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PEDIATRIC FUNGAL INFECTIONS (D CORZO LEON, SECTION EDITOR)

STAT Immunodeficiency Disorders and Fungal Infection Susceptibility

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Abstract

Purpose of Review Invasive fungal diseases (IFD) or complicated mucocutaneous fungal infections can occur secondary to both primary and acquired immunodeficiency disorders. The signal transducer and activator of transcription (STAT) proteins are critical transcription factors involved in a wide range of processes including the immune response. This review highlights the immune pathways, clinical phenotypes and current management options of fungal infections in patient with mutations in STAT1 and STAT3, the most relevant STAT molecules involved in the host response to fungal pathogens.

Recent Findings STAT1 gain of function (GOF) and STAT3 loss of function (LOF) (cause of autosomal dominant Hyper IgE syndrome) mutations have been associated with both chronic mucocutaneous candidiasis (CMC) and invasive fungal infections, not only inhaled moulds, mostly *Aspergillus* spp., but also *Pneumocystis*, *Cryptococcus* and other endemic dimorphic fungi. Significant progress has been made in the insights into the immunopathogenesis of fungal infections in these patients; nevertheless, the concrete mechanisms involved are still not fully elucidated. Early initiation of antifungal therapy followed by long-term secondary prophylaxis is normally required. Some adjunctive therapies have also been employed, although their use has not been completely established.

Summary Besides a developing knowledge in STAT1 GOF and STAT3 LOF mutations, additional research is needed. It should aim for a better understanding of the pathogenesis, diagnosis, and management of fungal infections in these patients. The identification of new therapeutic targets should help to improve patient quality of life and outcomes.

Keywords Fungal Infections · STAT · CMC · HIES-AD

Introduction

Globally, over a billion people are affected with fungal infections, with an estimated mortality of 1.5 million cases a year [1]. Both acquired and congenital immunodeficiencies can potentially result in an increased susceptibility to suffer from invasive fungal diseases (IFD) or complicated mucocutaneous fungal infections. The clinical presentation of these infections in immunocompromised hosts are variable, even within the same group of immunodeficiencies, indicating that other factors likely contribute to the observed heterogeneity [2]. In this context, fungal infections are often associated with a significant morbi-mortality if they are timely diagnosed and treated [3, 4•]. Prolonged antifungal prophylaxis and treatment regimens are indicated in many patients; however, these strategies are associated with an increased risk of side effects, drug interactions or the development of resistances.

Mucocutaneous and systemic fungal infections have been reported in several primary immunodeficiencies (PIDs) such

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as inborn errors of the oxidative burst (e.g. chronic granulomatous disease); disorders of cytokine signaling (e.g. IL-12/IFNg, IL-17, ACT1, RAG1/2) or disorders of signalling molecules (e.g. CARD9, Dectin, DOCK8, CD40L, NEMO) [4•].

In this review, we focus on the group of disorders related to the signal transducer and activator of transcription (STAT) proteins and, here in particular, on mutations in STAT1 and STAT3 as these are to date the most relevant STAT molecules involved in the host response to fungal pathogens. We aim to describe the most relevant underlying molecular mechanisms, immunopathogenesis, clinical manifestations as well as currently available therapies. Mutations in other relevant transcription factors such as GATA2, AIRE, IRF8 or proteins in the PID groups mentioned above will not be covered in this article but have been previously depicted in excellent reviews [4•, 5–7].

Overview of the STAT Proteins in Health and Disease

The STAT proteins are critical transcription factors involved in the regulation of a broad range of physiologic processes including the immune responses. Soluble signalling molecules such as interferons (IFNs), cytokines, growth factors, and hormones activate the STATs after binding to their corresponding receptor, which is linked to the Janus kinase (JAK) [8•, 9–11]. Subsequently, STAT homodimers circulating in the cytoplasm form homo- or heterodimers allowing their translocation into the nucleus, the binding to specific promoter elements and the initiation of the corresponding transcription programs [10]. Seven STAT proteins have been described: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [10, 12]. Somatic or inherited germline mutations with gain-of-function or loss-of-function characteristics have been reported for many of these proteins and were shown to increase the risk of infection susceptibility, higher risk of malignancy, autoimmunity and autoinflammation [8•].

The STAT Proteins

STAT-1

STAT1 is required for signalling of all types of interferons (α, β, γ, ω, λ). Immunodeficiencies related to mutations in the *STAT1* gene that result in a partial or complete loss-of-function have been described [13–15]. In general, complete loss of activity of STAT1 due to autosomal recessive (AR) mutations is part of the Mendelian susceptibility to mycobacterial disease group [15]. These patients show a severe phenotype and suffer from often lethal intracellular bacteria as well as viral and fungal infections; specially *Candida* spp., although other dimorphic fungi have also been described [13–15, 16•]. Patients with partial (AD or AR) STAT1 expel a less severe phenotype. A more detailed description of these pathologies is beyond the scope of this article, and the reader is referred to an outstanding review that provides a comprehensive overview of STAT1 related pathologies [16•].

Sequencing of patients and families with early onset chronic mucocutaneous candidiasis (CMC) revealed variants in the STAT1 gene that subsequently were shown to have gain-of-function (GOF) characteristics [17, 18]. The careful collection of clinical data showed that these patients display an extremely broad phenotype that ranges from autoimmunity or autoinflammatory features, malignancies and lymphoproliferation and an increased susceptibility to infection with (myco-) bacteria, virus, parasites and fungi. When focusing on fungal infections in these patients, childhood-onset CMC is by far the most characteristic clinical presentations and the most common genetic cause of CMC [19•]. Importantly, other disseminated IFD, such as coccidioidomycosis, disseminated histoplasmosis, or infections due to inhalation of moulds in the absence of structural lung diseases have been reported in STAT1 GOF [15, 20, 21].

Most pathogenic STAT1 variants have been found in the DNA-binding and SH2 domain, and although the number of patients identified to have a disease causing STAT1 GOF mutation is steadily crowing, no evidence of any genotype-phenotype correlation has been observed yet [22].

Despite intensive research in the last decade, the pathophysiologic mechanisms that lead to the observed fungal susceptibility still remain to be identified. Several groups have described reduced IL-17 production as the most likely link to fungal susceptibility [17, 18]. However, the concrete connection between hyperphosphorylated STAT1 and diminished IL-17 production remains to be elucidated.

In response to a cytokine signal (e.g. IFNg) hyperphosphorylation of STAT1 (pSTAT1) can be observed. Mechanistically, impaired nuclear dephosphorylation [23] or an overall increased cytoplasmic or nuclear availability of total STAT1 protein have been proposed as responsible for the characteristic increase of STAT1 tyrosine phosphorylation [21, 22]. Several groups have found STAT1 downstream effectors such as CXCL9 and CXCL10 to be up-regulated in these patients [23]. In a recent study dysregulated STAT1 signalling resulted in an up-regulation of PD-L1, a protein shown to be associated with impaired Th17 differentiation in mice [24]. The same study observed reduced expression of SOCS3 (a protein downstream of STAT1 and STAT3 which is involved in a negative feedback loop of these two STAT molecules). The authors proposed that the disbalance of (high) STAT1 and (low) STAT3 might result in a reduced STAT3-dependent Th17 gene transcription [24]. Recently, Weinacht et al. provided supporting data for this hypothesis as they found, in a more clinically orientated study, that patients with

STAT1 GOF displayed alterations in the T cell compartment favouring the development of TH1 and follicular helper cells over Th17 differentiation [25•].

In patients with STAT1 GOF mutations routine laboratory testing such as lymphocytes subpopulations (T, B and NK cells) and immunoglobulin isotype levels are often normal [19•]. More advanced profiling has shown overall low Th17 (75–82%) and memory B cells (about 50%) as well as low IgG2 (38%) and IgG4 (50%) [19•]. Progressive loss or impairment of B cells is not uncommon and warrants to include immunologic testing and monitoring the in routine follow-up.

In vitro stimulation assays determined via flow cytometry pSTAT1 expression in primary cells (most commonly monocytes) are considered the "gold-standard" for patients with a not previously validated variant in STAT1 [23]. As the performance of these test may vary, it seems prudent to collaborate with experienced groups or research institutions to ensure the correct interpretation of the results.

STAT-3

STAT3 is a fundamental transcription factor which expression is not only limited to hematopoietic tissues. A number of soluble signalling molecules (e.g. IL-6 and IL-10) induce the canonical STAT3 pathway [8, 9, 26]. Similar to STAT1, cytoplasmic monodimers are subsequently recruited to the JAK receptor, transformed into homo- or heterodimers and then translocate to the nucleus. Following its role as a transcription factor, STAT3 docks to the DNA inducing or repressing the corresponding transcription programs related to cell proliferation, apoptosis and (immune) cell differentiation [8, 27, 28]. Dominant negative loss-of-function (LOF) mutations in STAT3 cause the autosomal dominant hyper-IgE syndrome (AD-HIES or Job's syndrome) [29•]; whereas gain-of-function (GOF) STAT3 mutations are associated with a complex multiorgan disorder reported to include features of immunodeficiency, autoimmunity, lymphoproliferation and/or malignancy [30].

In the last years, in-depth analysis and the careful study of patients with AD-HIES helped to confirm or extend our knowledge of the STAT3 functions. Despite normal fractions of $CD4^+$ and $CD8^+$ T-cell populations, there is decreased humoral and cellular immune response to new antigens [27]. Furthermore, STAT3 is known to regulate the transcription of elements for the promotion and development of IL-17 producing $CD4^+$ T cells (Th17), involved in the host defence of *S. aureus* and *Candida* spp. [31••]. AD-HIES is a multisystem disorder characterized by skin abscesses with recurrent staphylococcal infections of the skin and lungs, formation of pneumatocele, CMC, eosinophilia and elevated serum levels of IgE. Other non-immunologic features of HIES include characteristic facial appearance, scoliosis, retained primary teeth, joint hyperextensibility and bone fractures following minimal trauma [5, 10, 32].

The adequate prevention and control of pulmonary infections, initially due to common bacteria such as *S. aureus* or *S. pneumoniae*, is fundamental in order to avoid the detrimental structural tissue damage. Importantly, inflammatory responses such as fever or inflammatory markers are often normal even in cases of clearly pyogenic lung infections [33]. Once lung tissue damage is established, inhalation of moulds can result in the development of IFD (about 30% of patients) being invasive aspergillosis the most common. Case series have also reported allergic bronchopulmonary aspergillosis (ABPA)-like presentation [34]. Infections caused by intracellular dimorphic fungi occur rather rarely [3, 35, 36]. Mortality varies depending on cohorts, from 7.7% in a French cohort up to 16.7% in the American cohort [34, 37, 38••], and recent data from the USIDNET indicates that the pulmonary function of patients is related to reduced quality of life and important comorbidities such as depression [38••].

Although raised IgE levels (>2000 IU/ml) and eosinophilia are the most common feature in patients with AD-HIES routine, immunological investigations such as lymphocyte subsets and immunoglobuline levels (other than IgE) are often normal [38••, 39, 40]. A more in-depth study of the immune function may detect cell type-specific alterations such as reduced Th17, central memory T, follicular T helper, CD27+ memory B and plasma cells. Furthermore, a considerable number of patients also show reduced specific antibody response capacity [31, 39, 41, 42].

Clinical Phenotypes of fungal Infections

Chronic Mucocutaneus Candidiasis

CMC is defined by recurrent or persistent symptomatic mucocutaneous infections caused by *Candida* spp., predominantly *Candida albicans,* affecting the nails, skin, oral cavity, and genital mucosa [43]. As described above, syndromic CMC is one of the most common infectious disease manifestations in patients with AD-HIES, as well as STAT1 GOF [44, 45]. Other conditions such as AR autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or AR CARD9, IL-12 receptor β1 (IL-12Rβ1), IL-12p40 or RORγT deficiencies also develop CMC as one of the main clinical manifestation [5, 20, 35]. This specific condition is defined as "syndromic" CMC and occurs in association with impaired IL-17 immunity [20, 46]. In contrast with syndromic CMC, CMC disease (CMCD) refers to patients presenting with CMC as the major clinical phenotype, and its aetiology is related neither to genes known to cause severe combined nor combined immunodeficiency, nor genes responsible for syndromic CMC. Patients with syndromic CMC can present oral

candidiasis from the neonatal period onwards in up to 64% of these cases [47, 48••].

CMC is very common in patients with STAT1 GOF; and in fact, mutations in this gene will be found in 50% of patients with CMC [49]. Most of these patients present their first episode in the first years of life. The oral mucosa is the most common localization (73-93%), followed by oesophageal and vulvovaginal involvement (approximately 56–65%) and skin and nails (50–57% and 56–64%, respectively) [19•, 49]. Although no systematic studies have been performed, recalcitrant CMC likely results in a diminished quality of life, and recent data suggests that prolonged CMC is at least in part responsible for the increased risk to develop squamous cell carcinomas (6%) of the upper gastrointestinal tract [19•, 50]. For patients with CMC independently of the genetic aetiology, it seems reasonable to recommend clinical follow-up and routine screening for this type of malignancies.

Approximately 85% of patients with AD-HIES develop CMC [46]. Similar to STAT1 GOF, patients are diagnosed with oral (63%), genital (18%), cutaneous (16%) and oesophageal (8%) candidiasis or chronic onychomycosis [6, 20, 46].

Invasive Fungal Diseases

IFDs have been described in STAT1 GOF, but less frequently (10%) than CMC [19•]. Invasive mould infections cause pulmonary disease in the absence of structural lung disease [5]. Dimorphic fungi (endemic mycosis), such as disseminated coccidioidomycosis and histoplasmosis have been reported in patients with heterozygous STAT1 GOF mutations [2, 19].

Approximately 20% of AD-HIES patients develop invasive aspergillosis, virtually always secondary to lung lesions (bronchiectasis or pneumatocyst) [6]. To date, most experts agree on the hypothesis that the underlying tissue repair abnormalities are most likely responsible for the predisposition to develop fungal infections (typically *Aspergillus* or *Scedosporium* spp.) as well as gram-negative bacterial infections (e.g. *P. aeruginosa*) [33, 36, 40]. In patients with AD-HIES, the pneumonias typically respond appropriately to antibiotics, but lung healing is aberrant and development of pneumatoceles and bronchiectasis is common [34]. In addition and unlike in CGD, a normal phagocytosis capacity against *A. fumigatus* has been described for AD-HIES patients [6, 51]. Disseminated aspergillosis with central nervous system involvement and formation of mycotic aneurysms has been reported in a number of cases [3]. In a recent autopsy case series [37], also *Scedosporium prolificans* was isolated from lung and brain lesions of an AD-HIES patients.

In AD-HIES, systemic *Candida* spp. infections are rare and occurred mostly in the setting of nosocomial acquired infections [3, 36, 40]. The localization is variable and cases of endocarditis, endophthalmitis, visceral candidiasis and disseminated disease with multiple pulmonary nodules, hepatic lesions as well blood stream infections have been reported [3].

Other infections such as disseminated *Cryptococcus* and *Histoplasma* infections can occur in the context of AD-HIES, although less frequently than invasive candidiasis [20, 36, 52]. *Pneumocystis jiroveci* pneumonia (PCP) occurs infrequently and may present in infants in a way similar to the initial presentation of PCP in infants infected with HIV [51, 53]. To date, it remains uncertain whether PCP is occurring in HIES secondary to immunologic abnormalities or, similar to aspergillosis, only in the context of a previously established lung tissue damage. Overall, most experts recommend to include PCP in the differential diagnosis of a suspected pneumonia in patients with HIES [53, 54].

Prophylaxis and Treatment

Although formal trials are lacking, most experts recommend antifungal prophylaxis in those AD-HIES patients with signs of structural damage of the lung tissue in order to prevent pulmonary aspergillosis (AIII) [51]. As primary prophylaxis, itraconazole is the most frequently prescribed antifungal agent, but once lung damage has been observed, switch to posaconazole should be considered [33, 36, 40, 55, 56], due to its high intrapulmonary penetration.

STAT1 GOF patients with recurrent or severe CMC episodes should receive fluconazole prophylaxis, and it is usually highly effective (AIII) [57]. Same regimes are employed to control CMC episodes in AD-HIES patients [55, 57]. Only scarce data exists regarding the highly relevant clinical question whether fluconazole continuously is superior to intermittent treatment regimens. Some experts recommend the latter as it appears to avoid the development of azole resistances or decreased susceptibility to azoles [44, 58]. Immunoglobulin substitution is often used in patients with recurrent airway infections and signs of humoral immunodeficiency such as reduced antibody responses or low Immunoglobulin levels [59].

Early initiation and prolonged antifungal therapy is the backbone in the management of fungal diseases in patients with an underlying immunodeficiency, but an increased knowledge of the pathogenesis of PID has helped to develop adjunctive therapies. If possible, an infectious disease specialist should be involved in the management of these patients. Currently, triazoles are the first line in cover and long-term treatment for most infections in these patients. Therapeutic drug monitoring, sensitivities profile, tissue drug penetration and toxicity profile need to be considered aiming to provide the most appropriate treatment strategy. Once initial remission has been achieved, premature discontinuation of antifungal treatment may result in relapses; therefore, secondary antifungal prophylaxis has been recommended in many case [60••]. For CMC, both topical and systemic treatment may be

indicated; topical treatment with combined polyenes (nystatin and amphotericin B lozenges) has been proposed, with a limitation on the courses of systemic azoles to 2–3 a year [44].

In the setting of STAT1 GOF, primary adjunctive immune-based therapies with JAK inhibition (ruxolitinib, baricitinib and tofacitinib) or granulocyte colony stimulating factors have been successfully employed in patients with refractory of treatment resistant CMC [59, 61, 62]. Although evidence is growing that JAK inhibition is effective for the control of CMC, its use still remains under investigations. The currently available data indicates that its effect is transitory and that long-term therapy is likely necessary [63]. Furthermore, it should be used with caution as a number of reports showed a worsening of IFD as well as viral infections or viral reactivations [25•, 59, 63, 64]. Some experts therefore recommend to consider antiviral prophylaxis and to monitor frequently while on JAK inhibitor therapy [56]. Importantly, the combination of azoles and JAK inhibitors should be avoided as these groups of antifungals increase the JAK-inhibitor levels and its toxicity remarkably [65].

Inhibitory molecules targeting histone deacetylases (HDACi, entinostat or RGFP966) have been also reported as possible candidates to be explored for patients with CMC and STAT1 GOF [66]. Other treatment options for CMC patients described in the literature include topical treatment with IV IgG mouthwash in combination with conventional antifungal therapy [67].

Some patients may require haematopoietic stem-cell transplantation (HSCT). HSCT has been performed in patients with STAT1 GOF. Although the numbers of transplants are low and many patients had treatment refractory disease manifestations, the overall results are rather disappointing with only 40% of survival as a result of graft failure and rejection [68•]. Previous JAK-inhibitor therapy might help to control and restore the pro-inflammatory cytokine profile pre-transplant that has been shown to be deleterious in other IFNg-related immunodeficiencies such as IFNGR deficiency [69].

Patients with AD-HIES have received HSCT aiming to cure or prevent clinical manifestations including fungal infection susceptibility with mixed results. Unfortunately, this approach has not resulted in a sustained clinical benefit which is likely due to STAT3 deficiency-related defects in non-hematopoietic tissues. Importantly, a recent study from the UK reported 8 patients receiving HSCT with a more favorable outcome. However patients should be selected carefully and in close collaboration with highly experienced PID transplant centers [70•, 71].

Conclusions

Fungal infections are well-defined clinical manifestations in patients with STAT1 GOF as well as patients with AD-HIES. Although significant progress has been made in the understanding of the immunopathogenesis, the concrete mechanisms involved are still to be elucidated. This is even more important in light of the limited prophylaxis and long-term treatment options, as well as the high impact that these infections have on the quality of life. Furthermore, many currently recommended regimens are related to an increased toxicity and drug interactions, further complicating the management of these complex patients. Thus, future research should aim to identify new drug targets that may be specific for each patient group. Well-designed clinical trials are necessary to find the most appropriate prophylactic and therapeutic strategies. Due to the low numbers of patients with STAT associated disorders this can only be achieved within well designed international collaboration studies.

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Peter Olbrich and Laura Ferreras-Antolin declare no conflicts of interest relevant to this manuscript.

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