

Immunity to infection in IL-17-deficient mice and humans

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Mice with defective IL-17 immunity display a broad vulnerability to various infectious agents at diverse mucocutaneous surfaces. In humans, the study of patients with various primary immunodeficiencies, including autosomal dominant hyper-IgE syndrome caused by dominant-negative STAT3 mutations and autosomal recessive autoimmune polyendocrinopathy syndrome type 1 caused by null mutations in AIRE, has suggested that IL-17A, IL-17F and/or IL-22 are essential for mucocutaneous immunity to *Candida albicans*. This hypothesis was confirmed by the identification of rare patients with chronic mucocutaneous candidiasis (CMC) due to autosomal recessive IL-17RA deficiency and autosomal dominant IL-17F deficiency. Heterozygosity for gain-of-function mutations in STAT1 in additional patients with CMC was recently shown to inhibit the development of IL-17 T cells. Although the infectious phenotype of patients with CMC and inborn errors of IL-17 immunity remains to be finely delineated, it appears that human IL-17A and IL-17F display redundancy for protective immunity in natural conditions that is not seen in their mouse orthologs in experimental conditions.

Keywords: Cytokines · IL-17 · Infectious diseases

Introduction

In mice and men, the IL-17 family of cytokines contains six sequence-related homologs: IL-17A through IL-17F [1]. The corresponding cytokine receptors belong to the IL-17R family, which has five members: IL-17RA through IL-17RE [1]. IL-17A and its close relative IL-17F are secreted principally by T cells and

form homo- and hetero-dimers that signal through a complex of IL-17RA and IL-17RC chains [2]. These receptors are widely expressed, but their expression levels differ, with IL-17RA being strongly expressed by hematopoietic cells and IL-17RC by epithelial cells [1]. In mice, IL-17A and IL-17F are thought to be key cytokines for the clearance of various pathogens at mucocutaneous surfaces ([3–5], Table 1). These cytokines induce the secretion of antimicrobial peptides by epithelial cells, thereby promoting the direct destruction of invading pathogens, and factors activating and recruiting granulocytes, further contributing to pathogen eradication [3]. As discussed in the next section, mice lacking the *Il17a* and *Il17ra* genes or, to a lesser extent, the

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Table 1. Infectious phenotypes of *Il17ra*, *Il17a*, and *Il17f*-deficient mice. The anatomical sites tested are listed. For *Il-17A* and *Il-17F*, both knock-out mice and the use of neutralizing antibody were considered (corresponding papers are indicated in brackets). MC, mucocutaneous. G, gram. ss RNA, single strand RNA

Pathogens	Phenotype of <i>Il17ra</i> ^{-/-} mice					Phenotype of <i>Il17a</i> ^{-/-} mice					Phenotype of <i>Il17f</i> ^{-/-} mice				
		Susceptible	Resistant	No phenotype	Not tested	Susceptible	Resistant	No phenotype	Not tested		Susceptible	Resistant	No phenotype	Not tested	
Bacterium	G-	<i>Klebsiella pneumoniae</i>	Lung [6]											X	X
Bacterium	G-	<i>Porphyromonas gingivalis</i>	Gingiva [10]											X	X
Bacterium	G+	<i>Bacillus anthracis</i>	Lung [7]											X	X
Bacterium	G-	<i>Neisseria gonorrhoeae</i>	Urogenital mucosa [12]											X	X
Bacterium	G+	<i>Listeria monocytogenes</i>	Invasive [19]			Invasive [116]									X
Bacterium	G+	<i>Mycobacterium BCG</i>	Lung [8]			Lung [8, 23]									X
Bacterium	G+	<i>Staphylococcus aureus</i>	Skin [14]			MC & invasive [24]									X
Bacterium	G-	<i>Helicobacter pylori</i>	Stomach [11]				Stomach [25]								X
Bacterium	G-	<i>Salmonella typhimurium</i>				Intestinal mucosa [117]				Intestinal mucosa [117]					Intestinal mucosa [117]
Bacterium	G-	<i>Chlamydia muridarum</i>				Genital mucosa [119]				Genital mucosa [119]					X
Bacterium	G+	<i>Escherichia coli</i>					Urinary tract [21]								X
Bacterium	G-	<i>Yersinia pestis</i>					Lung [22]								X
Bacterium	G-	<i>Acinetobacter baumannii</i>								Invasive [120]					X
Fungus		<i>Candida albicans</i> local	Oropharynx [17]			Skin [28]									X
Fungus		<i>Candida albicans</i> systemic	Invasive [18]												
Fungus		<i>Cryptococcus neoformans</i>													
Parasite		<i>Toxoplasma gondii</i>	Oral cavity [15]	Oral cavity [16]			Oral cavity [15]								X
Parasite		<i>Schistosoma mansoni</i>													
Parasite		<i>Leishmania major</i>					Liver [122]								X
Virus	ss RNA	Influenza virus	Lung [9]				Skin [26]							X	X
Virus	ss RNA	Coxsackievirus B3					Myocardium [123]								X

IL17f gene, are susceptible to a broad range of infections with bacterial and fungal pathogens at the mucosal surface. In contrast, human patients lacking a component of IL-17 immunity due to a genetic defect, have a narrower spectrum of pathogen susceptibility. Indeed, in the past few years, such patients have been shown to be susceptible principally to chronic mucocutaneous candidiasis (CMC) and, less commonly, to cutaneous *Staphylococcus aureus* infections. We review here current knowledge concerning the role of IL-17 cytokines in host defense in mice and humans.

Infectious phenotype of mice with impaired IL-17 immunity

In mice, IL-17RA has been shown to be essential for mucocutaneous immunity to several pathogens (Table 1), including pulmonary immunity to *Klebsiella pneumoniae*, *Bacillus anthracis*, and *Mycobacterium bovis* BCG [6–8] and to Influenza virus [9]; gingival immunity to *Porphyromonas gingivalis* [10]; gastric immunity to *Helicobacter pylori* [11]; urogenital immunity to *Neisseria gonorrhoeae* [12]; intestinal immunity to polymicrobial sepsis [13]; cutaneous immunity to *S. aureus* [14]; oral immunity to *Toxoplasma gondii* (in one study [15] but not in another [16]); and oropharyngeal immunity to *Candida albicans* [17]. In addition, IL-17RA is important for systemic immunity in mice to *Listeria monocytogenes* and *C. albicans* [18, 19].

Efforts to determine the respective roles of IL-17A and IL-17F in immunity to infection in mice, however, have only recently begun [5, 20]. IL-17A has been shown to be essential for immunity to *Escherichia coli* in the urinary tract [21], to *Yersinia pestis* [22] and BCG in the lung [23], and to *S. aureus* in the bone and synovial tissues [24], but seems to be detrimental for immunity to gastric infection with *H. pylori* [25] and cutaneous infection with *Leishmania major* [26]. Unlike *IL17f*-deficient mice, *IL17a*^{-/-} mice are susceptible to systemic candidiasis [27] and to cutaneous *C. albicans* infection, despite having normal levels of IL-17F [28]. The role of IL-17F in mucosal immunity to *C. albicans* remains unknown, but it seems to be redundant with IL-17A in mucocutaneous defense against *S. aureus* and *Citrobacter rodentium* [20]. Overall, these studies suggest that IL-17 cytokines in mice play nonredundant roles in host defense against mucosal bacterial, viral, parasitic, and fungal infections, including, in particular, mucocutaneous immunity to *C. albicans*.

Syndromic CMC in humans with primary immunodeficiencies (PIDs)

In humans, CMC is a relatively common fungal infection [29]. It is typically caused by *C. albicans*, a commensal fungus of the skin and gastrointestinal tract. *C. albicans* does not cause chronic disease in healthy individuals, but individuals with broad (combined immunodeficiency (CID)) and profound T-cell defects (severe combined immunodeficiency (SCID)), whether qualitative or

quantitative, inherited or acquired, are susceptible to CMC, particularly in the form of severe recurrent oral candidiasis. Such individuals are highly vulnerable to a broad range of microorganisms (virus, bacteria, fungi, and parasites) [30]. Patients with acquired immunodeficiencies, such as AIDS [31], and patients on immunosuppressive therapies [32], may suffer from CMC. Similarly, patients with severe combined immunodeficiency [33] and a lack of autologous T cells are prone to CMC. Even patients with CIDs (i.e. with a T-cell deficiency despite the presence of T cells) are prone to CMC. The defects predisposing patients to CMC include autosomal recessive (AR) TCR- α deficiency [34], AR ORAI1 deficiency [35], some forms of X-linked recessive (XR) NEMO disorders or autosomal dominant (AD) I κ B α disorders [36], AR MST1 deficiency ([37] and unpublished data), AR CD25 deficiency [38, 39], AR IRF8 deficiency [40], AR DOCK8 deficiency [41], and other syndromes with T-cell defects [30]. These patients are also susceptible to many microorganisms other than *C. albicans*. By contrast, CMC is very rare in patients with PIDs that do not affect T cells, including those with relatively pure B-cell, phagocyte, or complement PIDs [30]. Collectively, these observations indicate that T cells are essential for mucocutaneous immunity against *C. albicans*.

Recent investigations of patients with PIDs associated with a narrower range of infectious diseases, i.e. not restricted to CMC, but not quite as large as that seen in patients with the T-cell deficiencies mentioned above, gradually led to the notion that impaired IL-17 T-cell immunity may underlie CMC. An impairment of the development of IL-17 (and IL-22) T cells was demonstrated in patients with AD hyper-IgE syndrome (HIES) bearing heterozygous mutations in *STAT3*, who suffer mostly from severe cutaneous and pulmonary *S. aureus* infections and CMC [42–46]. Impaired *STAT3* signaling downstream from IL-6, IL-21, and/or IL-23 (Fig. 1) probably accounts for the poor development of IL-17 T cells, as these cytokines have been shown to be critical for the development of Th17 cells in the mouse model [47, 48]. Impaired development of IL-17 (and IL-22) T cells was also demonstrated in patients with AR IL-12p40 or IL-12R β 1 deficiency and Mendelian susceptibility to mycobacterial disease. About 25% of these patients develop mild CMC ([44, 49] and unpublished data), presumably due to a lack of IL-23 immunity, as IL-23 has been shown to be important for the development of Th17 cells in the mouse model [44, 50]. Reduced numbers of IL-17 T cells were also observed in a kindred with AR CARD9 deficiency displaying CMC, dermatophyte infections of the skin and invasive candidiasis [51]. CARD9 is an adaptor acting downstream from receptors involved in fungal recognition, such as the mannose receptor, Dectin-1, or Dectin-2 (Fig. 1) [52]; its deficiency may result in impaired production of the cytokines required for IL-17 T-cell differentiation and/or maintenance [51]. Finally, high titers of neutralizing autoantibodies against IL-17A, IL-17F, and/or IL-22 have been detected in patients with AR autoimmune polyendocrinopathy syndrome type 1 with CMC as the only major infection [53–55]. Altogether these studies suggested but did not formally prove that impaired IL-17 immunity may be the unifying mechanism underlying CMC.

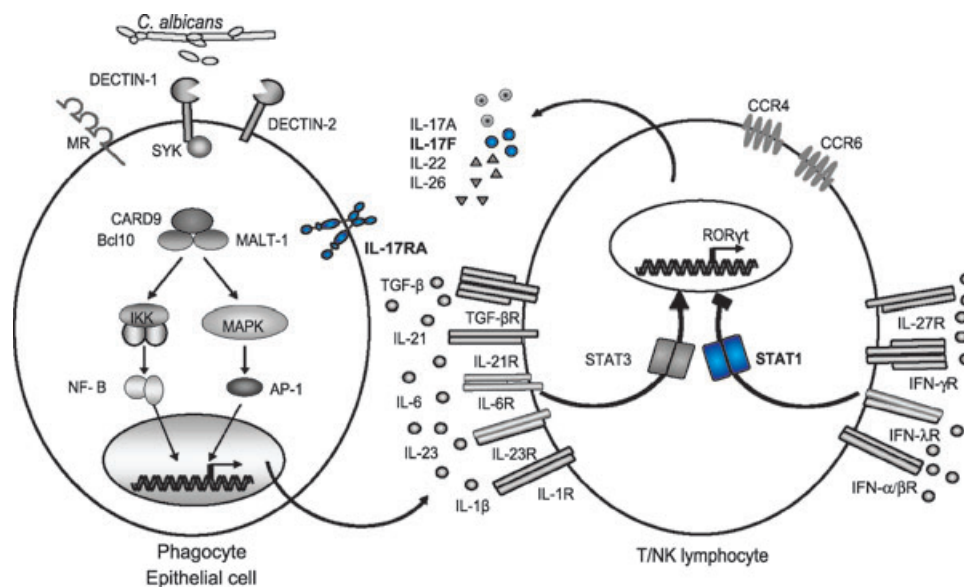


Figure 1. Schematic representation of IL-17 immunity, and cooperation between cells recognizing *C. albicans* (phagocytes and epithelial cells) and cells producing IL-17 cytokines (T and innate (NK) lymphocytes). Upon *C. albicans* recognition by PRRs (pathogen recognition receptors, including Dectin-1, Dectin-2, or the mannose receptor (MR)), adaptor molecules, such as CARD9, mediate via the NF- κ B and AP-1 pathways the induction of pro-inflammatory cytokines by myeloid or epithelial cells. These pro-inflammatory cytokines, such as IL-6 or IL-23, activate T lymphocytes via STAT3 resulting in cell differentiation into IL-17-producing T cells. CMCD-causing mutations (in blue) in IL-17F and IL-17RA impair IL-17 function and response, respectively. CMCD-causing GOF mutations (also shown in blue) in STAT1 impair the development of IL-17-producing T cells.

Isolated CMC and inborn errors of IL-17

The formal proof that impaired IL-17 immunity underlies CMC came from the study of patients with isolated CMC, often referred to as CMC disease (CMCD) [56]. CMCD was first described as a distinct entity in the late 1960s, with the description of familial and sporadic cases [57–68], but it has only recently been suggested that patients with this condition carry inborn errors of IL-17 immunity [56, 69]. This hypothesis was validated in 2011, with the identification of the first two genetic etiologies of CMCD (Fig. 1) [70]. Complete IL-17RA deficiency was found in a single patient with CMCD born to consanguineous parents of Moroccan origin. The previously unreported homozygous premature stop codon found in the *IL17RA* gene of this patient abolished the expression of the protein and the cellular responses to homo- and hetero-dimers of IL-17A and IL-17F [70], and potentially other IL-17 family members. The patient also developed *S. aureus* skin abscesses and folliculitis, as sometimes reported in CMCD patients [71], but was otherwise not susceptible to most common pathogens [70]. The patient being homozygous by descent for 1/16 of his genome meant that there remained the remote, but finite, possibility that the IL-17RA deficiency was not responsible for CMC. Final evidence was provided by the discovery of partial AD IL-17F deficiency in a multiplex Argentinian kindred with CMCD due to a heterozygous missense mutation (S65L) in the *IL17F* gene. The mutation was severely hypomorphic and dominant, as it impaired the function of both homo- (IL-17F/IL-17F) and hetero- (IL-17A/IL-17F) dimers containing the mutant isoform, by impairing the binding of the complexes to the receptor.

The affected members of this kindred appeared to be susceptible solely to *C. albicans* [70]. Another patient suffering only from CMC has been described with a heterozygous mutation *IL17F* and, although no functional characterization of the mutant allele was performed, this mutation might be causing CMC [72].

Studies based on genome-wide approaches led to the identification of a more common genetic etiology of CMCD, namely heterozygous mutations in the coiled coil domain of *STAT1* ([73–76] and unpublished data). Eighteen such CMCD-causing mutations have been identified in 92 patients from 43 unrelated families originating from 14 countries ([73–76] and unpublished data). These mutations occurred de novo in seven kindreds, and all mutant alleles displayed complete clinical penetrance ([75] and unpublished data). More recently, mutations in the DNA-binding domain of *STAT1* in CMC patients were identified ([77] and unpublished data). These discoveries were surprising, as previously reported human *STAT1* mutations, whether mono- or biallelic, were null or hypomorphic and conferred susceptibility to mycobacterial disease, with or without viral disease. The underlying mechanisms involve impaired cellular responses to IFN- γ (and probably IL-27) and/or IFN- α/β (and probably IFN- λ) [78–84]. The enigma was solved when CMCD-causing *STAT1* mutations were shown to be gain-of-function (GOF), by a mechanism involving a gain-of-phosphorylation due to the impairment of nuclear dephosphorylation rather than an enhancement of cytoplasmic phosphorylation [85]. These mutations thus result in enhanced *STAT1* responses to cytokines, including IFN- α/β , IFN- γ , and IL-27, which predominantly activate *STAT1* rather than *STAT3*, and to IL-6 and IL-21, which normally predominantly

activate STAT3 rather than STAT1 (Fig. 1) [75]. Moreover, these patients have low proportions of IL-17 T cells, accounting for CMC. This IL-17 phenotype may result from enhanced STAT1-mediated cellular responses to STAT1-dependent repressors of IL-17-producing T cells, such as IFN- γ , IFN- α/β , and IL-27 [86–99], and/or from enhanced and potentially competing STAT1 responses to cytokines predominantly activating STAT3, which are required for the development of IL-17 T cells, such as IL-6, IL-21, and IL-23 [48, 100, 101]. In any case, this IL-17 defect in patients carrying gain-of-function *STAT1* mutations lends weight to the argument that IL-17 immunity plays an important role in the development of CMC.

Conclusions

The recent discovery of the first genetic etiologies of CMCD — complete AR IL-17RA and partial AD IL-17 deficiencies and GOF *STAT1* mutations — has provided the first insight into the function of human IL-17 in host defense in natura (Fig. 1) [102–107]. These findings are consistent with the greater susceptibility of *IL17ra*- and *IL17a*-deficient mice to mucosal candidiasis and with the impaired IL-17 immunity observed in patients with PIDs associated with CMC, such as AD-HIES and autoimmune polyendocrinopathy syndrome type 1. In patients with IL-17RA deficiency, CMCD results from the abolition of responses to IL-17A and IL-17F homo- and IL-17A/IL-17F hetero-dimers. In patients with IL-17F deficiency, the function of IL-17F homodimers and IL-17A/IL-17F heterodimers containing the mutant protein is severely impaired. Finally, *STAT1* GOF mutations result in a developmental defect of IL-17-producing T cells. However, at odds with the mouse model, these experiments of Nature show that human IL-17 immunity is central to mucosal defense against *C. albicans* and, to a lesser extent, cutaneous staphylococcal infection, but largely redundant in host defense against most other common pathogens. This difference between mice and humans with IL-17 deficiencies is reminiscent of that observed for patients with inborn errors of IL-12 and IFN- γ immunity, whose infectious phenotype is much narrower than that of mice lacking the Th1 arm of immunity [49, 108, 109]. A careful clinical description of a large series of patients with inborn errors of IL-17 immunity, as previously carried out for IL-12 and IFN- γ immunity [50, 110], is required to determine the role of these cytokines more precisely, however. Moreover, the ongoing recruitment of new CMCD patients without mutations of *STAT1*, *IL17RA*, or *IL17F* and the use of genome-wide approaches should eventually lead to the identification of new players in IL-17 immunity. Finally, the use of recombinant IL-17 cytokines to treat patients with CMC due to GOF *STAT1* mutations or IL-17F deficiency, but not IL-17RA deficiency, might be considered, perhaps at the risk of promoting autoimmune diseases [111, 112]. Treatment of the patients with G-CSF or GM-CSF is another potential approach [113]. Conversely, the use of anti-IL-17 antibody to treat patients with autoimmunity should be carefully overseen to prevent or treat CMC [114, 115].

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Abbreviations: AD: autosomal dominant · AR: autosomal recessive · CMC: chronic mucocutaneous candidiasis · CMCD: CMC disease · PID: primary immunodeficiency

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