albicans* with some patients contracting mild to moderate candida infections localized to the skin and mucosa that are easily treatable. These data also highlight the fact that therapeutic interventions do not cause the same level of immunodeficiency as a genetic defect. Thus, Th17 cells play an important role in protective immunity against *Candida albicans* and to a lesser degree *Staphylococcus aureus* and are pathogenic in many autoimmune diseases. The different components of the pathway each have unique characteristics and variable involvement in protective and pathogenic immune responses.

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