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REVIEW

# Human inborn errors of immunity underlying superficial or invasive candidiasis

**Anne Puel**[1,2,3]

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## Abstract

*Candida* species, including *C. albicans* in particular, can cause superficial or invasive disease, often in patients with known acquired immunodeficiencies or iatrogenic conditions. The molecular and cellular basis of these infections in patients with such risk factors remained largely elusive, until the study of inborn errors of immunity clarified the basis of the corresponding inherited and "idiopathic" infections. Superficial candidiasis, also known as chronic mucocutaneous candidiasis (CMC), can be caused by inborn errors of IL-17 immunity. Invasive candidiasis can be caused by inborn errors of CARD9 immunity. In this chapter, we review both groups of inborn errors of immunity, and discuss the contribution of these studies to the deciphering of the critical mechanisms of anti-*Candida* immunity in patients with other conditions.

## Introduction

The genus *Candida,* which contains about 200 different species, belongs to the phylum Ascomycota. *Candida* spp. are the most common cause of fungal infection in humans (Kullberg and Arendrup 2016; Pfaller and Diekema 2007), but only a few species (approximately 20) can cause disease. *Candida albicans, C. glabrata*, *C. tropicalis, C. parapsilosis,* and *C. krusei* account for about 90% of these diseases, and their prevalence depends on the geographic location, patient populations, and clinical settings (Turner and Butler 2014). *C. albicans* remains the major cause of invasive candidiasis, but *C. glabrata* (in northern Europe, USA, Canada) and *C. parapsilosis* (in southern Europe, Asia, Latin America) have emerged as important or even major pathogens (Horn et al. 2009; Pfaller et al. 2019; Klingspor et al. 2015; Leroy et al. 2009). *Candida* spp. have been reported to be the fourth most common nosocomial pathogen in the bloodstream, or at least within the top ten of such pathogens (Kullberg and Arendrup 2016; Wisplinghoff et al. 2004). These *Candida* spp. are resident commensal yeasts in the oro-gastrointestinal and genitourinary tracts in healthy individuals. However, they can also act as pathogens in humans, causing superficial infections of the skin, scalp, nails, or oral and genital mucosae, or invasive, often life-threatening, systemic infections (candidemia) that may be disseminated to internal organs (leading to meningoencephalitis, brain abscesses, endophthalmitis, endocarditis, peritonitis, osteomyelitis, intra-abdominal abscesses, lung infections, etc.) (Kim and Sudbery 2011; Eggimann et al. 2011; Pappas et al. 2018). The infections they cause are a serious public health problem, with mortality often exceeding 40% (partly due to late diagnosis, the late initiation of antifungal therapies, and the emergence of resistance to antifungal drugs), and substantial costs associated with patient care and long hospital stays (Pappas et al. 2018; Chakrabarti and Singh 2011; Lass-Florl 2009; Casadevall 2019; Jeffery-Smith et al. 2018; Cheng et al. 2005; Almirante et al. 2005; Gudlaugsson et al. 2003).

Various risk factors, iatrogenic or acquired, are known, such as HIV infection, mainly associated with oro-pharyngeal candidiasis (de Repentigny et al. 2004). Invasive candidiasis is mostly associated with organ transplantation, hemodialysis, parenteral nutrition, intravenous catheters, abdominal surgery, extensive burns, long-term stay in intensive care units, or the administration of broad-spectrum antibiotics or of immunosuppressive agents such as chemotherapy (Kullberg and Arendrup 2016; Ortega et al. 2011). In this context, invasive candidiasis is an increasing

✉ Anne Puel
anne.puel@inserm.fr

[1] Laboratory of Human Genetics of Infectious Diseases, INSERM U1163, Necker Hospital for Sick Children, Necker Branch, 75015 Paris, France

[2] Imagine Institute, Paris University, 75015 Paris, France

[3] St. Giles Laboratory of Human Genetics of Infectious Diseases, The Rockefeller University, Rockefeller Branch, New York, NY 10065, USA

problem in elderly patients, with significantly higher mortality rates as compared to younger patients (Barchiesi et al. 2017; Wang et al. 2014a). Neonates are also at risk of invasive forms of candidiasis, such as the central nervous system (CNS) candidiasis reported in low-birth weight or preterm neonates (Barton et al. 2014; Fernandez et al. 2000; Huang et al. 1998; Pahud et al. 2009). These fungal diseases frequently strike individuals with many risk factors. As a result, their pathogenesis remains poorly understood at the molecular and cellular levels. The study of primary immunodeficiencies (PID) with "syndromic" candidiasis, whether superficial or invasive, and, more recently, that of inborn errors of immunity in otherwise healthy patients with "isolated" candidiasis, whether superficial or invasive, has progressively shed light on the mechanisms conferring protective immunity to *Candida* spp. (Drummond and Lionakis 2018; Li et al. 2017; Pilmis et al. 2016; Lanternier et al. 2013a; Antachopoulos et al. 2007; Corvilain et al. 2018; Okada et al. 2016; Puel et al. 2010a, 2012; Drummond et al. 2018). The elucidation of the pathogenesis of these fungal diseases in patients with inherited immunodeficiencies (ID) has important clinical implications for the patients and their families, with the possibility of genetic diagnoses and counseling, but should also facilitate the development of novel prophylactic or curative treatments with a rational basis, for PID patients and patients with other more common conditions (e.g. acquired ID). Research into the genetic basis of *Candida* diseases is important, given the high mortality associated with *Candida* diseases, despite the availability of antifungal drugs, and the increasing frequency of antifungal drug-resistant strains (Perfect 2017).

## Chronic mucocutaneous candidiasis and inborn errors of IL-17 immunity

Mucocutaneous candidiasis is characterized by *Candida spp.* infections of the nails, skin, scalp, and/or oral and genital mucosae (Puel et al. 2010a; Glocker and Grimbacher 2010; Vazquez and Sobel 2002; Eyerich et al. 2008; Kirkpatrick 2001; Lilic 2002; Eyerich et al. 2010). Mucosal candidiasis, such as oral thrush, is relatively frequent in individuals on steroid or antibiotic treatments. Up to 75% of women present at least one episode of vulvovaginal candidiasis during their lifetime, and recurrent (> 1 episode) vulvovaginal candidiasis has been estimated to have a global annual prevalence of 3871 per 100,000 women (Denning et al. 2018). Chronic mucocutaneous candidiasis (CMC) is characterized by severe, persistent or recurrent (relapse upon discontinuation of treatment) disease (Eyerich et al. 2010). CMC, present as severe oropharyngeal candidiasis, is very common in AIDS patients (de Repentigny et al. 2004; Pirofski and Casadevall 2009). Similarly, in the context of PID, CMC is frequent in patients with broad T-cell defects, such as combined or severe combined immunodeficiencies (CID or SCID, respectively) (Lanternier et al. 2013a; Antachopoulos et al. 2007; Vinh 2011; Picard et al. 2018; Tangye et al. 2020). This inherited form of CMC, usually referred to as CMC disease (CMCD), is rare, affecting approximately 1 in every 50,000 individuals. The CMC in affected patients is syndromic, as it is associated with many other clinical manifestations, mostly infectious and/or autoimmune. Syndromic CMC is also common in some PIDs without major global apparent T-cell deficiencies, albeit with milder clinical features. These PIDs include autosomal dominant (AD) STAT1 gain-of-function (GOF), a complex and heterogeneous PID in which CMC is one of the first features observed and is common to most patients, and often severe (Okada et al. 2016; Puel et al. 2012; Olbrich and Freeman 2018; Depner et al. 2016; Toubiana et al. 2016; Boisson-Dupuis et al. 2012; Engelhardt and Grimbacher 2012; Liu et al. 2011). It is frequently associated with other infectious diseases, typically mucocutaneous bacterial, viral, or fungal diseases, and less frequently with invasive infectious diseases, autoimmune manifestations, and oro-esophageal squamous cell carcinoma (Li et al. 2017; Lanternier et al. 2013a; Puel et al. 2010a, 2012; Eyerich et al. 2010; Depner et al. 2016; Toubiana et al. 2016; Boisson-Dupuis et al. 2012; Liu et al. 2011; van de Veerdonk et al. 2011). Another such PID is hyper-IgE syndrome (HIES), another complex PID characterized by severe skin and pulmonary staphylococcal disease, severe eczema, high serum IgE levels, and some developmental abnormalities (Olbrich and Freeman 2018; Zhang et al. 2018). It may be AD due to heterozygous-dominant negative mutations of the gene encoding the transcription factor STAT3 (Paulson et al. 2008; Minegishi 2009; Minegishi et al. 2007; Holland et al. 2007), or autosomal recessive (AR) due to bi-allelic loss-of-function (LOF) mutations of the gene encoding another transcription factor, Zinc Finger Protein (ZNF)341 (Frey-Jakobs et al. 2018; Beziat et al. 2018). About 80% of patients develop oral thrush, onychomycosis, and/or vaginal candidiasis. CMC is also frequent and the only infectious disease common to most patients with AR autoimmune polyendocrine syndrome type 1 (APS-1, also called APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy). This syndrome is characterized by multi-organ autoimmunity due to bi-allelic mutations of the gene encoding the transcription factor *AIRE* (Husebye et al. 2009; Constantine and Lionakis 2019; Ferre et al. 2016). Other PIDs in which CMC is milder or less frequent (25–35%) include AR RORγ/γT deficiency, characterized by disseminated BCG diseases (Okada et al. 2015), AR IL-12p40 and IL-12Rβ1 deficiencies, characterized by a selective predisposition to mycobacterial and *Salmonella* diseases (Rosain et al. 2019; Bustamante et al. 2014; Ouederni et al. 2014), and AR CARD9 deficiency, generally characterized by invasive

fungal diseases (Corvilain et al. 2018; Glocker et al. 2009; Lanternier et al. 2013b; Alves de-Medeiros et al. 2016). A final group of patients displays early CMCD in an otherwise healthy context, with the exception of mucocutaneous staphylococcal disease in some patients. This condition is often referred to as isolated CMCD (see below).

Investigations of the molecular and cellular bases of PID with syndromic CMCD suggested that IL-17A/F-mediated immunity might protect against mucocutaneous candidiasis and that CMCD might result from inborn errors of IL-17A/F immunity (Puel et al. 2010a, 2012; Kisand et al. 2011; Korn et al. 2009; Miossec et al. 2009). Indeed, all of them are characterized by impaired IL-17A/F immunity, due to abnormally low levels of circulating IL-17A/F-producing T (Th17) cells, or to the presence of autoantibodies directed against IL-17 cytokines. Indeed, patients with AD STAT1 GOF have very low proportions of Th17 cells, both ex vivo or and after differentiation in vitro (Toubiana et al. 2016; Liu et al. 2011; van de Veerdonk et al. 2011; Hiller et al. 2018; Zhang et al. 2017; Ma et al. 2016). This Th17 cell deficiency may result from enhanced/overt STAT1 signaling downstream from the STAT3-dependent IL-6, IL-21, and IL-23 cytokines, which is critical for the development and maintenance of Th17 cells (Korn et al. 2009; Miossec et al. 2009; Louten et al. 2009), enhanced STAT1 signaling downstream from IFN-α/β, IFN-γ, and IL-27, which has been shown to inhibit the development of Th17 cells via STAT1 (Guo et al. 2008; Diveu et al. 2009; El-behi et al. 2009), or both these mechanisms (Liu et al. 2011; Hirahara et al. 2010). Patients with AD HIES also have very low proportions of ex vivo and in vitro differentiated Th17 cells (Minegishi et al. 2009; Milner et al. 2008; Ma et al. 2008; de Beaucoudrey et al. 2008), due to an impairment of STAT3-dependent signaling downstream from IL-6R, IL-21R, and IL-23R (Korn et al. 2009). Similarly, patients with AR HIES and ZNF341 deficiency also have abnormally low proportions of ex vivo and in vitro differentiated Th17 cells, due to the disruption of ZNF341-dependent STAT3 transcription and activity (Zhang et al. 2018; Frey-Jakobs et al. 2018; Beziat et al. 2018). As expected, patients with AR deficiencies of RORγ/γT, a master transcription factor of Th17 cells (Manel et al. 2008; Ivanov et al. 2006; Yang et al. 2008a; Zhu et al. 2010), also have barely detectable levels of Th17 cells (Okada et al. 2015), and patients with IL-12p40 and IL-12Rβ1 deficiencies, in whom the production of and response to IL-23 and IL-12 are abolished, also have low levels of circulating Th17 cells (Ma et al. 2016; de Beaucoudrey et al. 2008). Most, but not all of the tested patients with deficiencies of CARD9, an adaptor transducing signals downstream from C-type lectin receptors following the recognition of fungal cell wall components, have low circulating levels of Th17 cells, probably due an impairment of the induction of pro-Th17 cytokines (e.g. IL-6, IL-23) by phagocytes after activation by fungal ligands (Corvilain et al. 2018; Glocker et al. 2009; Lanternier et al. 2013b; Wang et al. 2014b) (Fig. 1). Finally, APS1 patients, who suffer from multiple autoimmune endocrinopathies due to LOF mutations of the gene encoding AIRE, a transcription factor involved in the removal of self-reactive T cells (Finnish-German AC 1997; Nagamine et al. 1997), frequently harbor high levels of antibodies against various self-antigens (Meyer et al. 2016), including neutralizing autoantibodies directed not only against cytokines such as IFN-α and IFN-ω (Ferre et al. 2016; Meager et al. 2006) in particular, but also against Th17 cytokines, such as IL-17A, IL-17F, and IL-22 (Kisand et al. 2010, 2011; Puel et al. 2010b). These studies have paved the way for the identification of inborn errors of IL-17-mediated immunity conferring CMC in otherwise healthy individuals, or in individuals with mucocutaneous *Staphylococcus aureus* infections (Okada et al. 2016; Puel et al. 2010a, 2012).

A candidate approach identified AD IL-17F and AR IL-17RA deficiencies, each in a single family, in 2011, as the first genetic etiologies of isolated CMCD (Li et al. 2017; Puel et al. 2011). Indeed, a heterozygous private missense variation of *IL17F,* predicted to be deleterious, was identified in five relatives from an Argentinian multiplex family with early-onset CMC. The index patient had also had recurrent upper respiratory tract infections, asthma, and recurrent episodes of furunculosis since infancy. In these patients, the proportions of ex vivo IL-17A- and IL-22-producing T cells were within the control ranges, but IL-17F levels were not evaluated. The mutation was shown to impair the binding of IL-17F to its receptor, which consists of IL-17RA/IL-17RC, on the surface of control fibroblasts. Studies with control fibroblasts and keratinocytes revealed an impairment not only of the responses to mutant IL-17F homodimers, but also of that to heterodimers containing the mutant protein (IL-17A/mutant IL-17F, wild type IL-17F/mutant IL-17F), showing that the mutant IL-17F was hypomorphic and exerted a dominant-negative effect on IL-17A- or wild-type IL-17F-mediated responses (Puel et al. 2011). A second family of Tunisian-German origin has since been reported, in which a woman and her son carrying a heterozygous mutation of *IL17F* both presented CMC with an onset in early childhood, with no other infectious phenotype; the causal effect of the variant in this family has yet to be characterized (Bader et al. 2012). In parallel, AR complete IL-17RA was reported in a patient born to consanguineous Moroccan parents (Puel et al. 2011). This patient suffered from early-onset CMC and cutaneous *S. aureus* infection, and was homozygous for a nonsense mutation affecting the extracellular part of IL-17RA. Additional homozygous nonsense, missense, frameshift, splice site, and large deletion mutations have since been found in a total of 23 patients with AR IL-17RA deficiency, from 13 unrelated kindreds

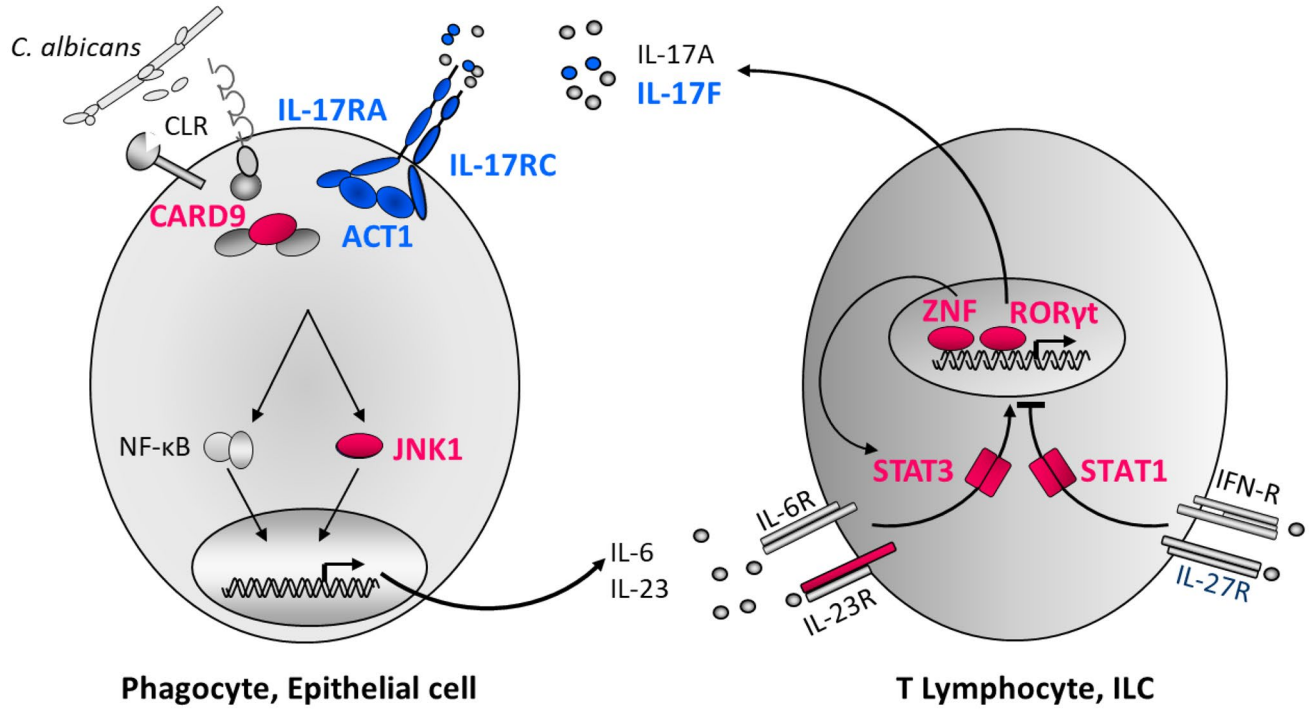


**Fig. 1** Inborn errors of IL-17 immunity in patients with isolated or syndromic CMCD. Schematic representation of IL-17A/F immunity and cooperation between cells recognizing *C. albicans* and responding to IL-17A/F (phagocytes and epithelial cells), and cells producing IL-17A/F (T and innate lymphocytes). Human IL-17A/F immunity is crucial for protective mucocutaneous immunity against *C. albicans*. Proteins for which mutations in the corresponding genes underlie CMCD are shown in blue or red. Monoallelic LOF mutations of *IL17F* and of *MAPK8* (encoding JNK1), and bi-allelic LOF mutations of *IL17RA*, *IL17RC* and *ACT1* impair IL-17A/F responses. Bi-allelic LOF mutations of *IL12RB1*, *RORC* (encoding RORγ/RORγT), *ZNF341*, monoallelic LOF mutations of *STAT3* and monoallelic GOF mutations of *STAT1* impair IL-17A/F production. Mutations of *IL17F*, *IL17RA*, *IL17RC* and *ACT1* underlie isolated CMCD (blue), whereas mutations of *CARD9*, *MAPK8*, *IL12RB1*, *STAT1*, *STAT3*, *ZNF341* and *RORC* underlie syndromic CMCD (in red)

originating from Morocco, Turkey, Japan, Saudi Arabia, Algeria, Argentina, and Sri Lanka (Li et al. 2017; Fellmann et al. 2016; Levy et al. 2016). All patients displayed early-onset CMC. About 70% of these patients also presented staphylococcal skin diseases, and 40% developed recurrent bacterial infections of the respiratory tract (Li et al. 2017; Puel et al. 2011; Fellmann et al. 2016; Levy et al. 2016). AR complete IL-17RC deficiency was subsequently identified by whole-exome sequencing in three unrelated patients with early-onset CMC in the absence of any other infectious phenotype, including staphylococcal disease in particular; these patients were born to consanguineous families originating from Turkey and Argentina (Ling et al. 2015). AR ACT1 deficiency is the fourth genetic defect responsible for isolated CMCD. It was identified in two siblings, born to consanguineous Algerian parents, with early-onset CMC and recurrent skin and scalp *S. aureus* disease (Boisson et al. 2013). Both patients were found to carry a homozygous missense mutation of *TRAF3IP2* encoding ACT1, which is a key downstream adapter in the IL-17 response pathway (Qian et al. 2007; Chang et al. 2006; Linden 2007). The fibroblasts of all IL-17RA-, IL-17RC-, and ACT1-deficient patients failed to respond to IL-17A and IL-17F homodimers and heterodimers (Puel et al. 2011; Fellmann et al. 2016; Levy et al. 2016; Ling et al. 2015; Boisson et al. 2013). In addition, IL-17RA-and ACT1-deficient PBMCs, unlike PBMCs from patients with AR IL-17RC deficiency, failed to respond to IL17E/IL-25 (Levy et al. 2016; Boisson et al. 2013), which signals through IL-17RA/IL-17RB in an ACT1-dependent manner (Gaffen 2009). An AD deficiency of JNK1, a component of the MAPK signaling pathway (Johnson and Nakamura 2007; Hotamisligil and Davis 2016), was recently identified in a multiplex family originating from France with syndromic CMCD, in which three individuals from three generations presented early-onset CMC, mucocutaneous *S. aureus* infections, and a complex connective tissue disorder (Li et al. 2019). In vitro studies showed that the private *MAPK8* c.311+1G>A identified in the three patients was a loss-of-expression variant. JNK1 is involved in various signaling pathways, including the IL-17 pathway in particular (Van der Velden et al. 2012; Chang and Dong 2011; Gaffen et al. 2014). Accordingly, the fibroblasts of heterozygous patients displayed impaired cellular responses to IL-17A and IL-17F. JNK1 also acts

downstream from TGFβ1, which has been shown to participate in human Th17 differentiation in vitro (Manel et al. 2008; Volpe et al. 2008; Yang et al. 2008b). The proportions of ex vivo and in vitro differentiated Th17 cells were indeed low for these patients. This study reported a fifth genetic disorder in the IL-17 response pathway, underlying AD CMCD by haploinsufficiency, with impaired cellular responses to IL-17A/F and impaired IL-17A/F production (Fig. 1). Altogether, these five human genetic disorders demonstrate the essential role of IL-17A- and IL-17F-mediated immunity in mucocutaneous protection against *Candida* and, to a lesser extent, as found in IL-17RA-, ACT1- and JNK1-deficient patients, against disease caused by *S. aureus*. They also suggest that IL-17A- and IL-17F-dependent immunity is otherwise redundant for protection against fungi other than *Candida*, bacteria other than *S. aureus*, viruses, or even against invasive candidiasis or staphylococcal disease.

## Invasive candidiasis and inborn errors of CARD9 immunity

Invasive candidiasis (IC) is defined as infections of the bloodstream (candidemia) or as deep-seated infections caused by *Candida* spp. and it ranks among the most frequent healthcare-associated bloodstream infections (Kullberg and Arendrup 2016; McCarty and Pappas 2016). Unlike CMC, patients with broad T-cell disorders are not particularly prone to IC. Furthermore, very few patients with CMC display IC, and vice versa. This suggests that T-cell dependent immunity is not essential for protection against IC and that different mechanisms are involved in immunity to superficial and invasive candidiasis. In IC, phagocytes, neutrophils in particular, but probably also, to a lesser extent, based on mouse studies, monocytes, macrophages and dendritic cells, are essential for protective immunity (Pappas et al. 2018). Indeed, IC is classically described in patients with acquired profound qualitative or quantitative disorders of neutrophils and monocytes/macrophages (Wisplinghoff et al. 2004). IC is relatively rare among patients with PID, and has been reported only occasionally in this context. Patients with severe congenital neutropenia (SCN), and mutations of *ELA2*, *HAX1*, or other genes, may develop syndromic IC. For example, IC was reported in 2% ($n=486$) of the patients from the French SCN registry (Lanternier et al. 2013a). A few patients with AR leukocyte adhesion disorder type-1 (LAD-1), due to CD18 deficiency resulting from bi-allelic mutations of *ITGB2* and leading to the impaired endothelial adhesion and transmigration of neutrophils into infected tissues, may display IC (Kuijpers et al. 2007; Fischer et al. 1988; Mellouli et al. 2010). In both cases, IC probably results from impaired neutrophil accumulation at the site of infection. Some patients with complete AR myeloperoxidase (MPO) deficiency and concomitant diabetes, or with X-linked or AR chronic granulomatous disease (CGD) caused by mutations of genes encoding NADPH oxidase subunits and impaired oxidative burst-dependent *Candida* killing by phagocytes, may also display syndromic IC (Winkelstein et al. 2000; Lehrer and Cline 1969). Cases of deep-seated organ candidiasis have been reported in CGD patients, with central nervous system (CNS), soft tissue, lymph node, or liver diseases, and enhanced susceptibility to *C. lusitaniae*, a *Candida* spp. rarely disease-causing in non-CGD patients (Estrada et al. 2006; Levy et al. 2002; Segal et al. 2000). Finally, in a large international study of patients with STAT1 GOF ($n=274$), 3.6% were reported to have syndromic IC (Toubiana et al. 2016).

Since its discovery in 2009, in a large multiplex consanguineous family from Iran with CMC and possible brain disease caused by *Candida* spp. (Glocker et al. 2009), AR CARD9 (C-type lectin receptor adaptor caspase recruitment domain-containing protein 9) deficiency has emerged as the only known inborn error of immunity conferring a selective susceptibility to fungal diseases in otherwise healthy individuals, with no other infectious or noninfectious manifestations (Corvilain et al. 2018; Drummond et al. 2018; Drummond and Lionakis 2016). Over 70% of patients with CARD9 deficiency have developed IC, with a strong tropism for the CNS. Indeed, about 80% of patients with probable or proven IC have CNS diseases, such as meningoencephalitis, brain abscesses, masses mimicking metastasis, or a combination of these manifestations (Corvilain et al. 2018; Glocker et al. 2009; Alves de-Medeiros et al. 2016; Drewniak et al. 2013; Gavino et al. 2014; Lanternier et al. 2015; Herbst et al. 2015; Gavino et al. 2016; Drummond et al. 2015; Celmeli et al. 2016; Cetinkaya et al. 2018). Strikingly, these patients present no concomitant diseases of the kidney, liver, or spleen, as typically seen in CARD9-expressing (but usually strongly immunosuppressed) infected patients, probably as a result of CARD9-independent mechanisms of protective immunity (Drummond et al. 2015). Gastrointestinal tract, bone, eye, intra-abdominal organ (liver and mesenteric LNs), or mucocutaneous surface involvement may also occur, as some patients have been reported to have severe colitis, osteomyelitis, endophthalmitis, intra-abdominal candidiasis, or CMC (Glocker et al. 2009; Lanternier et al. 2013b, 2015; Alves de-Medeiros et al. 2016; Gavino et al. 2016; Drummond et al. 2015; Rieber et al. 2016; Jones et al. 2016; Gavino et al. 2018). The onset of invasive disease is particularly variable, with a substantial proportion of CARD9-deficient patients presenting with IC as adults, with a mean age of 21.9 years [median age: 17.5 years; range (3.5–58.0 years)]. CARD9-deficient patients with CMC and/or IC have been identified in nine countries around the world (Algeria, Morocco, Iran, Turkey, Pakistan, Canada, Italy, El Salvador, and South Korea), and one patient was of mixed European origin. Of all

*Candida* spp., *C. albicans* is the most frequently involved in infections. It has been detected in 93% of patients, the other *Candida* spp. detected, *C. glabrata* and *C. dubliniensis,* each being found in a single patient (Corvilain et al. 2018).

CARD9, which is part of the CARD9/BCL10/MALT1 (CBM) complex, is mainly expressed in phagocytic cells, and transduces signals downstream from C-type lectin receptors (CLRs), including Dectin-1 (*CLEC7A*), Dectin-2 (*CLEC6A*), Dectin-3 (*CLEC4D*), and Mincle (*CLEC4E*), which are specific for β-glucans (Dectin-1), α-mannans (Dectin-2 and Dectin-3), and glycolipids (Mincle) from the fungal cell walls (Shiokawa et al. 2017; Perez de Diego et al. 2015). In humans, upon receptor stimulation and SYK activation, the CBM complex activates the NF-κB, MAPK, and ERK pathways, thereby stimulating the transcription of genes encoding pro-inflammatory cytokines and chemokines, such as IL-2, IL-10, IL-12, tumor necrosis factor (TNF)-α, pro-Th17 cytokines (IL-1β, IL-6, IL-23), granulocyte–macrophage colony-stimulating factor (GMCSF), and CXCL1 or CXCL2 (Roth and Ruland 2013).

CARD9-deficient patients have no overt immunological phenotype: they have normal leukocyte counts; when tested, T-cell proliferation in response to mitogen or antigens is mostly normal, and the phagocyte oxidative burst, tested in vitro in the dihydrorhodamine (DHR) assay, is also normal. However, high eosinophil counts, high serum IgE levels, or both, have been observed in several CARD9-deficient patients, and the reasons for this remain unknown (Corvilain et al. 2018). CSF samples were analyzed in some patients and revealed hyperproteinorrhachia, and hypoglycorrhachia and pleocytosis, mostly with mononuclear cells (lymphocytes and/or monocytes) and eosinophils, but, remarkably, no neutrophils (Drummond et al. 2015) [by contrast to patients with *Candida* meningitis wild-type for CARD9, for whom neutrophils generally predominate in the CSF (Drummond et al. 2015)]. IL-17-mediated immunity was evaluated in about half the CARD9-deficient patients (with candidiasis or other fungal diseases), and was impaired in two-thirds of those tested, with no clear correlation between impaired or normal IL-17 immunity and the presence or absence of CMC (Corvilain et al. 2018). PBMCs, monocytes, and in vitro monocyte-derived macrophages or DCs tested in vitro upon stimulation with heat-killed *C. albicans* displayed impaired responses in terms of pro-inflammatory cytokine or chemokine production (Corvilain et al. 2018). A selective defect of the killing of unopsonized (but not opsonized) *C. albicans* yeasts but not hyphae by neutrophils has been reported in vitro and has been suggested to contribute to *Candida* CNS disease, due to the lower levels of opsonization in the CNS (Corvilain et al. 2018; Drewniak et al. 2013). However, a lack of neutrophil recruitment to infection sites (e.g. CNS), consistent with the absence of neutrophils from the CSF fluids of CARD9-deficient patients with *Candida* CNS infections, contrasting with their blood neutrophil counts within the normal range, appears to be the major CARD9-dependent mechanism underlying IC in these patients (Drummond and Lionakis 2016, 2018; Drummond et al. 2015). Recently, based on *Card9*$^{-/-}$ mouse studies, abnormally low levels of IL-1β-dependent CXCL1 production by microglial cells following stimulation with the fungal toxin candidalysin were proposed as an explanation for the defective recruitment of neutrophils to the *Candida*-infected CNS, and impaired CNS *Candida* clearance (Drummond et al. 2015, 2019).

## Conclusion

The investigation of patients with PID and syndromic CMC or IC, or of otherwise healthy patients with CMC or IC provides us with a unique opportunity to elucidate the molecular and cellular bases of these diseases and to gain insight into the pathophysiological mechanisms underlying them. The knowledge gained in the context of PID can be applied to other settings, such as hematological malignancies or AIDS, for example. The spectrum of inborn errors underlying CMC and, to a lesser extent, IC, is expanding and has already provided important insight into the role of specific immune pathways in anti-*Candida* host defense. Indeed, IL-17-mediated immunity has emerged over the last 10 years as crucial against CMC and, to a lesser extent, mucocutaneous *S. aureus* diseases. However, it seems to be redundant against IC, invasive staphylococcal diseases, and other common microbes (including fungi and bacteria). Inherited CARD9 deficiency is a genetic etiology of CMC and IC. Remarkably, *Candida* diseases can occur at any age, from early childhood to late adulthood. The adult onset seen in several CARD9-deficient patients is an uncommon feature of inborn errors of immunity and should lead clinicians to consider CARD9 deficiency in adults presenting with unexplained *Candida* diseases. Next-generation sequencing in patients with CMC or IC without inborn errors of the IL-17 pathway or CARD9 will probably reveal new genetic defects that may further elucidate the pathogenesis of *Candida* infections in patients with inborn errors of IL-17 immunity or CARD9. The comprehensive genetic dissection of *Candida* diseases (in patients with syndromic PID or in otherwise healthy individuals) should shed new light on the molecular and cellular mechanisms conferring protective immunity to *Candida* spp., and should pave the way for more rational therapies based on a better understanding of the underlying pathophysiological mechanisms. The clinical implications extend well beyond patients with fungal diseases due to inborn errors of immunity to patients with fungal diseases due to other causes.

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## References

Almirante B, Rodriguez D, Park BJ, Cuenca-Estrella M, Planes AM, Almela M, Mensa J, Sanchez F, Ayats J, Gimenez M, Saballs P, Fridkin SK, Morgan J, Rodriguez-Tudela JL, Warnock DW, Pahissa A, Barcelona Candidemia Project Study G (2005) Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 43(4):1829–1835

Alves de-Medeiros AK, Lodewick E, Bogaert DJ, Haerynck F, Van Daele S, Lambrecht B, Bosma S, Vanderdonckt L, Lortholary O, Migaud M, Casanova JL, Puel A, Lanternier F, Lambert J, Brochez L, Dullaers M (2016) Chronic and invasive fungal infections in a family with CARD9 deficiency. J Clin Immunol 36(3):204–209

Antachopoulos C, Walsh TJ, Roilides E (2007) Fungal infections in primary immunodeficiencies. Eur J Pediatr 166(11):1099–1117

Bader O, Weig MS, Gross U, Schon MP, Mempel M, Buhl T (2012) Photo quiz. A 32-year-old man with ulcerative mucositis, skin lesions, and nail dystrophy. Chronic mucocutaneous candidiasis by multidrug-resistant Candida albicans. Clin Infect Dis 54(7):972 **(1035–1036)**

Barchiesi F, Orsetti E, Mazzanti S, Trave F, Salvi A, Nitti C, Manso E (2017) Candidemia in the elderly: what does it change? PLoS One 12(5):e0176576

Barton M, O'Brien K, Robinson JL, Davies DH, Simpson K, Asztalos E, Langley JM, Le Saux N, Sauve R, Synnes A, Tan B, de Repentigny L, Rubin E, Hui C, Kovacs L, Richardson SE (2014) Invasive candidiasis in low birth weight preterm infants: risk factors, clinical course and outcome in a prospective multicenter study of cases and their matched controls. BMC Infect Dis 14:327

Beziat V, Li J, Lin JX, Ma CS, Li P, Bousfiha A, Pellier I, Zoghi S, Baris S, Keles S, Gray P, Du N, Wang Y, Zerbib Y, Levy R, Leclercq T, About F, Lim AI, Rao G, Payne K, Pelham SJ, Avery DT, Deenick EK, Pillay B, Chou J, Guery R, Belkadi A, Guerin A, Migaud M, Rattina V, Ailal F, Benhsaien I, Bouaziz M, Habib T, Chaussabel D, Marr N, El-Benna J, Grimbacher B, Wargon O, Bustamante J, Boisson B, Muller-Fleckenstein I, Fleckenstein B, Chandesris MO, Titeux M, Fraitag S, Alyanakian MA, Leruez-Ville M, Picard C, Meyts I et al (2018) A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. Sci Immunol 3(24):eaat4956

Boisson B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M, Belkadi A, Picard C, Abel L, Fieschi C, Puel A, Li X, Casanova JL (2013) An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 39(4):676–686

Boisson-Dupuis S, Kong XF, Okada S, Cypowyj S, Puel A, Abel L, Casanova JL (2012) Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. Curr Opin Immunol 24(4):364–378

Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL (2014) Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol 26(6):454–470

Casadevall A (2019) Global catastrophic threats from the fungal kingdom: fungal catastrophic threats. Curr Top Microbiol Immunol 424:21–32

Celmeli F, Oztoprak N, Turkkahraman D, Seyman D, Mutlu E, Frede N, Koksoy S, Grimbacher B (2016) Successful granulocyte colony-stimulating factor treatment of relapsing *Candida albicans* meningoencephalitis caused by card9 deficiency. Pediatr Infect Dis J 35(4):428–431

Cetinkaya PG, Ayvaz DC, Karaatmaca B, Gocmen R, Soylemezoglu F, Bainter W, Chou J, Chatila TA, Tezcan I (2018) A young girl with severe cerebral fungal infection due to card 9 deficiency. Clin Immunol 191:21–26

Chakrabarti A, Singh R (2011) The emerging epidemiology of mould infections in developing countries. Curr Opin Infect Dis 24(6):521–526

Chang SH, Dong C (2011) Signaling of interleukin-17 family cytokines in immunity and inflammation. Cell Signal 23(7):1069–1075

Chang SH, Park H, Dong C (2006) Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. J Biol Chem 281(47):35603–35607

Cheng MF, Yang YL, Yao TJ, Lin CY, Liu JS, Tang RB, Yu KW, Fan YH, Hsieh KS, Ho M, Lo HJ (2005) Risk factors for fatal candidemia caused by *Candida albicans* and non-albicans Candida species. BMC Infect Dis 5:22

Constantine GM, Lionakis MS (2019) Lessons from primary immunodeficiencies: autoimmune regulator and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Immunol Rev 287(1):103–120

Corvilain E, Casanova JL, Puel A (2018) Inherited CARD9 deficiency: invasive disease caused by ascomycete fungi in previously healthy children and adults. J Clin Immunol 38(6):656–693

de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, von Bernuth H, Samarina A, Janniere L, Fieschi C, Stephan JL, Boileau C, Lyonnet S, Jondeau G, Cormier-Daire V, Le Merrer M, Hoarau C, Lebranchu Y, Lortholary O, Chandesris MO, Tron F, Gambineri E, Bianchi L, Rodriguez-Gallego C, Zitnik SE, Vasconcelos J, Guedes M, Vitor AB, Marodi L, Chapel H, Reid B, Roifman C, Nadal D, Reichenbach J, Caragol I, Garty BZ, Dogu F, Camcioglu Y, Gulle S, Sanal O, Fischer A, Abel L, Stockinger B, Picard C, Casanova JL (2008) Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med 205(7):1543–1550

de Repentigny L, Lewandowski D, Jolicoeur P (2004) Immunopathogenesis of oropharyngeal candidiasis in human immunodeficiency virus infection. Clin Microbiol Rev 17(4):729–759

Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R (2018) Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect Dis 18(11):e339–e347

Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Doffinger R, Gkrania-Klotsas E, Kumararatne D, Atkinson TP, Schroeder Jr HW, Niehues T, Duckers G, Stray-Pedersen A, Baumann U, Schmidt R, Franco JL, Orrego J, Ben-Shoshan M, McCusker C, Jacob CM, Carneiro-Sampaio M, Devlin LA, Edgar JD, Henderson P, Russell RK, Skytte AB, Seneviratne SL, Wanders J, Stauss H, Meyts I, Moens L, Jesenak M, Kobbe R, Borte S, Borte M, Wright DA, Hagin D, Torgerson TR, Grimbacher B (2016) The extended clinical phenotype of 26 patients with chronic mucocutaneous candidiasis due to gain-of-function mutations in STAT1. J Clin Immunol 36(1):73–84

Diveu C, McGeachy MJ, Boniface K, Stumhofer JS, Sathe M, Joyce-Shaikh B, Chen Y, Tato CM, McClanahan TK, de Waal Malefyt R, Hunter CA, Cua DJ, Kastelein RA (2009) IL-27 blocks RORc

expression to inhibit lineage commitment of Th17 cells. J Immunol 182(9):5748–5756

Drewniak A, Gazendam RP, Tool AT, van Houdt M, Jansen MH, van Hamme JL, van Leeuwen EM, Roos D, Scalais E, de Beaufort C, Janssen H, van den Berg TK, Kuijpers TW (2013) Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. Blood 121(13):2385–2392

Drummond RA, Lionakis MS (2016) Mechanistic insights into the role of C-type lectin receptor/CARD9 signaling in human antifungal immunity. Front Cell Infect Microbiol 6:39

Drummond RA, Lionakis MS (2018) Candidiasis of the central nervous system in neonates and children with primary immunodeficiencies. Curr Fungal Infect Rep 12(2):92–97

Drummond RA, Collar AL, Swamydas M, Rodriguez CA, Lim JK, Mendez LM, Fink DL, Hsu AP, Zhai B, Karauzum H, Mikelis CM, Rose SR, Ferre EM, Yockey L, Lemberg K, Kuehn HS, Rosenzweig SD, Lin X, Chittiboina P, Datta SK, Belhorn TH, Weimer ET, Hernandez ML, Hohl TM, Kuhns DB, Lionakis MS (2015) CARD9-dependent neutrophil recruitment protects against fungal invasion of the central nervous system. PLoS Pathog 11(12):e1005293

Drummond RA, Franco LM, Lionakis MS (2018) Human CARD9: a critical molecule of fungal immune surveillance. Front Immunol 9:1836

Drummond RA, Swamydas M, Oikonomou V, Zhai B, Dambuza IM, Schaefer BC, Bohrer AC, Mayer-Barber KD, Lira SA, Iwakura Y, Filler SG, Brown GD, Hube B, Naglik JR, Hohl TM, Lionakis MS (2019) CARD9 (+) microglia promote antifungal immunity via IL-1beta- and CXCL1-mediated neutrophil recruitment. Nat Immunol 20(5):559–570

Eggimann P, Bille J, Marchetti O (2011) Diagnosis of invasive candidiasis in the ICU. Ann Intensive Care 1:37

El-behi M, Ciric B, Yu S, Zhang GX, Fitzgerald DC, Rostami A (2009) Differential effect of IL-27 on developing versus committed Th17 cells. J Immunol 183(8):4957–4967

Engelhardt KR, Grimbacher B (2012) Mendelian traits causing susceptibility to mucocutaneous fungal infections in human subjects. J Allergy Clin Immunol 129(2):294–305 **(quiz 306–307)**

Estrada B, Mancao MY, Polski JM, Figarola MS (2006) Candida lusitaniae and chronic granulomatous disease. Pediatr Infect Dis J 25(8):758–759

Eyerich K, Foerster S, Rombold S, Seidl HP, Behrendt H, Hofmann H, Ring J, Traidl-Hoffmann C (2008) Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. J Invest Dermatol 128(11):2640–2645

Eyerich K, Eyerich S, Hiller J, Behrendt H, Traidl-Hoffmann C (2010) Chronic mucocutaneous candidiasis, from bench to bedside. Eur J Dermatol 20(3):260–265

Fellmann F, Angelini F, Wassenberg J, Perreau M, Arenas Ramirez N, Simon G, Boyman O, Demaria O, Christen-Zaech S, Hohl D, Belfiore M, Von Scheven-Gete A, Gilliet M, Bochud PY, Perrin Y, Beck Popovic M, Bart PA, Beckmann JS, Martinet D, Hofer M (2016) IL-17 receptor A and adenosine deaminase 2 deficiency in siblings with recurrent infections and chronic inflammation. J Allergy Clin Immunol 137(4):1189–1196e2

Fernandez M, Moylett EH, Noyola DE, Baker CJ (2000) Candidal meningitis in neonates: a 10-year review. Clin Infect Dis 31(2):458–463

Ferre EM, Rose SR, Rosenzweig SD, Burbelo PD, Romito KR, Niemela JE, Rosen LB, Break TJ, Gu W, Hunsberger S, Browne SK, Hsu AP, Rampertaap S, Swamydas M, Collar AL, Kong HH, Lee CR, Chascsa D, Simcox T, Pham A, Bondici A, Natarajan M, Monsale J, Kleiner DE, Quezado M, Alevizos I, Moutsopoulos NM, Yockey L, Frein C, Soldatos A, Calvo KR, Adjemian J, Similuk MN, Lang DM, Stone KD, Uzel G, Kopp JB, Bishop RJ, Holland SM, Olivier KN, Fleisher TA, Heller T, Winer KK, Lionakis MS (2016) Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. JCI Insight 1(13):e88782

Finnish-German AC (1997) An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 17(4):399–403

Fischer A, Lisowska-Grospierre B, Anderson DC, Springer TA (1988) Leukocyte adhesion deficiency: molecular basis and functional consequences. Immunodefic Rev 1(1):39–54

Frey-Jakobs S, Hartberger JM, Fliegauf M, Bossen C, Wehmeyer ML, Neubauer JC, Bulashevska A, Proietti M, Frobel P, Noltner C, Yang L, Rojas-Restrepo J, Langer N, Winzer S, Engelhardt KR, Glocker C, Pfeifer D, Klein A, Schaffer AA, Lagovsky I, Lachover-Roth I, Beziat V, Puel A, Casanova JL, Fleckenstein B, Weidinger S, Kilic SS, Garty BZ, Etzioni A, Grimbacher B (2018) ZNF341 controls STAT3 expression and thereby immunocompetence. Sci Immunol 3(24):eaat4941

Gaffen SL (2009) Structure and signalling in the IL-17 receptor family. Nat Rev Immunol 9(8):556–567

Gaffen SL, Jain R, Garg AV, Cua DJ (2014) The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 14(9):585–600

Gavino C, Cotter A, Lichtenstein D, Lejtenyi D, Fortin C, Legault C, Alirezaie N, Majewski J, Sheppard DC, Behr MA, Foulkes WD, Vinh DC (2014) CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. Clin Infect Dis 59(1):81–84

Gavino C, Hamel N, Zeng JB, Legault C, Guiot MC, Chankowsky J, Lejtenyi D, Lemire M, Alarie I, Dufresne S, Boursiquot JN, McIntosh F, Langelier M, Behr MA, Sheppard DC, Foulkes WD, Vinh DC (2016) Impaired RASGRF1/ERK-mediated GM-CSF response characterizes CARD9 deficiency in French-Canadians. J Allergy Clin Immunol 137(4):1178–1188e7

Gavino C, Mellinghoff S, Cornely OA, Landekic M, Le C, Langelier M, Golizeh M, Proske S, Vinh DC (2018) Novel bi-allelic splice mutations in CARD9 causing adult-onset Candida endophthalmitis. Mycoses 61(1):61–65

Glocker E, Grimbacher B (2010) Chronic mucocutaneous candidiasis and congenital susceptibility to Candida. Curr Opin Allergy Clin Immunol 10(6):542–550

Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, Jamal S, Manguiat A, Rezaei N, Amirzargar AA, Plebani A, Hannesschlager N, Gross O, Ruland J, Grimbacher B (2009) A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 361(18):1727–1735

Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D (2003) Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 37(9):1172–1177

Guo B, Chang EY, Cheng G (2008) The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. J Clin Invest 118(5):1680–1690

Herbst M, Gazendam R, Reimnitz D, Sawalle-Belohradsky J, Groll A, Schlegel PG, Belohradsky B, Renner E, Klepper J, Grimbacher B, Kuijpers T, Liese J (2015) Chronic *Candida albicans* meningitis in a 4-year-old girl with a homozygous mutation in the CARD9 Gene (Q295X). Pediatr Infect Dis J 34(9):999–1002

Hiller J, Hagl B, Effner R, Puel A, Schaller M, Mascher B, Eyerich S, Eyerich K, Jansson AF, Ring J, Casanova JL, Renner ED, Traidl-Hoffmann C (2018) STAT1 gain-of-function and dominant negative STAT3 mutations impair IL-17 and IL-22 immunity associated with CMC. J Invest Dermatol 138(3):711–714

Hirahara K, Ghoreschi K, Laurence A, Yang XP, Kanno Y, O'Shea JJ (2010) Signal transduction pathways and transcriptional

regulation in Th17 cell differentiation. Cytokine Growth Factor Rev 21(6):425–434

Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schaffer AA, Puck JM, Grimbacher B (2007) STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 357(16):1608–1619

Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM (2009) Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 48(12):1695–1703

Hotamisligil GS, Davis RJ (2016) Cell signaling and stress responses. Cold Spring Harb Perspect Biol 8(10):a006072

Huang CC, Chen CY, Yang HB, Wang SM, Chang YC, Liu CC (1998) Central nervous system candidiasis in very low-birth-weight premature neonates and infants: US characteristics and histopathologic and MR imaging correlates in five patients. Radiology 209(1):49–56

Husebye ES, Perheentupa J, Rautemaa R, Kampe O (2009) Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. J Int Med 265(5):514–529

Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR (2006) The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 126(6):1121–1133

Jeffery-Smith A, Taori SK, Schelenz S, Jeffery K, Johnson EM, Borman A, Candida auris Incident Management T, Manuel R, Brown CS (2018) *Candida auris*: a review of the literature. Clin Microbiol Rev 31(1):e00029-17

Johnson GL, Nakamura K (2007) The c-jun kinase/stress-activated pathway: regulation, function and role in human disease. Biochim Biophys Acta 1773(8):1341–1348

Jones N, Garcez T, Newman W, Denning D (2016) Endogenous Candida endophthalmitis and osteomyelitis associated with CARD9 deficiency. BMJ Case Rep. https://doi.org/10.1136/bcr-2015-214117

Kim J, Sudbery P (2011) *Candida albicans*, a major human fungal pathogen. J Microbiol 49(2):171–177

Kirkpatrick CH (2001) Chronic mucocutaneous candidiasis. Pediatr Infect Dis J 20(2):197–206

Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, Ersvaer E, Perheentupa J, Erichsen MM, Bratanic N, Meloni A, Cetani F, Perniola R, Ergun-Longmire B, Maclaren N, Krohn KJ, Pura M, Schalke B, Strobel P, Leite MI, Battelino T, Husebye ES, Peterson P, Willcox N, Meager A (2010) Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 207(2):299–308

Kisand K, Lilic D, Casanova JL, Peterson P, Meager A, Willcox N (2011) Mucocutaneous candidiasis and autoimmunity against cytokines in APECED and thymoma patients: clinical and pathogenetic implications. Eur J Immunol 41(6):1517–1527

Klingspor L, Tortorano AM, Peman J, Willinger B, Hamal P, Sendid B, Velegraki A, Kibbler C, Meis JF, Sabino R, Ruhnke M, Arikan-Akdagli S, Salonen J, Doczi I (2015) Invasive Candida infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008). Clin Microbiol Infect 21(1):87e1–87e10

Korn T, Bettelli E, Oukka M, Kuchroo VK (2009) IL-17 and Th17 Cells. Annu Rev Immunol 27:485–517

Kuijpers TW, van Bruggen R, Kamerbeek N, Tool AT, Hicsonmez G, Gurgey A, Karow A, Verhoeven AJ, Seeger K, Sanal O, Niemeyer C, Roos D (2007) Natural history and early diagnosis of LAD-1/variant syndrome. Blood 109(8):3529–3537

Kullberg BJ, Arendrup MC (2016) Invasive candidiasis. N Engl J Med 374(8):794–795

Lanternier F, Cypowyj S, Picard C, Bustamante J, Lortholary O, Casanova JL, Puel A (2013a) Primary immunodeficiencies underlying fungal infections. Curr Opin Pediatr 25(6):736–747

Lanternier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C, Migaud M, Taibi L, Ammar-Khodja A, Stambouli OB, Guellil B, Jacobs F, Goffard JC, Schepers K, Del Marmol V, Boussofara L, Denguezli M, Larif M, Bachelez H, Michel L, Lefranc G, Hay R, Jouvion G, Chretien F, Fraitag S, Bougnoux ME, Boudia M, Abel L, Lortholary O, Casanova JL, Picard C, Grimbacher B, Puel A (2013b) Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med 369(18):1704–1714

Lanternier F, Mahdaviani SA, Barbati E, Chaussade H, Koumar Y, Levy R, Denis B, Brunel AS, Martin S, Loop M, Peeters J, de Selys A, Vanclaire J, Vermylen C, Nassogne MC, Chatzis O, Liu L, Migaud M, Pedergnana V, Desoubeaux G, Jouvion G, Chretien F, Darazam IA, Schaffer AA, Netea MG, De Bruycker JJ, Bernard L, Reynes J, Amazrine N, Abel L, Van der Linden D, Harrison T, Picard C, Lortholary O, Mansouri D, Casanova JL, Puel A (2015) Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species-induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol 135(6):1558–1568e2

Lass-Florl C (2009) The changing face of epidemiology of invasive fungal disease in Europe. Mycoses 52(3):197–205

Lehrer RI, Cline MJ (1969) Leukocyte myeloperoxidase deficiency and disseminated candidiasis: the role of myeloperoxidase in resistance to Candida infection. J Clin Invest 48(8):1478–1488

Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, Carlet J, Reynes J, Rosenheim M, Regnier B, Lortholary O, AmarCand Study, G (2009) Epidemiology, management, and risk factors for death of invasive Candida infections in critical care: a multicenter, prospective, observational study in France (2005–2006). Crit Care Med 37(5):1612–1618

Levy O, Bourquin JP, McQueen A, Cantor AB, Lachenauer C, Malley R (2002) Fatal disseminated *Candida lusitaniae* infection in an infant with chronic granulomatous disease. Pediatr Infect Dis J 21(3):262–264

Levy R, Okada S, Beziat V, Moriya K, Liu C, Chai LY, Migaud M, Hauck F, Al Ali A, Cyrus C, Vatte C, Patiroglu T, Unal E, Ferneiny M, Hyakuna N, Nepesov S, Oleastro M, Ikinciogullari A, Dogu F, Asano T, Ohara O, Yun L, Della Mina E, Bronnimann D, Itan Y, Gothe F, Bustamante J, Boisson-Dupuis S, Tahuil N, Aytekin C, Salhi A, Al Muhsen S, Kobayashi M, Toubiana J, Abel L, Li X, Camcioglu Y, Celmeli F, Klein C, AlKhater SA, Casanova JL, Puel A (2016) Genetic, immunological, and clinical features of patients with bacterial and fungal infections due to inherited IL-17RA deficiency. Proc Natl Acad Sci USA 113(51):E8277–E8285

Li J, Vinh DC, Casanova JL, Puel A (2017) Inborn errors of immunity underlying fungal diseases in otherwise healthy individuals. Curr Opin Microbiol 40:46–57

Li J, Ritelli M, Ma CS, Rao G, Habib T, Corvilain E, Bougarn S, Cypowyj S, Grodecka L, Levy R, Beziat V, Shang L, Payne K, Avery DT, Migaud M, Boucherit S, Boughorbel S, Guennoun A, Chrabieh M, Rapaport F, Bigio B, Itan Y, Boisson B, Cormier-Daire V, Syx D, Malfait F, Zoppi N, Abel L, Freiberger T, Dietz HC, Marr N, Tangye SG, Colombi M, Casanova JL, Puel A (2019) Chronic mucocutaneous candidiasis and connective tissue disorder in humans with impaired JNK1-dependent responses to IL-17A/F and TGF-beta. Sci Immunol 4(41):eaax7965

Lilic D (2002) New perspectives on the immunology of chronic mucocutaneous candidiasis. Curr Opin Infect Dis 15(2):143–147

Linden A (2007) A role for the cytoplasmic adaptor protein Act1 in mediating IL-17 signaling. Sci STKE 2007(398):re4

Ling Y, Cypowyj S, Aytekin C, Galicchio M, Camcioglu Y, Nepesov S, Ikinciogullari A, Dogu F, Belkadi A, Levy R, Migaud M, Boisson B, Bolze A, Itan Y, Goudin N, Cottineau J, Picard C, Abel L, Bustamante J, Casanova JL, Puel A (2015) Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis. J Exp Med 212(5):619–631

Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, Toubiana J, Itan Y, Audry M, Nitschke P, Masson C, Toth B, Flatot J, Migaud M, Chrabieh M, Kochetkov T, Bolze A, Borghesi A, Toulon A, Hiller J, Eyerich S, Eyerich K, Gulacsy V, Chernyshova L, Chernyshov V, Bondarenko A, Grimaldo RM, Blancas-Galicia L, Beas IM, Roesler J, Magdorf K, Engelhard D, Thumerelle C, Burgel PR, Hoernes M, Drexel B, Seger R, Kusuma T, Jansson AF, Sawalle-Belohradsky J, Belohradsky B, Jouanguy E, Bustamante J, Bue M, Karin N, Wildbaum G, Bodemer C, Lortholary O, Fischer A, Blanche S et al (2011) Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 208(8):1635–1648

Louten J, Boniface K, de Waal Malefyt R (2009) Development and function of TH17 cells in health and disease. J Allergy Clin Immunol 123(5):1004–1011

Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, Fulcher DA, Tangye SG, Cook MC (2008) Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 205(7):1551–1557

Ma CS, Wong N, Rao G, Nguyen A, Avery DT, Payne K, Torpy J, O'Young P, Deenick E, Bustamante J, Puel A, Okada S, Kobayashi M, Martinez-Barricarte R, Elliott M, Sebnem Kilic S, El Baghdadi J, Minegishi Y, Bousfiha A, Robertson N, Hambleton S, Arkwright PD, French M, Blincoe AK, Hsu P, Campbell DE, Stormon MO, Wong M, Adelstein S, Fulcher DA, Cook MC, Stepensky P, Boztug K, Beier R, Ikinciogullari A, Ziegler JB, Gray P, Picard C, Boisson-Dupuis S, Phan TG, Grimbacher B, Warnatz K, Holland SM, Uzel G, Casanova JL, Tangye SG (2016) Unique and shared signaling pathways cooperate to regulate the differentiation of human CD4+ T cells into distinct effector subsets. J Exp Med 213(8):1589–1608

Manel N, Unutmaz D, Littman DR (2008) The differentiation of human T (H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgammat. Nat Immunol 9(6):641–649

McCarty TP, Pappas PG (2016) Invasive candidiasis. Infect Dis Clin N Am 30(1):103–124

Meager A, Visvalingam K, Peterson P, Moll K, Murumagi A, Krohn K, Eskelin P, Perheentupa J, Husebye E, Kadota Y, Willcox N (2006) Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med 3(7):e289

Mellouli F, Ksouri H, Barbouche R, Maamer M, Hamed LB, Hmida S, Hassen AB, Bejaoui M (2010) Successful treatment of Fusarium solani ecthyma gangrenosum in a patient affected by leukocyte adhesion deficiency type 1 with granulocytes transfusions. BMC Dermatol 10:10

Meyer S, Woodward M, Hertel C, Vlaicu P, Haque Y, Karner J, Macagno A, Onuoha SC, Fishman D, Peterson H, Metskula K, Uibo R, Jantti K, Hokynar K, Wolff ASB, Collaborative AP, Krohn K, Ranki A, Peterson P, Kisand K, Hayday A (2016) AIRE-deficient patients harbor unique high-affinity disease-ameliorating autoantibodies. Cell 166(3):582–595

Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, Davis J, Hsu A, Asher AI, O'Shea J, Holland SM, Paul WE, Douek DC (2008) Impaired T (H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 452(7188):773–776

Minegishi Y (2009) Hyper-IgE syndrome. Curr Opin Immunol 21(5):487–492

Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, Metin A, Karasuyama H (2007) Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature 448(7157):1058–1062

Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, Agematsu K, Yamada M, Kawamura N, Ariga T, Tsuge I, Karasuyama H (2009) Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med 206(6):1291–1301

Miossec P, Korn T, Kuchroo VK (2009) Interleukin-17 and type 17 helper T cells. N Engl J Med 361(9):888–898

Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N (1997) Positional cloning of the APECED gene. Nat Genet 17(4):393–398

Okada S, Markle JG, Deenick EK, Mele F, Averbuch D, Lagos M, Alzahrani M, Al-Muhsen S, Halwani R, Ma CS, Wong N, Soudais C, Henderson LA, Marzouqa H, Shamma J, Gonzalez M, Martinez-Barricarte R, Okada C, Avery DT, Latorre D, Deswarte C, Jabot-Hanin F, Torrado E, Fountain J, Belkadi A, Itan Y, Boisson B, Migaud M, Arlehamn CSL, Sette A, Breton S, McCluskey J, Rossjohn J, de Villartay JP, Moshous D, Hambleton S, Latour S, Arkwright PD, Picard C, Lantz O, Engelhard D, Kobayashi M, Abel L, Cooper AM, Notarangelo LD, Boisson-Dupuis S, Puel A, Sallusto F, Bustamante J, Tangye SG et al (2015) IMMUNODEFICIENCIES. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic RORC mutations. Science 349(6248):606–613

Okada S, Puel A, Casanova JL, Kobayashi M (2016) Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. Clin Transl Immunol 5(12):e114

Olbrich P, Freeman AF (2018) STAT1 and STAT3 mutations: important lessons for clinical immunologists. Expert Rev Clin Immunol 14(12):1029–1041

Ortega M, Marco F, Soriano A, Almela M, Martinez JA, Lopez J, Pitart C, Mensa J (2011) Candida species bloodstream infection: epidemiology and outcome in a single institution from 1991 to 2008. J Hosp Infect 77(2):157–161

Ouederni M, Sanal O, Ikinciogullari A, Tezcan I, Dogu F, Sologuren I, Pedraza-Sanchez S, Keser M, Tanir G, Nieuwhof C, Colino E, Kumararatne D, Levy J, Kutukculer N, Aytekin C, Herrera-Ramos E, Bhatti M, Karaca N, Barbouche R, Broides A, Goudouris E, Franco JL, Parvaneh N, Reisli I, Strickler A, Shcherbina A, Somer A, Segal A, Angel-Moreno A, Lezana-Fernandez JL, Bejaoui M, Bobadilla-Del Valle M, Kachboura S, Sentongo T, Ben-Mustapha I, Bustamante J, Picard C, Puel A, Boisson-Dupuis S, Abel L, Casanova JL, Rodriguez-Gallego C (2014) Clinical features of Candidiasis in patients with inherited interleukin 12 receptor beta1 deficiency. Clin Infect Dis 58(2):204–213

Pahud BA, Greenhow TL, Piecuch B, Weintrub PS (2009) Preterm neonates with candidal brain microabscesses: a case series. J Perinatol 29(4):323–326

Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ (2018) Invasive candidiasis. Nat Rev Dis Primers 4:18026

Paulson ML, Freeman AF, Holland SM (2008) Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3. Curr Opin Allergy Clin Immunol 8(6):527–533

Perez de Diego R, Sanchez-Ramon S, Lopez-Collazo E, Martinez-Barricarte R, Cubillos-Zapata C, Ferreira Cerdan A, Casanova JL, Puel A (2015) Genetic errors of the human caspase recruitment domain-B-cell lymphoma 10-mucosa-associated lymphoid tissue lymphoma-translocation gene 1 (CBM) complex: molecular, immunologic, and clinical heterogeneity. J Allergy Clin Immunol 136(5):1139–1149

Perfect JR (2017) The antifungal pipeline: a reality check. Nat Rev Drug Discov 16(9):603–616

Pfaller MA, Diekema DJ (2007) Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 20(1):133–163

Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN (2019) Twenty years of the SENTRY antifungal surveillance program: results for Candida species from 1997–2016. Open Forum Infect Dis 6(Suppl 1):S79–S94

Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Crow YJ, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Puck J, Tang MLK, Tangye SG, Torgerson TR, Sullivan KE (2018) International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol 38(1):96–128

Pilmis B, Puel A, Lortholary O, Lanternier F (2016) New clinical phenotypes of fungal infections in special hosts. Clin Microbiol Infect 22(8):681–687

Pirofski LA, Casadevall A (2009) Rethinking T cell immunity in oropharyngeal candidiasis. J Exp Med 206(2):269–273

Puel A, Picard C, Cypowyj S, Lilic D, Abel L, Casanova JL (2010a) Inborn errors of mucocutaneous immunity to Candida albicans in humans: a role for IL-17 cytokines? Curr Opin Immunol 22(4):467–474

Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachee-Chardin M, Toulon A, Bustamante J, Al-Muhsen S, Al-Owain M, Arkwright PD, Costigan C, McConnell V, Cant AJ, Abinun M, Polak M, Bougneres PF, Kumararatne D, Marodi L, Nahum A, Roifman C, Blanche S, Fischer A, Bodemer C, Abel L, Lilic D, Casanova JL (2010b) Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 207(2):291–297

Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, Gumbleton M, Toulon A, Bodemer C, El-Baghdadi J, Whitters M, Paradis T, Brooks J, Collins M, Wolfman NM, Al-Muhsen S, Galicchio M, Abel L, Picard C, Casanova JL (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 332(6025):65–68

Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL (2012) Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 12(6):616–622

Qian Y, Liu C, Hartupee J, Altuntas CZ, Gulen MF, Jane-Wit D, Xiao J, Lu Y, Giltiay N, Liu J, Kordula T, Zhang QW, Vallance B, Swaidani S, Aronica M, Tuohy VK, Hamilton T, Li X (2007) The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. Nat Immunol 8(3):247–256

Rieber N, Gazendam RP, Freeman AF, Hsu AP, Collar AL, Sugui JA, Drummond RA, Rongkavilit C, Hoffman K, Henderson C, Clark L, Mezger M, Swamydas M, Engeholm M, Schule R, Neumayer B, Ebel F, Mikelis CM, Pittaluga S, Prasad VK, Singh A, Milner JD, Williams KW, Lim JK, Kwon-Chung KJ, Holland SM, Hartl D, Kuijpers TW, Lionakis MS (2016) Extrapulmonary *Aspergillus* infection in patients with CARD9 deficiency. JCI insight 1(17):e89890

Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, Okada S, Boisson-Dupuis S, Casanova JL, Bustamante J (2019) Mendelian susceptibility to mycobacterial disease: 2014–2018 update. Immunol Cell Biol 97(4):360–367

Roth S, Ruland J (2013) Caspase recruitment domain-containing protein 9 signaling in innate immunity and inflammation. Trends Immunol 34(6):243–250

Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM (2000) Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore) 79(3):170–200

Shiokawa M, Yamasaki S, Saijo S (2017) C-type lectin receptors in anti-fungal immunity. Curr Opin Microbiol 40:123–130

Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Picard C, Puck J, Torgerson TR, Casanova JL, Sullivan KE (2020) Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. https://doi.org/10.1007/s10875-019-00737-x

Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, Ouachee-Chardin M, Fouyssac F, Girisha KM, Etzioni A, Van Montfrans J, Camcioglu Y, Kerns LA, Belohradsky B, Blanche S, Bousfiha A, Rodriguez-Gallego C, Meyts I, Kisand K, Reichenbach J, Renner ED, Rosenzweig S, Grimbacher B, van de Veerdonk FL, Traidl-Hoffmann C, Picard C, Marodi L, Morio T, Kobayashi M, Lilic D, Milner JD, Holland S, Casanova JL, Puel A, International, S. G.-o.-F. S. G. (2016) Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 127(25):3154–3164

Turner SA, Butler G (2014) The Candida pathogenic species complex. Cold Spring Harb Perspect Med 4(9):a019778

van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, Kullberg BJ, van der Meer JW, Lilic D, Veltman JA, Netea MG (2011) STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med 365(1):54–61

Van der Velden J, Janssen-Heininger YM, Mandalapu S, Scheller EV, Kolls JK, Alcorn JF (2012) Differential requirement for c-Jun N-terminal kinase 1 in lung inflammation and host defense. PLoS One 7(4):e34638

Vazquez JA, Sobel JD (2002) Mucosal candidiasis. Infect Dis Clin N Am 16(4):793–820 **(v)**

Vinh DC (2011) Insights into human antifungal immunity from primary immunodeficiencies. Lancet Infect Dis 11(10):780–792

Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupe P, Barillot E, Soumelis V (2008) A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T (H)-17 responses. Nat Immunol 9(6):650–657

Wang H, Liu N, Yin M, Han H, Yue J, Zhang F, Shan T, Guo H, Wu D (2014a) The epidemiology, antifungal use and risk factors of death in elderly patients with candidemia: a multicentre retrospective study. BMC Infect Dis 14:609

Wang X, Wang W, Lin Z, Wang X, Li T, Yu J, Liu W, Tong Z, Xu Y, Zhang J, Guan L, Dai L, Yang Y, Han W, Li R (2014b) CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 133(3):905–908e3

Winkelstein JA, Marino MC, Johnston Jr RB, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79(3):155–169

Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 39(3):309–317

Yang XO, Pappu BP, Nurieva R, Akimzhanov A, Kang HS, Chung Y, Ma L, Shah B, Panopoulos AD, Schluns KS, Watowich SS, Tian Q, Jetten AM, Dong C (2008a) T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma. Immunity 28(1):29–39

Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, Kuchroo VK, Hafler DA (2008b) IL-21 and TGF-beta are required for differentiation of human T (H)17 cells. Nature 454(7202):350–352

Zhang Y, Ma CA, Lawrence MG, Break TJ, O'Connell MP, Lyons JJ, Lopez DB, Barber JS, Zhao Y, Barber DL, Freeman AF, Holland SM, Lionakis MS, Milner JD (2017) PD-L1 up-regulation restrains Th17 cell differentiation in STAT3 loss- and STAT1 gain-of-function patients. J Exp Med 214(9):2523–2533

Zhang Q, Boisson B, Beziat V, Puel A, Casanova JL (2018) Human hyper-IgE syndrome: singular or plural? Mamm Genome 29(7–8):603–617

Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations. Annu Rev Immunol 28:445–489