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Genetic susceptibility to *Candida* infections

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Candida spp. are medically important fungi causing severe mucosal and life-threatening invasive infections, especially in immunocompromised hosts. However, not all individuals at risk develop *Candida* infections, and it is believed that genetic variation plays an important role in host susceptibility. On the one hand, severe fungal infections are associated with monogenic primary immunodeficiencies such as defects in *STAT1*, *STAT3* or *CARD9*, recently discovered as novel clinical entities. On the other hand, more common polymorphisms in genes of the immune system have also been associated with fungal infections such as recurrent vulvovaginal candidiasis and candidemia. The discovery of the genetic susceptibility to *Candida* infections can lead to a better understanding of the pathogenesis of the disease, as well as to the design of novel immunotherapeutic strategies. This review is part of the review series on host-pathogen interactions. See more reviews from this series.

Infections with *Candida* species

Candida spp, especially *Candida albicans*, are commensal fungi that reside on the skin, mucosa and gastrointestinal tract of 30 to 50% of healthy individuals at any given time, with everyone being colonized at a certain moment of his/her lifetime (Brown & Netea, 2007). Although *C. albicans* is not pathogenic under normal host conditions, it can cause severe mucosal or systemic infections when host defense is compromised.

Mucosal infections

Mucosal infections affect the skin and mucous membranes. Common sites for these superficial infections are the mouth, vagina, external ear, skin and nails, of which oral candidiasis is the most common (Odds, 1988). Mucosal infections are usually sporadic, but some patients experience severe and recurrent infections of the skin and oropharyngeal cavities termed chronic mucocutaneous candidiasis (CMC). In addition, most women suffer at least once in their lifetime from vulvovaginal candidiasis, while up to 8% of them have recurrent infections (Sobel, 2007).

Systemic infections

In contrast to mucosal candidiasis which is highly prevalent but does not cause high mortality, systemic infections are life threatening, with mortality rates reaching up to 26–60% (Das et al, 2011). When the organisms enter the blood stream they can invade deep tissues and organs such as brain, heart and kidneys. Considering the number of patients diagnosed each year, *Candida* has emerged in the recent decades as one of the most important pathogens in sepsis, causing significant morbidity and mortality. Moreover, mortality due to these severe infections has not been significantly changed in the last decade, despite the introduction of potent antifungals such as azoles and echinocandins (Fortún et al, 2012). It is currently believed that only a combination of standard antimycotic treatment with adjuvant immunotherapy may significantly improve the outcome of fungal infections, and both immunological and genetic studies are needed to accomplish the necessary understanding of the pathogenesis of these infections.

Candida albicans host defense

The *C. albicans* cell wall can be divided into two distinct layers: the inner layer consisting mainly of polysaccharides like chitin, 1,3-β-glucans and 1,6-β-glucans, and the outer layer consisting mainly of proteins that are heavily mannosylated with mannan side-chains. These pathogen-associated molecular patterns (PAMPs) can be recognized by several pathogen recognition receptors (PRRs), such as the Toll-like receptors (TLRs) and C-type lectins (CLRs) on the surface of antigen presenting cells (APCs). TLR2 recognizes phospholipomannans (Jouault et al, 2003), and TLR4 recognizes *O*-linked mannans (Netea et al,

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2006). *N*-linked mannans are recognized by the macrophage mannose receptor (MMR) (Netea et al, 2006), with other CLRs which can recognize mannose residues being Dectin-2 (McGreal et al, 2006), Mincle (Wells et al, 2008), DC-specific ICAM-grapping non-integrin (DC-SIGN) (Cambi et al, 2003) and the soluble receptor mannose-binding lectin (MBL) (Brouwer et al, 2008). The CLR Dectin-1 recognizes β-glucan (Brown & Gordon, 2001) (Fig 1).

When a PRR recognizes its corresponding ligand, adaptor molecules engage with the receptor. Different types of PRRs use different adaptor molecules, which transduce a signal by activating a kinase cascade, in order to induce the transcription of proinflammatory cytokines. Dectin-1 signals through Syk (Rogers et al, 2005) and caspase recruitment domain 9 (CARD9) (Gross et al, 2006). Dectin-1 can induce cytokine production independently of other receptors, as well as synergize with TLRs for an optimal stimulation of the cell. When ligands are recognized by TLRs, signals are transduced intracellularily through adaptor proteins like myeloid differentiation factor (MYD)88. Subsequently, a mitogen-activated protein kinase (MAPK) response is activated leading to the nuclear translocation of transcription factors like NF-κB and c-Jun, inducing the transcription of cytokines and chemokines (Akira et al, 2006). Interestingly, depending on the fungal burden and amount of hyphae formation a second MAPK phase, consisting of MKP1 and c-Fos activation, can be initiated, further promoting proinflammatory responses (Moyes et al, 2010).

The recognition of *C. albicans* by cells of the innate immune system will lead to phagocytosis (Heinsbroek et al, 2008) and killing of the invading pathogen. At the same time, the production of cytokines is induced that on the one hand activate inflammation, and on the other hand engage and direct the adaptive immune response. Activation of the caspase-1 component of the inflammasome, mediated by the intracellular activation of the NOD-like receptor NLRP3, is a central event leading to the processing of pro-IL-1β and pro-IL-18 into their respective bioactive cytokines, directing the induction of Th17 and Th1 responses, respectively (Cheng et al, 2011; Lalor et al, 2011). IFN-γ production by Th1 cells, and IL-17 production by Th17 cells are important characteristics of the *Candida*-induced immune response (Netea et al, 2008). Inflammasome and Th17 activation is considered to be a central event for the discrimination of colonization *versus* invasion with *C. albicans* at the level of the mucosa (Gow et al, 2011).

General risk factors for *Candida* infections

C. albicans is an opportunistic fungal pathogen. In healthy individuals, the immune response will usually clear infections, but an immunocompromised immune system causes a significant increase in the risk for *Candida* infections. Das et al demonstrated that 92% of *Candida* bloodstream infections are preceded by a course of broad-spectrum antibiotics (Das et al, 2011), which suppress the growth of the normal bacterial flora and eliminates natural antagonism of fungal colonization of the mucosa. There are several other examples in which *Candida* acts as an opportunistic pathogen. For example, almost all AIDS and oncologic patients with neutropenia suffer from oropharyngeal candidiasis (Grabar et al, 2008; Viscoli et al, 1999). Furthermore, 41% of patients undergoing hematopoietic stem cell transplantation, for which the immune system is destroyed beforehand, suffer from one or more bloodstream infections within the first ten years after transplantation, 4% of which are caused by *Candida* spp. The crude mortality rate associated with these *Candida*-infections is 42% (Ortega et al, 2005). Also

Glossary

Autosomal-dominant
Mode of inheritance in which the presence of only one copy of a gene on one of the 22 autosomal–non-sex chromosomes, will result in the phenotypic expression of that gene.

Candidemia
The presence of *Candida* species in the blood.

Candidiasis
Fungal infection with any of the *Candida* species. Includes candidemia (in case of systemic infection).

Chronic mucocutaneous candidiasis (CMC)
An immune disorder characterized by chronic infections with *Candida* that are limited to mucosal surfaces, skin and nails.

Genetic variation
Variations of genomes between members of species or between groups of species. Includes SNP (in case it is a common genetic variant), mutation (in case it is a rare genetic variant) and copy-number variation.

Immunocompromised
State in which the immune system is not functioning properly, increasing susceptibility to infection.

Immunodeficiency
A state in which the immune system's ability to fight infectious disease is compromised or entirely absent.

Immune paralysis
A state in which induction of tolerance is due to injection of large amounts of antigen that remains poorly metabolized.

Neutropenia
An immune disorder characterized by an abnormally low level of neutrophils.

Pathogenesis
The mechanism by which the disease is caused.

Pathogen recognition receptors (PRRs)
Proteins expressed by cells of the innate immune system, which recognize pathogen-associated molecular patterns (PAMPs) from microbial pathogens.

Polymorphism
Having multiple alleles of a gene within a population, usually linked to different phenotypes.

Single nucleotide polymorphism (SNP)
DNA sequence variation occurring when a single nucleotide in the genome differs between members of a biological species or paired chromosomes in an individual.

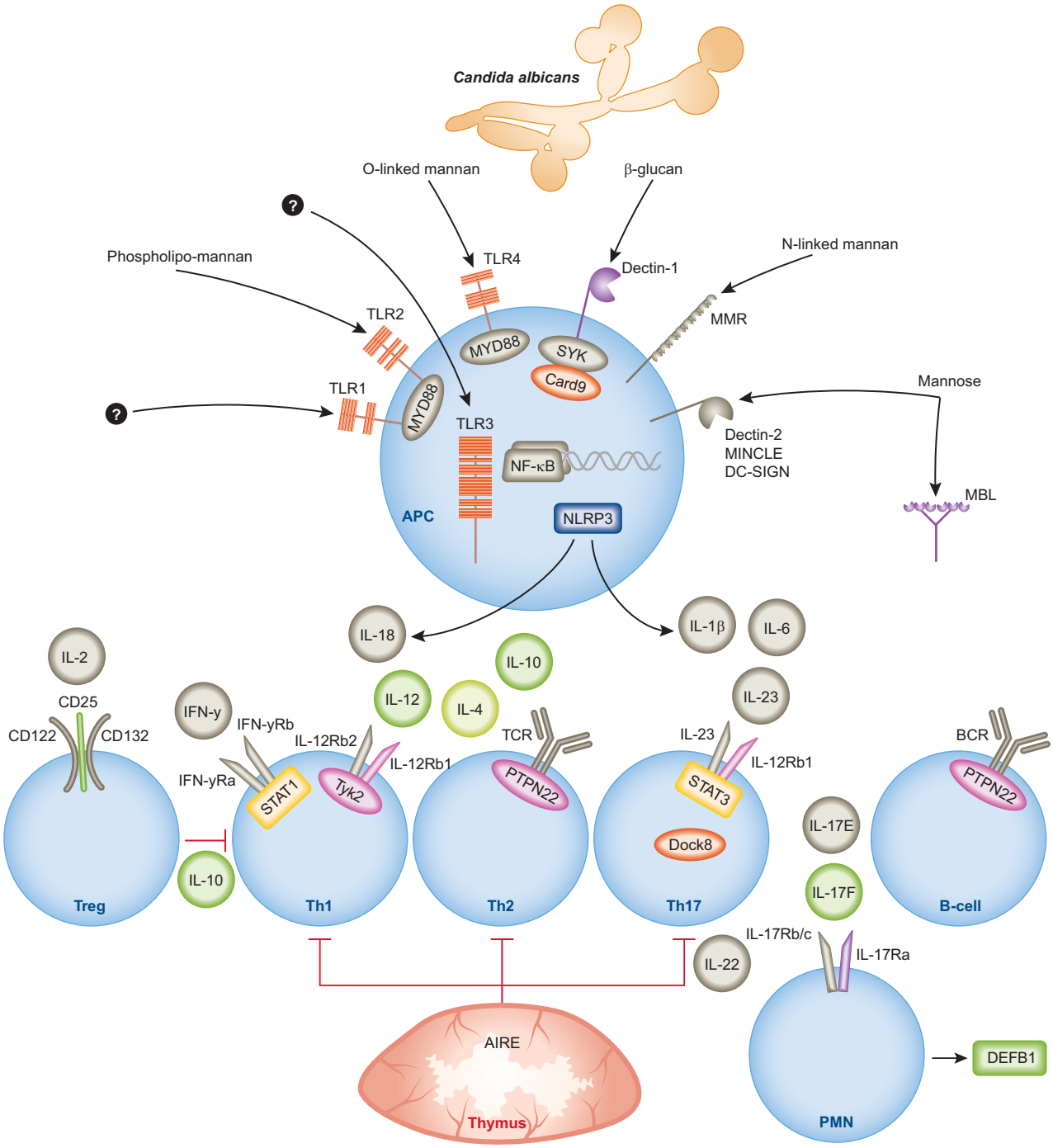

Figure 1. Schematic overview of the anti-*Candida albicans* immune response. When *Candida* is recognized by Toll-like receptors (TLRs) and C-type lectin receptors, the production of cytokines is initiated through activation of transcription factors like NF-κB. IL-1β and IL-18 first need to be cleaved by the NLRP3 inflammasome before they can be secreted. IL-2 is involved in the differentiation of all effector T-cells. The IL-2 receptor is highly expressed on regulatory T-cells (T_{reg}). IL-12 and IL-18 promote the differentiation of T helper 1 (Th1) cells, with IFN-γ being their main product. IL-4 and IL-10 promote the differentiation of Th2 cells, while IL-10 can also suppress Th1 cells. IL-1β, IL-6 and IL-23 drive the development of Th17 cells. DOCK8 is involved in the maintenance of Th17 cells. IL-17 promotes the recruitment of neutrophils, which have tissue protective effects by the production of beta-defensins. Cytokines are recognized by cytokine receptors, which use several adaptor molecules like STAT1, STAT3 and TYK2. PTPN22 is involved in B- and T-cell receptor signaling. Components with mutations and/or genetic variation known to be associated with *Candida* infection are shown in color. APC: antigen presenting cell, BCR: B-cell receptor, CARD9: caspase recruitment domain 9, DC-SIGN: dendritic cell-specific ICAM-grapping non-integrin, MBL: mannose binding lectin, MMR: macrophage mannose receptor, NLRP3: NACHT, LRR and PYD domains-containing protein 3, TCR: T-cell receptor, TLR: Toll-like receptor.

patients with systemic lupus erythematosus (SLE), which are treated with glucocorticoids and other immunosuppressive agents, have an increased risk for invasive fungal infections (IFI), which are predominantly caused by *Candida* spp. (Fan et al, 2012).

Not only a weakened immune system increases the risk for *Candida* infections, also the extent to which individuals are colonized with pathogens plays a significant role in the development of candidiasis. Candidiasis typically affects patients with prolonged hospitalization. Fifty-one percent of *Candida* blood-stream infections is associated with being admitted to the ICU (Das et al, 2011). The mean time of onset of systemic *Candida* infections is 22 days after hospitalization (Wisplinghoff et al, 2004). Furthermore, when barriers to the outside world are damaged or breached by medical devices or surgery, this creates a portal of entry for pathogens like *C. albicans*. For instance, major abdominal surgery poses an increased risk for systemic *Candida* infections, which is underlined by the observation that in a cohort of 107 patients with candidemia, 50% underwent recent surgery (Das et al, 2011). Another factor contributing to systemic candidiasis is the fact that *Candida* spp. can form biofilms on many medical devices like central venous catheters (CVC), contact lenses, intrauterine devices (IUDs) (Donlan & Costerton, 2002) and pacemakers (Glöckner, 2011). *Candida* can even cause prosthetic joint infections, although they are considered to be rare (Springer & Chatterjee, 2012). Indeed, neonates on the intensive care unit (ICU) with a central line often suffer from infections, with the third most causative pathogen being *Candida* spp. Fortunately this incidence is decreasing due to the use of anti-fungal prophylaxis (Chitnis et al, 2012).

Genetic risk factors for *Candida* infections

In spite of the important role played by these risk factors, they do not explain all *Candida* infections, and only a minority of individuals at risk will eventually develop a fungal infection. It is therefore believed that also genetic factors must play an important role in determining the susceptibility to *Candida* infections. Indeed, mutations in single genes were found to be responsible for severe *Candida* infections in several primary immunodeficiencies that display the clinical picture of monogenetic disorders. However, these disorders are rare, and in the majority of patients no sole causative genetic factor can be found. In most patients a combination of gene polymorphisms and/or environmental factors will determine whether a patient will develop a *Candida* infection. The genetic susceptibility to more common *Candida* infections such as RVVC or candidemia is likely polygenic, but the understanding of the genetic factors that determine it is nevertheless crucial for future immunotherapeutic approaches in these patients.

Monogenetic disorders

Several monogenetic disorders have been described in the literature to be associated with an increased susceptibility to fungal infections. Glocker et al described that a homozygous mutation in the *CARD9* gene, coding for a protein downstream of Dectin-1, results in an increased susceptibility to both mucosal and invasive *Candida* infections (Glocker et al, 2009; Lanternier et al, 2012). Disease severity in these patients is likely explained by the fact that CARD9 is also involved in the downstream signaling of several other CLR receptors, such as Dectin-2 and Mincle (Robinson et al, 2009; Saijo et al, 2010; Strasser et al, 2012; Yamasaki et al, 2008), implying that CARD9 is a central mediator of anti-*Candida* host defense.

Another monogenetic disorder that results in an important primary immunodeficiency associated with *Candida* infections is CMC. Both autosomal recessive and autosomal dominant variants of the disease have been described. Mutations in the CC-domain of *STAT1*, a signaling molecule downstream of the type I and type II IFN receptor (Darnell et al, 1994), but also IL-23 and IL-12 receptors (as heterodimer with STAT3 or STAT4), have recently been demonstrated to be the main cause of autosomal-dominant CMC (van de Veerdonk et al, 2011), and these findings were confirmed by several other research groups (Depner et al, 2012; Hirata et al, 2012; Liu et al, 2011; Martinez-Martinez et al, 2012; Moreira et al, 2012; Okada et al, 2012; Smeekens et al, 2011). In addition to *STAT1* mutations, Puel et al demonstrated the presence of mutations in *IL-17RA* and *IL-17F* in some unexplained CMC cases (Puel et al, 2012). In contrast, patients with autosomal recessive autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) not only suffer from CMC, but also experience autoimmune phenomena (Lilic, 2002). APECED has been linked to mutations in the *autoimmune regulator* (*AIRE*) gene (Björses et al, 1998) that result in a loss-of-function phenotype, causing the production of neutralizing autoantibodies against important cytokines with antifungal properties such as IL-17E, IL-17F and IL-22 (Puel et al, 2010).

Another monogenetic defect resulting in a primary immunodeficiency syndrome associated with *Candida* infections of the skin is hyper-IgE syndrome (HIES). HIES was first described as Job's syndrome and is characterized by high serum IgE levels, eczema, recurrent mucosal infections with *C. albicans*, and skin and pulmonary infections with *Staphylococcus aureus* (Davis et al, 1966). There are a number of mutations known to be associated with HIES. Several mutations have been found in *STAT3* (Holland et al, 2007; Minegishi et al, 2007), a signaling molecule downstream of the IL-23 receptor, resulting in absent IL-17 production (de Beaucoudrey et al, 2008; Ma et al, 2008; Milner et al, 2008; Sharfe et al, 1997). Other genes which have been associated with HIES include *dedicator of cytokinesis* (*DOCK*)*8 that codes* for a protein involved in Th17 polarization (Engelhardt et al, 2009) and *TYK2* (Minegishi et al, 2006), coding for a Janus kinase (JAK) downstream of the IL-12 receptor (Shimoda et al, 2000). All in all, defective Th17 responses underlie both CMC and HIES, two immunodeficiencies associated with severe, chronic, mucosal *Candida* infections. This emphasizes the importance of the Th17 response in mucosal *Candida* immunity.

Also mutations in genes coding for cytokines and their receptors have been described to be associated with *Candida* infections. For example, IL-12Rb1 deficiency has been linked to

mucocutaneous *Candida* infections, and these patients also have increased susceptibility for invasive candidiasis (Rodríguez-Gallego et al, 2012). Sharfe et al described a patient with a deletion in the *CD25* gene, suffering from esophageal candidiasis. CD25 is the α-subunit of the IL-2 receptor, which is constitutively expressed on T regulatory cells (Sakaguchi et al, 1995). Furthermore, IL-2 is involved in the differentiation of effector T cells. Although Sharfe et al only described a single patient, this again emphasizes the importance of T cells in the anti-*Candida* host response. A complete overview of monogenetic disorders causing fungal infections is depicted in Table 1 and Fig 1.

Common genetic variants and susceptibility to *Candida* infections

Despite the presence of primary immunodeficiency syndromes with fungal infections, the vast majority of fungal infections is not present in these individuals, but are common diseases with a polygenic pattern of increased susceptibility. Several studies have been published showing a link between genetic variation and an increased risk for *Candida* infections, with different genetic pattern being discerned between mucosal and systemic candidiasis. An example of this dichotomy is the role of a *Dectin-1* polymorphism for susceptibility to mucosal, but not systemic, candidiasis. We have recently described a family in which its members suffered from recurrent vulvo-vaginal candidiasis (RVVC) and onychomycosis. Their symptoms could be explained by an early stop codon in *Dectin-1* (Y238X) that resulted in defective β-glucan recognition and Th17 responses. Interestingly, this polymorphism is present in up to 8% of the Europeans and up to 40% of some sub-Saharan African populations (Ferwerda et al, 2009), being associated with mucosal *Candida* colonization and treatment in haematopoetic patients (Plantinga et al, 2009), but not with systemic candidiasis (Rosentul et al, 2011).

Genetic variation localized in other PRRs, such as the TLRs, has also been associated with an increased susceptibility to fungal infections. Three single nucleotide polymorphisms (SNPs) in the *TLR1* gene have been shown to influence susceptibility to candidemia, presumably mediated by decreased levels of IL-8 and IFN-γ (Plantinga et al, 2012). However, these findings need to be replicated in independent studies, and it is unclear which component of *Candida* is recognized by TLR1. A similar observation has been made for TLR2 and TLR4, which recognize phospholipomannans and *O*-linked mannans, respectively. The R753Q *TLR2* polymorphism increased the risk for candidemia in one small study through decreased IFN-γ and IL-8 levels (Woehrle et al, 2008), and two SNPs in the TLR4 gene were shown to be a risk factor for candidemia through increased IL-10 production (Van der Graaf et al, 2006), but these observations were not replicated in a larger study of patients (Plantinga et al, 2012). Nahum et al suggested that the L412F *TLR3* polymorphism increases the risk for CMC, an effect mediated by decreased IFN-γ production (Nahum et al, 2011). Furthermore, variable number of tandem repeats in *MBL2* gene that codes for the soluble PRR MBL has been linked to RVVC in two separate studies (Babula et al, 2003; Giraldo et al, 2007). Finally, length polymorphisms in the *NLPR3* gene, coding for the receptor subunit of the NLRP3 inflammasome, can increase the risk for RVVC (Lev-Sagie et al, 2009).

In addition to the first step of pathogen recognition, genetic variation in several cytokines has been linked to an increased risk for *Candida* infections. Choi et al demonstrated that the −1089T/G, −589C/T and the −33C/T polymorphisms in *IL-4* are associated with chronic disseminated candidiasis (Choi et al, 2003). Interestingly, the −589T/C SNP has also been

Table 1. Monogenetic disorders

Gene	Mutation	Mode of inheritance	Phenotype	Disease	Refs.
AIRE	R257X	Autosomal-dominant	Autoantibodies against IL-17 and IL-22	CMC	Nagamine et al (1997), Pearce et al (1998)
CARD9	Q295X	Autosomal-recessive	Reduced TNF-α production and Th17 cells	CMC	Glocker et al (2009)
	Q289X R101C	Autosomal-recessive	Reduced Th17 responses	Invasive dermamtophytic disease	Lanternier et al (2012)
CD25	Deletion (60–64)	Autosomal recessive	Reduced number of CD4+ cells	*Candida* esophagitis	Sharfe et al (1997)
DOCK8	Multiple deletions and point mutations	Autosomal-recessive	Reduced Th17 cells	Hyper IgE syndrome	Engelhardt et al (2009)
IL-12Rb1	Multiple point mutations	Autosomal-recessive	Low levels of IFN-γ	Mucosal candidiasis	Rodríguez-Gallego et al (2012)
IL-17RA	Q284X	Autosomal-recessive	Absent IL-6 and GRO-a production	CMC	Puel et al (2011)
IL-17F	S65L	Autosomal-dominant	Reduced IL-6 and GRO-a production	CMC	Puel et al (2011)
STAT1	R274W A267V	Autosomal-dominant	Reduced IL-17, IL-22 and IFN-γ production	CMC	van de Veerdonk et al (2011)
STAT3	Multiple point mutations	Autosomal-dominant	Reduced IL-17 production	HIES	Holland et al (2007)
TYK2	Deletion (550–553)	Autosomal-recessive	Reduced Th1 and Type I IFN responses	HIES	Minegishi et al (2006)

Table 2. Common genetic variants

Gene	SNP (rs-number)	Phenotype	Disease	Refs.
Dectin-1	Y238X **(rs16910526)**	Decreased IL-1β and Th17 responses	*Candida* colonization	Plantinga et al (2009)
DEFB1	−44C/G (rs1800972)	Unknown	*Candida* carriage	Jurevic et al (2003)
IL-4	−589T/C (rs2243250)	Increased vaginal IL-4, reduced NO and MBL levels	RVVC	Babula et al (2005)
	−1098T/G (rs2243248), −589C/T (rs2243250), −33C/T (rs2070874)	Unknown	Chronic disseminated candidiasis	Choi et al (2003)
IL-10	−1082A/G (rs1800896)	Higher *Candida*-induced IL-10 production	Persisting candidemia	Johnson et al (2012)
IL-12B	2724INS/DEL (rs17860508)	Lower *Candida*-induced IFN-γ production	Persisting candidemia	Johnson et al (2012)
MBL2	Variable number of tandem repeats in intron 4	Reduced vaginal MBL levels	RVVC	Babula et al (2003), Giraldo et al (2007)
NLPR3	Length polymorphism	Impaired IL-1β production	RVVC	Lev-Sagie et al (2009)
PTPN22	R620W (rs2476601)	Unknown	Increased risk for CMC	Nahum et al (2008)
TLR1	R80T (rs5743611), S248N (rs4833095), I602S (rs5743618)	Decreased production of IL-1β, IL-6 and IL-8 after TLR1-TLR2 stimulation	Increased susceptibility to candidemia	Plantinga et al (2012)
TLR2	R753Q (rs5743708)	Decreased levels of IFN-γ and IL-8	Increased susceptibility to candidemia	Woehrle et al (2008)
TLR3	L412F (rs3775291)	Decreased IFN-γ levels	Increased risk for CMC	Nahum et al (2011, 2012)
TLR4	D299G (rs4986790), Y399I (rs4986791)	Increased IL-10 production	Increased susceptibility to candidemia	Van der Graaf et al (2006)

demonstrated to pose a risk for RVVC (Babula et al, 2005). The −1082A/G polymorphism in the anti-inflammatory cytokine gene *IL-10* and the 274INS/DEL polymorphism in *IL-12b*, are associated with persisting candidemia (Johnson et al, 2012). These data strongly suggest that the balance between pro- and anti-inflammatory cytokines represent an important component of host defense against both mucosal and systemic candidiasis.

The −44C/G polymorphism in *DEFB1*, coding for beta-defensin 1, is correlated with increased *Candida* carriage (Jurevic et al, 2003). The exact underlying mechanism is unclear, but in general beta-defensins are secreted by neutrophils and epithelial cells and contribute to epithelial immunity. The R620W polymorphism in PTPN22, a protein involved in T-cell and B-cell receptor signaling, was suggested to be associated with an increased risk for CMC. Although the potential mechanism of this association is unclear (Nahum et al, 2008). A complete overview of common genetic variants associated with fungal infection is depicted in Table 2 and Fig 1.

Future developments

The current body of evidence has provided many new insights into the working mechanism of the anti-*Candida* immune response. These new insights can pinpoint novel potential targets for immunotherapy. For example, several studies have demonstrated a correlation between decreased IFN-γ levels and an increased risk for systemic *Candidiasis* (Johnson et al, 2012; Woehrle et al, 2008). A double-blind, randomized, placebo-controlled study is currently being performed using adjuvant IFN-γ therapy in sepsis. It would be also very relevant to try and reverse the immunoparalysis (Leentjens et al, 2012). This suggests that IFN-γ is a promising treatment option in sepsis-induced immune paralysis. We are currently investigating the efficacy of recombinant IFN-γ in patients with *Candida* sepsis.

Despite the significant progress of the last few years for uncovering susceptibility to fungal infections, there are still a significant number of *Candida* infections for which the environmental and/or genetic risk factors are not yet deciphered. Even more importantly, in spite of current treatment regimens, mortality rates associated with systemic infections are still very high, and in order to improve diagnostic- and treatment options, future efforts should be directed towards gaining more insight into the anti-*Candida* host immune response. This can be achieved in several ways. Discovering novel mutations that underlie monogenetic disorders associated with *Candida* infections can generate crucial information about a particular gene or protein, and the pathway in which this protein is involved. For example, the use of next generation sequencing and whole exome sequencing to discover *STAT1* mutations as a cause of CMC (van de Veerdonk et al, 2011), has also led in the understanding of its role for the generation of Th1 and Th17 responses and the anti-*Candida* host defense (Smeekens et al, 2011). This discovery can lead to novel approaches to the therapy of CMC, some of them being currently tested.

Of course, the list of existing monogenetic disorders is relatively small, as the majority of *Candida* cases are likely polygenic and/or multifactorial. In order to investigate this type of disorders other methods will have to be employed such as genome-wide association studies (GWAS), deep sequencing, and systems biology. We have recently used a combination of transcriptional analysis and functional genomics to demonstrate that type I IFNs play an important role in the anti-*Candida* host defense (Smeekens et al, 2013). Stimulation of circulating leukocytes with *C. albicans* led to a transcription profile with

Pending issues

- Integration efforts from immunology, genetics, microbiology and systems biology to increase the level of understanding of the host defense against fungal (and other) pathogens.
- Design of novel immunotherapeutic strategies for an improved treatment.
- Discovering novel mutations that underlie monogenetic disorders associated with *Candida* infections by GWAS or deep sequencing.

overrepresentation of genes from the type I IFN pathway. Subsequently, we showed that polymorphisms in these genes modify *Candida*-induced cytokine production and influence susceptibility to systemic *Candida* infections. Furthermore, validation studies showed that type I IFNs skew *Candida*-induced cytokine responses from Th17 toward Th1, while STAT1-deficient CMC patients display defective expression of genes in the type I IFN pathway. This 'systems approach', that integrates the information on anti-*Candida* host defense from several types of studies, provides information with respect to potential novel anti-*Candida* immune responses that may represent targets for immunotherapy. It is to be expected that an integration of efforts from immunology, genetics, microbiology and systems biology will represent the novel level of understanding of host defense against fungal (and other) pathogens, improving the outcome of these severe infections.

The authors declare that they have no conflict of interest.

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References

Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124: 783-801

Babula O, Lazdāne G, Kroica J, Ledger WJ, Witkin SS (2003) Relation between recurrent vulvovaginal candidiasis, vaginal concentrations of mannose-binding lectin, and a mannose-binding lectin gene polymorphism in Latvian women. Clin Infect Dis 37: 733-737

Babula O, Lazdāne G, Kroica J, Linhares IM, Ledger WJ, Witkin SS (2005) Frequency of interleukin-4 (IL-4) −589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide, and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. Clin Infect Dis 40: 1258-1262

Björses P, Aaltonen J, Horelli-Kuitunen N, Yaspo ML, Peltonen L (1998) Gene defect behind APECED: a new clue to autoimmunity. Hum Mol Genet 7: 1547-1553

Brouwer N, Dolman KM, van Houdt M, Sta M, Roos D, Kuijpers TW (2008) Mannose-binding lectin (MBL) facilitates opsonophagocytosis of yeasts but not of bacteria despite MBL binding. J Immunol 180: 4124-4132

Brown GD, Gordon S (2001) Immune recognition. A new receptor for beta-glucans. Nature 413: 36-37

Brown GD, Netea MG (2007) *Immunology of Fungal Infections*. Dordrecht: Springer

Cambi A, Gijzen K, de Vries LJM, Torensma R, Joosten B, Adema GJ, Netea MG, Kullberg BJ, Romani L, Figdor CG (2003) The C-type lectin DC-SIGN (CD209) is an antigen-uptake receptor for *Candida albicans* on dendritic cells. Eur J Immunol 33: 532-538

Cheng S-C, van de Veerdonk FL, Lenardon M, Stoffels M, Plantinga T, Smeekens S, Rizzetto L, Mukaremera L, Preechasuth K, Cavalieri D, *et al* (2011) The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of *Candida albicans*. J Leukoc Biol 90: 357-366

Chitnis AS, Magill SS, Edwards JR, Chiller TM, Fridkin SK, Lessa FC (2012) Trends in Candida central line-associated bloodstream infections among NICUs, 1999–2009. Pediatrics 130: e46-e52

Choi EH, Foster CB, Taylor JG, Erichsen HC, Chen RA, Walsh TJ, Anttila V-J, Ruutu T, Palotie A, Chanock SJ (2003) Association between chronic disseminated candidiasis in adult acute leukemia and common IL4 promoter haplotypes. J Infect Dis 187: 1153-1156

Darnell JE, Kerr LM, Stark GR (1994) Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellularsignaling proteins. Science 264: 1415-1421

Das I, Nightingale P, Patel M, Jumaa P (2011) Epidemiology, clinical characteristics, and outcome of candidemia: experience in a tertiary referral center in the UK. Int J Infect Dis 15: e759-e763

Davis SD, Schaller J, Wedgwood RJ (1966) Job's syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet 1: 1013-1015

de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, Bernuth von H, Samarina A, Jannière L, *et al* (2008) Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med 205: 1543-1550

Depner M, van de Veerdonk F, Wanders J, Stauss H, Raabe J, Atkinson TP, Schroeder HW Jr, Niehues T, Duckers G, Puck J, *et al* (2012) Mutation screening in STAT1, CARD9 and PKC-delta in patients with chronic mucocutaneous candidiasis. J Clin Immunol 32: S334-S335

Donlan RM, Costerton JW (2002) Biofilms: survival mechanisms of clinically relevant microorganisms. Clin Microbiol Rev 15: 167-193

Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, Chen A, Kim HS, Lloret MG, Schulze I, *et al* (2009) Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol 124: 1289.e4-1302.e4

Fan Y-C, Li W-G, Zheng M-H, Gao W, Zhang Y-Y, Song L-J (2012) Invasive fungal infection in patients with systemic lupus erythematosus: experience from a single institute of Northern China. Gene 506: 184-187

Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spriel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C, *et al* (2009) Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 361: 1760-1767

Fortún J, Martín-Dávila P, Gómez-García de la Pedrosa E, Pintado V, Cobo J, Fresco G, Meije Y, Ros L, Alvarez ME, Luengo J, *et al* (2012) Emerging trends in candidemia: a higher incidence but a similar outcome. J Infect 65: 64-70

Giraldo PC, Babula O, Gonçalves AKS, Linhares IM, Amaral RL, Ledger WJ, Witkin SS (2007) Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. Obstet Gynecol 109: 1123-1128

Glocker E-O, Hennigs A, Nabavi M, Schäffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, *et al* (2009) A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 361: 1727-1735

Glöckner A (2011) Recurrent candidaemia and pacemaker wire infection with *Candida albicans*. Mycoses 54: 20-23

Gow NAR, van de Veerdonk FL, Brown AJP, Netea MG (2011) *Candida albicans* morphogenesis and host defence: discriminating invasion from colonization. Nat Rev Microbiol 10: 112-122

Grabar S, Lanoy E, Allavena C, Mary-Krause M, Bentata M, Fischer P, Mahamat A, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French

Hospital Database on HIV. (2008) Causes of the first AIDS-defining illness and subsequent survival before and after the advent of combined antiretroviral therapy. HIV Med 9: 246-256

Gross O, Gewies A, Finger K, Schäfer M, Sparwasser T, Peschel C, Förster I, Ruland J (2006) Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. Nature 442: 651-656

Heinsbroek SEM, Taylor PR, Martinez FO, Martinez-Pomares L, Brown GD, Gordon S (2008) Stage-specific sampling by pattern recognition receptors during *Candida albicans* phagocytosis. PLoS Pathog 4: e1000218

Hirata O, Tsumura M, Mizoguchi Y, Okada S, Minegishi S, Morio T, Kobayashi M (2012) Gain-of-function mutations of STAT1 in Japanese patients with CMCD. J Clin Immunol 32: S104-S105

Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, *et al* (2007) STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 357: 1608-1619

Johnson MD, Plantinga TS, van de Vosse E, Velez Edwards DR, Smith PB, Alexander BD, Yang JC, Kremer D, Laird GM, Oosting M, *et al* (2012) Cytokine gene polymorphisms and the outcome of invasive candidiasis: a prospective cohort study. Clin Infect Dis 54: 502-510

Jouault T, Ibata-Ombetta S, Takeuchi O, Trinel P-A, Sacchetti P, Lefebvre P, Akira S, Poulain D (2003) *Candida albicans* phospholipomannan is sensed through toll-like receptors. J Infect Dis 188: 165-172

Jurevic RJ, Bai M, Chadwick RB, White TC, Dale BA (2003) Single-nucleotide polymorphisms (SNPs) in human beta-defensin 1: high-throughput SNP assays and association with Candida carriage in type I diabetics and nondiabetic controls. J Clin Microbiol 41: 90-96

Lalor SJ, Dungan LS, Sutton CE, Basdeo SA, Fletcher JM, Mills KHG (2011) Caspase-1-processed cytokines IL-1β and IL-18 promote IL-17 production by γδ and CD4 T cells that mediate autoimmunity. J Immunol 186: 5783-5784

Lanternier F, Pathan S, Vincent Q, Liu L, Cypowij S, Prando C, Migaud M, Taibi L, Ammar-Khodja A, Stambouli OB, *et al* (2012) Human invasive dermatophytic disease is caused by inborn errors of CARD9. J Clin Immunol 32: S94

Leentjens J, Kox M, Koch RM, Preijers F, Joosten LAB, van der Hoeven JG, Netea MG, Pickkers P (2012) Reversal of immunoparalysis in humans in vivo: a double-blind, placebo-controlled, randomized pilot study. Am J Respir Crit Care Med 186: 838-845

Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS (2009) Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol 200: 303.e1-303.e6

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

Liu L, Okada S, Kong X-F, Kreins AY, Cypowyj S, Abhyankar A, Toubiana J, Itan Y, Audry M, Nitschke P, *et al* (2011) Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 208: 1635-1648

Ma CS, Chew GYJ, 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: 1551-1557

Martinez-Martinez L, Fuentes-Prior P, Herrera-Ramos E, Rubiales MV, Lopez-Rodriguez M, Barnadas M, Badell I, Rodriguez-Gallego C, la Calle-Martin de O (2012) A novel STAT1 muation responsible for chronic mucocutaneous candidiasis. J Clin Immunol 32: S314-S315

McGreal EP, Rosas M, Brown GD, Zamze S, Wong SYC, Gordon S, Martinez-Pomares L, Taylor PR (2006) The carbohydrate-recognition domain of Dectin-2 is a C-type lectin with specificity for high mannose. Glycobiology 16: 422-430

Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, *et al* (2008) Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 452: 773-776

Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, Takada H, Hara T, Kawamura N, Ariga T, *et al* (2006) Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 25: 745-755

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

Moreira I, Filardi L, Bravo Kleiman A, Seminario A, Ballve DD, Comas D, Gaillard MI, Gomez Raccio A, Di Giovanni D, Bezrodnik L (2012) Laboratory findings in three patients with gain-of-function mutations in STAT1. J Clin Immunol 32: S112-S113

Moyes DL, Runglall M, Murciano C, Shen C, Nayar D, Thavaraj S, Kohli A, Islam A, Mora-Montes H, Challacombe SJ, *et al* (2010) A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells. Cell Host Microbe 8: 225-235

Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, *et al* (1997) Positional cloning of the APECED gene. Nat Genet 17: 393-398

Nahum A, Bates A, Sharfe N, Roifman CM (2008) Association of the lymphoid protein tyrosine phosphatase, R620W variant, with chronic mucocutaneous candidiasis. J Allergy Clin Immunol 122: 1220-1222

Nahum A, Dadi H, Bates A, Roifman CM (2011) The L412F variant of Toll-like receptor 3 (TLR3) is associated with cutaneous candidiasis, increased susceptibility to cytomegalovirus, and autoimmunity. J Allergy Clin Immunol 127: 528-531

Nahum A, Dadi H, Bates A, Roifman CM (2012) The biological significance of TLR3 variant, L412F, in conferring susceptibility to cutaneous candidiasis, CMV and autoimmunity. Autoimmun Rev 11: 341-347

Netea MG, Gow NAR, Munro CA, Bates S, Collins C, Ferwerda G, Hobson RP, Bertram G, Hughes HB, Jansen T, *et al* (2006) Immune sensing of *Candida albicans* requires cooperative recognition of mannans and glucans by lectin and Toll-like receptors. J Clin Invest 116: 1642-1650

Netea MG, Brown GD, Kullberg BJ, Gow NAR (2008) An integrated model of the recognition of *Candida albicans* by the innate immune system. Nat Rev Microbiol 6: 67-78

Odds FC (1988) *Candida and Candidosis*, 2nd ed. London: Bailliere Tindall

Okada S, Kong XF, Cypowyj S, Kreins A, Liu L, Abel L, Picard C, Boisson-Dupuis S, Puel A, Casanova JL (2012) Gain-of-function mutations in STAT1 underlie autosomal dominant chronic mucocutaneous candidiasis. J Clin Immunol 32: S92-S93

Ortega M, Rovira M, Almela M, Marco F, la Bellacasa de JP, Martínez JA, Carreras E, Mensa J (2005) Bacterial and fungal bloodstream isolates from 796 hematopoietic stem cell transplant recipients between 1991 and 2000. Ann Hematol 84: 40-46

Pearce SH, Cheetham T, Imrie H, Vaidya B, Barnes ND, Bilous RW, Carr D, Meeran K, Shaw NJ, Smith CS, *et al* (1998) A common and recurrent 13-bp deletion in the autoimmune regulator gene in British kindreds with autoimmune polyendocrinopathy type 1. Am J Hum Genet 63: 1675-1684

Plantinga TS, van der Velden WJFM, Ferwerda B, van Spriel AB, Adema G, Feuth T, Donnelly JP, Brown GD, Kullberg BJ, Blijlevens NMA, *et al* (2009) Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis 49: 724-732

Plantinga TS, Johnson MD, Scott WK, van de Vosse E, Velez Edwards DR, Smith PB, Alexander BD, Yang JC, Kremer D, Laird GM, *et al* (2012) Toll-like receptor 1 polymorphisms increase susceptibility to candidemia. J Infect Dis 205: 934-943

Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachée-Chardin M, Toulon A, Bustamante J, *et al* (2010) 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: 291-297

Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, *et al* (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 332: 65-68

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

Robinson MJ, Osorio F, Rosas M, Freitas RP, Schweighoffer E, Groß O, Verbeek JS, Ruland J, Tybulewicz V, Brown GD, *et al* (2009) Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. J Exp Med 206: 2037-2051

Rodríguez-Gallego JC, Ouederni M, Boisson-Dupuis S, Puel A, Picard C, Sologuren I, Bustamante J, Samarina A, Herrera-Ramos E, López-Rodríguez M *et al* (2012) Clincal features of candidiasis in patients with interleukin-12 receptor B1 deficiency. J Clin Immunol 32: S305

Rogers NC, Slack EC, Edwards AD, Nolte MA, Schulz O, Schweighoffer E, Williams DL, Gordon S, Tybulewicz VL, Brown GD, Reis e Sousa C (2005) Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity 22: 507-517

Rosentul DC, Plantinga TS, Oosting M, Scott WK, Velez Edwards DR, Smith PB, Alexander BD, Yang JC, Laird GM, Joosten LAB, *et al* (2011) Genetic variation in the dectin-1/CARD9 recognition pathway and susceptibility to candidemia. J Infect Dis 204: 1138-1145

Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung S-H, *et al* (2010) Dectin-2 recognition of α-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. Immunity 32: 681-691

Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 155: 1151-1164

Sharfe N, Dadi HK, Shahar M, Roifman CM (1997) Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. Proc Natl Acad Sci USA 94: 3168-3171

Shimoda K, Kato K, Aoki K, Matsuda T, Miyamoto A, Shibamori M, Yamashita M, Numata A, Takase K, Kobayashi S, *et al* (2000) Tyk2 plays a restricted role in IFNα signaling, although it is required for IL-12-mediated T cell function. Immunity 13: 561-571

Smeekens SP, Plantinga TS, van de Veerdonk FL, Heinhuis B, Hoischen A, Joosten LAB, Arkwright PD, Gennery A, Kullberg BJ, Veltman JA, *et al* (2011) STAT1 hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. PLoS ONE 6: e29248

Smeekens SP, Ng A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, Arts P, Verwiel ETP, Gresnigt MS, Fransen K, *et al* (2013) Functional genomics identifies type I interferon pathway as central for host defense against *Candida albicans*. Nat Commun 4: 1342

Sobel JD (2007) Vulvovaginal candidosis. Lancet 369: 1961-1971

Springer J, Chatterjee S (2012) *Candida albicans* prosthetic shoulder joint infection in a patient with rheumatoid arthritis on multidrug therapy. J Clin Rheumatol 18: 52-53

Strasser D, Neumann K, Bergmann H, Marakalala MJ, Guler R, Rojowska A, Hopfner K-P, Brombacher F, Urlaub H, Baier G, *et al* (2012) Syk kinase-coupled C-type lectin receptors engage protein kinase C-δ to elicit card9 adaptor-mediated innate immunity. Immunity 36: 36-42

van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LAB, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CAA, *et al* (2011) STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med 365: 54-61

Van der Graaf CAA, Netea MG, Morré SA, Heijer Den M, Verweij PE, van der Meer JWM, Kullberg BJ (2006) Toll-like receptor 4 Asp299Gly/Thr399Ile polymorphisms are a risk factor for Candida bloodstream infection. Eur Cytokine Netw 17: 29-34

Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, Doyen C, Lebeau B, Spence D, Krcmery V, *et al* (1999) Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 28: 1071-1079

Wells CA, Salvage-Jones JA, Li X, Hitchens K, Butcher S, Murray RZ, Beckhouse AG, Lo Y-L-S, Manzanero S, Cobbold C, *et al* (2008) The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to *Candida albicans*. J Immunol 180: 7404-7413

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: 309-317

Woehrle T, Du W, Goetz A, Hsu H-Y, Joos TO, Weiss M, Bauer U, Brueckner UB, Marion Schneider E (2008) Pathogen specific cytokine release reveals an effect of TLR2 Arg753Gln during Candida sepsis in humans. Cytokine 41: 322-329

Yamasaki S, Ishikawa E, Sakuma M, Hara H, Ogata K, Saito T (2008) Mincle is an ITAM-coupled activating receptor that senses damaged cells. Nat Immunol 9: 1179-1188