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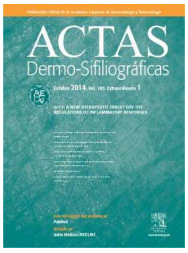

IL-17 and infections

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Abstract IL-17 immunity has been shown to be essential for mucocutaneous protection against *Candida albicans* in mice and humans. However, mice with defective IL-17 immunity display broader susceptibility, as they are also prone to infections with diverse infectious agents at various sites. Humans with genetic defects affecting their IL-17 immunity usually suffer from chronic mucocutaneous candidiasis (CMC): recurrent or persistent infections of the skin, nails, and mucosae with *C. albicans*, with or without other clinical signs. Most patients with autosomal dominant (AD) hyper-IgE syndrome (HIES) due to STAT3 deficiency or AD STAT1 gain-of-function display impaired IL-17-producing T-cell development, and CMC is one of their principal clinical manifestations. Similarly, patients with autosomal recessive (AR) autoimmune polyendocrine syndrome type 1 (APS-1) caused by AIRE deficiency have high levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22 and present CMC as their only infectious disease. Finally, CMC is the main clinical phenotype observed in patients with inborn errors specifically affecting IL-17 immunity. Indeed, patients with AD IL-17F deficiency or AR IL-17RA or ACT1 deficiency display CMC and, to a lesser extent, superficial staphylococcal diseases. *Candida* infection was recently reported in psoriasis patients treated with anti-IL-17A antibodies. Careful monitoring for CMC is thus important during anti-IL-17 treatment.

PALABRAS CLAVE
IL-17;
Inmunodeficiencias primarias;
Candidiasis mucocutánea crónica;
Errores innatos de la inmunidad IL-17

IL-17 e infecciones

Resumen Se ha demostrado que la inmunidad IL-17 es esencial para la protección mucocutánea contra la *Candida albicans* en ratones y humanos. Independientemente, los ratones con inmunidad IL-17 defectuosa muestran una susceptibilidad más amplia, de modo que también son propensos a infecciones por diversos agentes infecciosos en varios lugares. Los humanos con defectos genéticos que afectan su inmunidad IL-17 habitualmente padecen candidiasis mucocutánea crónica (CMC): infecciones cutáneas recurrentes o persistentes de uñas y mucosas por *C. albicans*, con o sin otros signos clínicos. Muchos pacientes con síndrome de hiper IgE autosómico dominante (AD-HIES) debido a

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deficiencia STAT3 o a aumento de función AD STAT1 muestran un desarrollo dañado de células T productoras de IL-17 y la CMC es una de sus principales manifestaciones. De igual manera, los pacientes con síndrome poliendocrino autoinmune tipo 1 recesivo autosómico (AR-APS-1) causado por deficiencia de AIRE (regulador autoinmune) presentan altos niveles de anticuerpos neutralizantes contra IL-17A, IL-17F y/o IL-22 y padecen CMC como su única enfermedad infecciosa. Finalmente, la CMC es el principal fenotipo clínico observado en pacientes con errores innatos, específicamente aquellos que afectan la inmunidad IL-17. De hecho, los pacientes con deficiencia AD IL-17F o deficiencia IL-17RA o ACT1 presentan CMC y, en menor medida, enfermedades estafilocócicas superficiales. Se ha informado recientemente CMC en pacientes tratados con anticuerpos anti-IL-17A. Es importante el control cuidadoso de la CMC en estos pacientes durante el tratamiento con anti-IL-17A.

Introduction

In both mice and humans, the IL-17 family of cytokines contains six members: IL-17A through IL-17F.[1] The receptors for these cytokines belong to the IL-17R family, which has five members: IL-17RA through IL-17RE.[1] In mice, IL-17A and IL-17F induce the secretion of antimicrobial peptides by epithelial cells and of factors activating and recruiting granulocytes, thereby contributing to the destruction and eradication of invading pathogens.[2,3] Mice lacking the genes encoding IL-17A or IL-17RA are susceptible to a broad range of infections with bacterial, fungal, parasitic or viral pathogens, at various mucosal surfaces. They are also susceptible to disseminated infections with certain pathogens, such as *Candida albicans*[2,4] and *Listeria monocytogenes*.[5,6] In recent years, patients with impaired or abolished IL-17 immunity have been shown to be susceptible to chronic mucocutaneous candidiasis (CMC).[7-9] We review here current knowledge about the role of IL-17 cytokines in host defense in mice and humans.

IL-17 immunity

Studies of both mice and humans lacking proteins involved in IL-17 signaling have helped to clarify the role of IL-17 in immunity. Loss-of-function mutations of *IL17F,*[7] *IL17RA,*[7] and *ACT1,*[8] and gain-of-function mutations of *STAT1*[9-22] have been identified as genetic etiologies of CMC in humans. IL-17F belongs to the IL-17 family and IL17RA belongs to the IL-17R family.[1] IL-17F and IL-17A bind, as homodimers (IL-17F/IL-17F and IL-17A/IL-17A) or heterodimers (IL-17F/IL-17A) to their receptor, which consists of the IL-17RA and IL-17RC chains.[23-25] IL-17RA and IL-17RC have been shown to be essential for signaling downstream from IL-17A, IL-17F, and IL-17A/F, in both mice[24-26] and humans.[7] Indeed, fibroblasts from *IL17RA*[27] or *IL17RC*[26] deficient mice display no induction of IL-6 and KC/CXCL1 upon stimulation with IL-17A, IL-17A/F, and IL-17F. Similarly, fibroblasts from IL-17RA deficient patients do not respond to IL-17A and IL-17F homo- and heterodimers in terms of IL-6 and GRO-α production.[7] Moreover, following its heterodimerization with IL-17RB, IL-17RA has been shown to be involved in the IL-25/IL-17E signaling pathway in mice,[26,28] and IL-17RA-deficient patients do not respond to IL-25/IL-17E.[8] By contrast, IL-17RC has not been shown to be part of any other receptor in mice,[29] at least not one required for IL-25/IL-17E signaling.[30] ACT1 is an adaptor protein acting downstream from IL-17RA, IL-17RC and IL-17RB, in mice[31-34] and humans.[8] Mouse embryonic fibroblasts lacking ACT1, display low levels of KC/CXCL1 and IL-6 expression in response to stimulation with IL-17A[32,35] and IL-17F.[36] In addition, abolition of the IL-25/IL-17E-induced expression of IL-4, IL-5, IL-13, eotaxin-1 (CCL11) and pulmonary eosinophilia has also been observed in the lung tissues of *Act1*-deficient mice.[35-37] Human patients with AR ACT1 deficiency and CMC have recently been described.[8] These siblings were found to be homozygous for the T536I mutation of *ACT1*, impairing homotypic interactions of ACT1 with IL-17RA, IL-17RC and IL-17RB.[8] As a result, the fibroblasts of these patients did not respond to IL-17A and IL-17F, and their T cells did not respond to IL-17E.[8]

Impaired or abolished IL-17 immunity and superficial *C. albicans* infections

Mouse models

Wild-type adult mice are naturally resistant to oropharyngeal colonization and disease caused by *C. albicans*. Complete clearance of *C. albicans* is observed within three to four days of oral inoculation, with no evidence of oral mucosal plaque formation[4]. However, a number of knockout mouse models and mice into which neutralizing antibodies have been injected have been tested for oropharyngeal candidiasis (OPC)[4,38-40] or cutaneous *C. albicans* infections. Mice lacking IL17A have been shown to be susceptible to cutaneous *C. albicans* infection.[41] In addition, mice treated with injections of neutralizing antibodies directed against IL-17A and IL-17F have been shown to be susceptible to OPC. However, mice treated with anti-IL17A or anti-IL-17F Abs alone seem to be less susceptible to OPC than mice treated with a combination of these two antibodies, with anti-IL-17A antibodies being slightly more efficient than anti-IL-17F.[38] Mice lacking IL-17RA,[39] IL-17RC[24] or ACT1[40] have much larger fungal loads in the oral cavity during

Table 1 Clinical phenotypes of CMCD patients with inborn errors of IL-17 immunity

Gene	Imheritance	Allele	Cytokines		Disease phenotype/ infections	
			IL-17A/F	IL-17E	CMC	Others
IL17F	AD	Partial loss-of-function (hypomorphic)	Impaired	Normal?	CMC	
IL17RA	AR	Complete loss-of-function (null)	Abolished	Abolished	CMC	*Staphylococcus aureus* dermatitis
ACT1	AR	Complete loss-of-function (null)	Abolished	Abolished	CMC	*Staphylococcus aureus* blepharitis
STAT1	AD	Gain-of-function (hypermorphic)	Normal?	Normal?	Broader infectious phenotype	

AD: autosomal dominant; AR: autosomal recessive; CMC: chronic mucocutaneous candidiasis.

OPC than wild-type mice. In addition, a number of mice lacking proteins involved in IL-17 T-cell development have been shown to be susceptible to OPC. In particular, mice lacking the retinoic acid–related orphan receptor (ROR)-γt, a transcription factor inducing the production of IL-17 and IL-22, and possibly of other cytokines, have been shown to be susceptible to OPC.[38] By contrast, despite the prior demonstration that IL-1 and IL-6 are important for Th17 cell differentiation in mice, mice lacking IL-1R or IL-6 were found to be able to clear the fungal infection.[38] However, mice lacking *IL23p19*, one of the two subunits of IL-23, essential for Th17 cell expansion and function in mice[42-45] and humans,[46-48] displayed impaired IL-17A production and were highly susceptible to OPC.[39,49]

Primary immunodeficiencies (PIDs) in humans

IL-17 immunity was shown to be essential for mucocutaneous protection against *C. albicans* in humans, in investigations of primary immunodeficiencies (PIDs) involving syndromic CMC,[2-50-53] as patients with these PIDs were found to have impaired IL-17 immunity.[51,52] Indeed, most patients with autosomal dominant (AD) hyper-IgE syndrome (AD-HIES) and STAT3 deficiency,[53-57] some patients with invasive fungal infections and autosomal recessive (AR) CARD9 deficiency[58-62] or with Mendelian susceptibility to mycobacterial diseases (MSMD) and AR IL-12p40 or IL-12Rβ1 deficiency[55,63,64] display CMC and have low proportions of IL-17A-producing T cells.[2,51,52] Most patients with AR autoimmune polyendocrine syndrome type 1 (APS-1) and AIRE deficiency display CMC and have high levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22.[65,66] These findings paved the way for the discovery of the first genetic etiologies of CMC disease (CMCD), an inherited condition affecting individuals without any of the abovementioned PIDs.[67-69] The pathogenesis of human CMC was eventually deciphered by studies of patients with CMC disease (CMCD), in which CMC is the only overt clinical sign.[52] Four genetic etiologies of CMCD have been described to date (Table 1). AR IL-17RA and AD IL-17F deficiencies were the first two genetic etiologies of CMCD to be discovered.[7] IL-17RA deficiency was complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers,[7] and to IL-17E (IL-25).[8] By contrast, IL-17F deficiency was partial, with impaired, but not abolished, cellular responses to the homo- and heterodimers containing the mutant IL-17F protein.[7] An AR deficiency of the IL-17R adaptor molecule ACT1 was later identified in two siblings with CMCD.[8] The patients' fibroblasts failed to respond to IL-17A and IL-17F, and their T cells did not respond to IL-17E.[8] The most frequent genetic etiology of CMCD identified to date is caused by heterozygous gain-of-function mutations of the gene encoding the STAT1 transcription factor, which impair the development of IL-17-producing T cells.[9-22] Abnormally strong STAT1-dependent cellular responses to the IL-17 inhibitors IFN-α/β, IFN-γ, and IL-27, and/or to the STAT3-dependent IL-17 inducers IL-6, IL-21, and IL-23 may account for the poor development of IL-17-producing T cells observed in patients bearing such mutations.[9]

IL-17 and other infections

Staphyloccocus aureus skin infections have been reported in patients with AR IL-17RA or ACT1 deficiency[7,8] (Table 1). Indeed, the only patient with IL-17RA deficiency reported to date displayed *S. aureus* dermatitis at five months of age.[7] The two siblings with ACT1 deficiency suffered from recurrent blepharitis due to *S. aureus*. However, the phenotype of IL-17F-deficient patients is restricted to CMC with no other infectious disease, and these patients present no *S. aureus* skin disease, in particular. The *S. aureus* skin infections observed in IL-17RA- or ACT1-deficient patients may therefore be due to impaired IL-17A signaling and/or to other IL-17RA- and ACT-1-dependent cytokines (e.g. IL-17E). Similarly, mice deficient for IL-17RA[2,70-72] and IL-17A[73] have been shown to be susceptible to cutaneous staphylococcal diseases, but mice lacking IL-17RC, ACT1, or IL-17F have not yet been tested.[39] Mice lacking IL-17RA or IL-17A have also been shown to be susceptible to Gram-positive bacteria,[74,65] Gram-negative bacteria[76-78], viruses[79] and parasites[80] injected intravenously or into joints. These findings suggest that IL-17 immunity may play non-redundant roles in host defense against these pathogens in mice, in these infection conditions.[2] By contrast, human IL-17 immunity is essential for host defense against mucocutaneous infections with *C. albicans* but appears to

be otherwise largely redundant against most other common pathogens *in natura*, as patients with inborn errors of IL-17 immunity display a narrow spectrum of pathogen susceptibility.[2,7,8] Only patients with AD STAT1 gain-of-function (GOF) mutations display a broader infectious phenotype, with susceptibility to other fungal, bacterial and/or viral diseases reported in some cases.[9-22,81] Indeed, some patients present fungal infections, such as severe dermatophytosis,[12] disseminated histoplasmosis,[82] or invasive coccidioidomycosis.[82] Severe skin infections and unusual viral infections have also been reported: recurrent herpes virus infection,[13,16,19,21,81] cytomegalovirus (CMV) infections,[12,13,20,83] varicella zoster virus (VZV) infection,[16,21,81] Epstein–Barr virus (EBV) infection,[11,20,83] respiratory syncytial virus (RSV) bronchiolitis,[81,84] chicken pox,[11,20] and influenza infections.[19,83] Bacterial infections, mostly caused by *S. aureus*, have also frequently been reported.[21,81]

CMC in humans following anti-17A treatment

"Naturally" occurring antibodies (Abs) against IL-17 cytokines may be present in patients with APS-I,[66] who suffer from CMC with no marked susceptibility to other pathogens.[66] Indeed, high titers of neutralizing auto-Abs against IL-17A, IL-17F, and/or IL-22 have been detected in the serum of APS-1 patients.[65,66,85] By contrast to the role of impaired IL-17A production in susceptibility to mucocutaneous candidiasis, IL-17 overproduction has been implicated in the pathogenesis of several immune-mediated inflammatory diseases in humans in which this cytokine has been found in the skin and/or joints of patients. These diseases include psoriasis, rheumatoid arthritis (RA), psoriatic arthritis (PsA),[86-89] and uveitis.[90] In some RA cohorts, higher IL-17A concentrations have been associated with a more severe clinical course.[91-95] Several blockers of IL-17A, including the monoclonal anti-IL-17A Abs secukinumab and ixekizumab, and the monoclonal anti-IL-17RA Ab brodalumab, have been evaluated in phase II clinical trials[91] and phase III studies.[96] Secukinumab is a fully human immunoglobulin (Ig)-G1-κ monoclonal Ab that neutralizes IL-17A and has been used to treat patients with psoriasis,[97,98] RA,[91,98] or uveitis.[99] Ixekizumab is a humanized IgG4 anti-IL-17A monoclonal Ab[91,97] used to treat RA.[91] Brodalumab is a fully human IgG2 anti-IL-17RA monoclonal Ab[100] that has not been demonstrated to have meaningful clinical efficacy for the treatment of RA[91]. The three randomized, double-blind, multicenter pivotal trials of secukinumab for the treatment of psoriasis collectively included 3,367 patients with moderate to severe chronic plaque psoriasis. *Candida* infections occurred in 4.7% of the patients on 300 mg secukinumab, 2.3% of those on 150 mg, and 1.2% of the etanercept (tumor necrosis factor, TNF) group.[101] All cases of candidiasis in the group of patients treated with secukinumab were mild or moderate and easily treated[97]. No other serious infections were reported.[91,102] Treatment with recombinant IL-17 cytokines may be considered in patients with *STAT1* GOF mutations or IL-17F deficiency, but not in patients with complete IL-17RA or ACT1 deficiency. However, preliminary tests should be performed to decrease the risk of the patient developing autoimmune diseases.[8,103,104] Conversely, the use of anti-IL-17 Abs to treat patients with autoimmunity must be monitored carefully to prevent CMC.[98,105]

Conclusion

Loss-of-function mutations of *IL17RA*[7], *ACT1*[8] and *IL17F*[7], and gain-of-function mutations of *STAT1*[6,32-43,106] are the four genetic etiologies of CMCD described to date. Patients with these PIDs display recurrent or persistent oral candidiasis, with or without skin and/or nail involvement, from early infancy onwards. As in patients with APS-1 and high levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22, *Candida* infection was reported in patients with psoriasis treated with anti-IL17A Abs. Careful monitoring for candidiasis is thus essential during anti-IL-17 treatment.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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