IL-17 and infections

Y. Ling\textsuperscript{a,b} and A. Puel\textsuperscript{a,b,c,*}

\textsuperscript{a}Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM 1163, Paris, France
\textsuperscript{b}Imagine Institute, University Paris Descartes, Paris, France
\textsuperscript{c}St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, the Rockefeller University, New York, NY, USA

Abstract

IL-17 immunity has been shown to be essential for mucocutaneous protection against \textit{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 \textit{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. \textit{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.

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*Corresponding author.
E-mail address: anne.puel@inserm.fr (A. Puel).

PALABRAS CLAVE

IL-17; Inmunodeficiencias primarias; Candidiasedis 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 \textit{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 \textit{C. albicans}, con o sin otros signos clínicos. Muchos pacientes con síndrome de hiper IgE autosómico dominante (AD-HIES) debido a
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 poliendocrinocrino autoinmune tipo 1 recesivo autoinmune (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.

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Introduction

In both mice and humans, the IL-17 family of cytokines contains six members: IL-17A through IL-17F. The receptors for these cytokines belong to the IL-17R family, which has five members: IL-17RA through IL-17RE. 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. 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 and Listeria monocytogenes. In recent years, patients with impaired or abolished IL-17 immunity have been shown to be susceptible to chronic mucocutaneous candidiasis (CMC). 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, IL17RA, and ACT1, and gain-of-function mutations of STAT1 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. IL-17A/F and IL-17C/F chains. 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 and humans. Indeed, fibroblasts from IL17RA or IL17RC 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. 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.

IL-17RA-deficient patients do not respond to IL-25/IL-17E. By contrast, IL-17RC has not been shown to be part of any other receptor in mice, at least not one required for IL-25/IL-17E signaling. ACT1 is an adaptor protein acting downstream from IL-17RA, IL-17RC and IL-17RB, in mice and humans. Mouse embryonic fibroblasts lacking ACT1 display low levels of KC/CXCL1 and IL-6 expression in response to stimulation with IL-17A and IL-17F. 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. Human patients with AR ACT1 deficiency and CMC have recently been described. The fibroblasts of these patients did not respond to IL-17A and IL-17F, and their T cells did not respond to IL-17E.

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. However, a number of knockout mouse models and mice into which neutralizing antibodies have been injected have been tested for oropharyngeal candidiasis (OPC). Mice lacking IL17A or IL-17E have been shown to be susceptible to OPC. 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-IL17F Abs alone seem to be less susceptible to OPC than mice treated with a combination of these two antibodies, with anti-IL17A antibodies being slightly more efficient than anti-IL17F. Mice lacking IL17RA, IL-17RC or ACT1 have much larger fungal loads in the oral cavity during
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. 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. However, mice lacking IL23p19, one of the two subunits of IL-23, essential for Th17 cell expansion and function in mice and humans, displayed impaired IL-17A production and were highly susceptible to OPC.

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,50,51 as patients with these PIDs were found to have impaired IL-17 immunity. Indeed, most patients with autosomal dominant (AD) hyper-IgE syndrome (AD-HIES) and STAT3 deficiency,51,52 some patients with invasive fungal infections and autosomal recessive (AR) ACT1 deficiency,53,54 with a complete loss-of-function (null) and IL-17RA deficiency,55,56 display CMC and have low proportions of IL-17A-producing T cells. Most patients with AD autoimmune polyendocrine syndrome type 1 (APS-1) and AIRE deficiency display CMC and have high levels of neutralizing autoreactivities against IL-17A, IL-17F and/or IL-22.55,63,64 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. 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. Four genetic etiologies of CMCD have been described to date (Table 1). AR IL-17RA and AD IL-17F deficiences were the first two genetic etiologies of CMCD to be discovered. IL-17RA deficiency was complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers, and to IL-17E (IL-25). 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. An AR deficiency of the IL-17R adaptor molecule ACT1 was later identified in two siblings with CMCD. The patients’ fibroblasts failed to respond to IL-17A and IL-17F, and their T cells did not respond to IL-17E. 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. 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.

IL-17 and other infections

Staphylococcus aureus skin infections have been reported in patients with AR IL-17RA or ACT1 deficiency. Indeed, the only patient with IL-17RA deficiency reported to date displayed S. aureus dermatitis at five months of age. 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-17A- and ACT1-dependent cytokines (e.g. IL-17E). Similarly, mice deficient for IL-17RA or IL-17A have also been shown to be susceptible to cutaneous staphylococcal diseases, but mice lacking IL-17RC, ACT1, or IL-17F have not yet been tested. Mice lacking IL-17RA or IL-17A have also been shown to be susceptible to Gram-positive bacteria, Gram-negative bacteria, viruses, and parasites 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. By contrast, human IL-17 immunity is essential for host defense against mucocutaneous infections with C. albicans but appears to

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Allele</th>
<th>Cytokines</th>
<th>Disease phenotype/ infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IL-17A/F</td>
<td>IL-17E</td>
</tr>
<tr>
<td>IL17F</td>
<td>AD</td>
<td>Partial loss-of-function</td>
<td>Impaired</td>
<td>Normal?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(hypomorphomic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL17RA</td>
<td>AR</td>
<td>Complete loss-of-function</td>
<td>Abolished</td>
<td>Abolished</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(null)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT1</td>
<td>AR</td>
<td>Complete loss-of-function</td>
<td>Abolished</td>
<td>Abolished</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(null)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAT1</td>
<td>AD</td>
<td>Gain-of-function</td>
<td>Normal?</td>
<td>Normal?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(hypermorphic)</td>
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</tr>
</tbody>
</table>

AD: autosomal dominant; AR: autosomal recessive; CMC: chronic mucocutaneous candidiasis.
be otherwise largely redundant against most other common pathogens \textit{in natura}, as patients with inborn errors of IL-17 immunity display a narrow spectrum of pathogen susceptibility.\textsuperscript{2,4,6} 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.\textsuperscript{9-22,81} Indeed, some patients present fungal infections, such as severe dermatophytosis,\textsuperscript{12} disseminated histoplasmosis,\textsuperscript{82} or invasive coccidioidomycosis.\textsuperscript{83} Severe skin infections and unusual viral infections have also been reported: recurrent herpes virus infection,\textsuperscript{13,16,19,21,81} cytomegalovirus (CMV) infections,\textsuperscript{12,13,20,83} varicella zoster virus (VZV) infection,\textsuperscript{16,21,81} Epstein-Barr virus (EBV) infection,\textsuperscript{11,20,8} respiratory syncytial virus (RSV) bronchiolitis,\textsuperscript{81,84} chicken pox,\textsuperscript{11,20} and influenza infections.\textsuperscript{19,82} Bacterial infections, mostly caused by \textit{S. aureus}, have also frequently been reported.\textsuperscript{21,81}

**CMC in humans following anti-17A treatment**

“Naturally” occurring antibodies (Abs) against IL-17 cytokines may be present in patients with APS-1,\textsuperscript{66} who suffer from CMC with no marked susceptibility to other pathogens.\textsuperscript{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.\textsuperscript{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),\textsuperscript{86,89} and uveitis.\textsuperscript{90} In some RA cohorts, higher IL-17A concentrations have been associated with a more severe clinical course.\textsuperscript{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\textsuperscript{96} and phase III studies.\textsuperscript{97} Secukinumab is a fully human immunoglobulin (Ig)-G1-κ monoclonal Ab that neutralizes IL-17A and has been used to treat patients with psoriasis,\textsuperscript{97,98} RA,\textsuperscript{97,98} or uveitis.\textsuperscript{99} Ixekizumab is a humanized IgG4 anti-IL-17A monoclonal Ab\textsuperscript{100} used to treat RA.\textsuperscript{101} Brodalumab is a fully human IgG2 anti-IL-17RA monoclonal Ab\textsuperscript{100} that has not been demonstrated to have meaningful clinical efficacy for the treatment of RA.\textsuperscript{101} 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. \textit{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.\textsuperscript{102} All cases of candidiasis in the group of patients treated with secukinumab were mild or moderate and easily treated\textsuperscript{97}. No other serious infections were reported.\textsuperscript{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.\textsuperscript{8,103,104} Conversely, the use of anti-IL-17 Abs to treat patients with autoimmunity must be monitored carefully to prevent CMC.\textsuperscript{96,105}

**Conclusion**

Loss-of-function mutations of \textit{IL17RA}\textsuperscript{7}, \textit{ACT1}\textsuperscript{10} and \textit{IL17F}\textsuperscript{7}, and gain-of-function mutations of \textit{STAT1}\textsuperscript{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, \textit{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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