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FUNGAL GENOMICS AND PATHOGENESIS (S SHOHAM, SECTION EDITOR)

Pathogenesis of Coccidioidomycosis

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Abstract Coccidioidomycosis is a systemic fungal infection endemic to the American Southwest, caused by *Coccidioides immitis* and *Coccidioides posadasii.* The infection has a wide variety of clinical manifestations in humans, from asymptomatic infection to severe disease. Infection occurs through inhalation of fungal spores, leading to primary pulmonary infection and occasionally to hematogenous dissemination to other sites. Both fungal and host factors contribute to pathogenesis of this infection. Cellular and innate immune responses are involved in the protective response in both humans and mice. This review summarizes recent research on microbial and host factors involved in the pathogenesis of coccidioidomycosis.

Keywords *Coccidioides* · Coccidioidomycosis · Innate and adaptive immunity · Virulence factors · Systemic fungal infection · Fungal infection · Coccidioidomycosis pathogenesis · Fungal pathogenesis

Introduction

Coccidioidomycosis (Valley fever, San Joaquin Valley fever) is a systemic fungal infection caused by two fungal species, *Coccidioides immitis* and *Coccidioides posadasii*, which are endemic in certain parts of the southwestern USA, central California, and northern Mexico. While most human infection is asymptomatic and results in long-lived immunity, coccidioidal infection can also be associated with a wide range of clinical syndromes from community-acquired pneumonia to severe disease disseminated beyond the thoracic cavity. Here, we review recent advances in our understanding of the pathogenesis of coccidioidomycosis, with an emphasis on the immune response both in humans and in murine models.

In the vast majority of cases, infection is initiated when fungal spores called arthroconidia, present in soil or the air, are inhaled. Approximately 60 % of all infections are asymptomatic [1]. For patients who do become ill, the most common manifestation is pneumonia, which develops 1–3 weeks after inhalation and may be clinically and radiographically indistinguishable from community-acquired pneumonia due to other causes. As much as one third of the cases of community-acquired pneumonia in highly endemic regions may be caused by *Coccidioides* spp. [2, 3]. About 0.5 % of all infected persons will develop disease outside the lungs [4]. The most common site of dissemination is the skin, followed by the bones and/or joints. Meningitis is the least common manifestation of extrathoracic dissemination but is also the most serious form of coccidioidomycosis. Human-to-human transmission does not occur.

Both asymptomatic cases and those who become symptomatic appear to acquire long-lasting protection from reinfection [5]. Although coccidioidal infections produce antibodies, protection appears to depend on cellular and innate immune responses. Suppression of cellular immunity, as by high-dose corticosteroids, cancer chemotherapy, organ transplantation, or HIV infection, is well recognized to cause reactivation of prior coccidioidal infection. Such reactivation is very rare in the absence of immune suppression.

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Microbial Pathogenesis and Virulence

After inhalation, arthroconidia are deposited in the terminal bronchioles, where they enlarge and remodel to form spherules. Within the spherule, internal septations develop containing endospores. The spherule wall ruptures, releasing the endospores to infect nearby tissue or spread elsewhere in the body, where they develop into spherules and continue the parasitic cycle. Spherule rupture induces a local inflammatory response with infiltration of neutrophils and eosinophils. As endospores mature into spherules, a granulomatous response develops with B and T lymphocytes and macrophages [6].

Virulence factors include an immunodominant antigen present on the spherule outer wall, SOWgp, which stimulates both antibody-mediated and CD4+ T cell immune responses. Mutants of *C. posadasii* deficient in this antigen showed attenuated virulence in a mouse model [7]. Further, an enzyme responsible for the digestion of SOWgp, Mep1, is also an important virulence factor. It is expressed during endospore formation and is thought to degrade SOWgp when endospores are released from the spherule, preventing efficient recognition of the endospore by the host during this stage [8]. Indeed, deletion of the *MEP1* gene from *Coccidioides* improved the survival of infected mice. It has recently been found that *MEP* genes of *Coccidioides* species show evidence of rapid functional divergence and positive selection, suggesting their importance to host immune system interaction or survival in the environment [9].

Coccidioides infection induces the host enzyme arginase I, which hydrolyzes L-arginine to L-ornithine and urea. It competes for the L-arginine substrate with nitric oxide synthase, leading to decreased nitric oxide levels in macrophages. In addition, cultures of *Coccidioides* have been found to produce a soluble factor that inhibits nitric oxide production by murine macrophages in vitro [10]. However, macrophages from mice deficient in nitric oxide synthase were able to phagocytose and kill fungal cells as efficiently as those from wild-type mice. When infected with *Coccidioides* by inhalation of arthroconidia, mice deficient in nitric oxide synthase showed similar survival and fungal burden in their lungs and spleens as wild-type mice [11]. These results suggest that unlike many fungal pathogens, *Coccidioides* does not use reduction in nitric oxide production to improve intracellular pathogen survival.

Arginase activity also results in a high level of urea, which is hydrolyzed by coccidioidal urease to produce ammonia. Ammonia increases the pH of the environment, which is proposed to be damaging to host tissue and also compromise the cellular immune response [7, 12•]. In addition, an alkaline environment is more optimal for the growth of *Coccidioides* spp. A strain deficient in urease showed reduced pathogenicity in mice and evidence of a more robust host inflammatory response at sites of lung infection [7, 13]. More recently, disruption of an additional ammonia production pathway, allantoin catabolism, was shown to reduce virulence in mice, especially when combined with a urease deletion [12•].

Immunity to *Coccidioides* in Mice and Humans

Murine Studies

Previous murine and human studies have suggested that both cellular immunity and innate immune responses play an important role in controlling coccidioidal infection and in preventing illness upon reinfection [14]. However, mice appear to respond to coccidioidal infection differently than humans. In experimental murine systems, dissemination beyond the lungs is common and death occurs rapidly after intranasal injection of even a small number of arthroconidia, events that are unusual in humans. Moreover, different strains of mice have different susceptibilities to coccidioidal infection, with the C57BL/6 mouse strain being particularly susceptible [15]. Despite these issues, murine studies have done much to illuminate the mechanisms of host defense against coccidioidomycosis.

There have been several recent publications examining the response to coccidioidomycosis using the murine model, and these have deepened our understanding of the mammalian immune response to coccidioidal infection. For example, Wüthrich and colleagues created a transgenic mouse using the α- and β-chains of the T cell receptor (TCR) cloned from a CD4+ T cell line that is responsive to a protective epitope of *Blastomyces dermatiditis*. They found that this TCR also responds to a shared antigen in *C. posadasii* and that this was associated with the development of protective coccidioidal immunity after vaccination [16]. Hung and colleagues were able to enhance the vaccine response to an attenuated strain of *C. posadasii* by using an adjuvant that is an agonist of the C5a portion of complement, indicating the importance of vaccine adjuvants in enhancing vaccine efficacy [17]. These investigators also demonstrated that interleukin-10 impedes the initial immune response to coccidioidal infection but does not block the development of a memory response after vaccination [18]. In other work, Hurtgen and coworkers developed a novel vaccine by preparing a single polypeptide vaccine consisting of three immunodominant T cell epitopes from *C. posadasii* that resulted in a high degree of protection. These epitopes were originally identified using analysis of the primary structure of the original antigens and were predicted to bind to at least 80 % of the class II major histocompatibility complex (MHCII) molecules expressed by the 51 human HLA-DR alleles used in their computational algorithm. Because of this, this vaccine should have broad applicability in the general population [19]. Finally, Woelk and colleagues used a microarray technique to examine gene expression in

lung tissue among mice experimentally infected with *Coccidioides* [20]. In relatively resistant DBA/2 mice, genes related to interferon-mediated innate immune responses were upregulated compared to those in the highly susceptible C57BL/6 strain. Taken together, these studies support the primacy of the cellular immune response in control and subsequent protection in coccidioidomycosis.

Viriyakosol and colleagues have examined the innate receptors associated with recognition of *Coccidioides* and initiation of the cellular immune response. Mice deficient in Dectin-1, a C-type lectin (CLR) that binds to β-1,3-glucans, were found to be more susceptible to experimental pulmonary coccidioidal infection than wild-type mice [21]. In a follow-up study [22], the mannose receptor (MR), which binds terminal mannoses, was associated with binding of coccidioidal spherules by immune cells, an observation noted in humans [23]. On the other hand, Dectin-2, whose ligands are high mannose residues, was not. Neither a deficiency of MR nor of Dectin-2 was associated with increased mortality among C57BL/6 mice after experimental challenge with *Coccidioides*. On the other hand, Wang and colleagues, using a different model, found that both Dectin-1 and Dectin-2 bound *C. posadasii* [24]. These data suggest that the precise innate receptors responsible for initiation of the cellular immune response have yet to be fully defined.

There has been much recent focus on cellular signal transduction for activation of cytokine genes that initiates the immune response. In particular, the role of the cytokine interleukin-17A (IL-17A) and its conjugate cell type, the T-helper type 17 (Th17) cell, has been of intense interest. As noted by Wüthrich and coworkers [25•], IL-17 and Th17 cells participate in the host response to fungi during primary infections in non-immune hosts, but the literature is at odds as to whether Th17 cells play a helpful or harmful role. In their model examining the three major endemic fungi in North America, *Blastomyces dermatiditis*, *Histoplasma capsulatum*, and *C. posadasii*, they found that IL-17A and Th17 cells were required for the development of vaccine immunity but that T-helper type 1 (Th1) cells, which are associated with the release of interleukin-2 (IL-2) and interferon-γ (IFN-γ) were not. This group also examined the role of deletion of the caspase adaptor recruitment domain family member 9 (card9) gene, which encodes proteins involved in signal transduction for CLRs, on the development of a cellular immune response using the transgenic TCR mouse described above [24]. Card9 has been found to be important in fungal immunity [26]. They found that card9 was necessary for vaccine protection in coccidioidomycosis but not in resistance to primary infection. Hung and coworkers confirmed and expanded these findings by demonstrating that mice with knockout genes for myeloid differentiation factor 88 (MyD88), also part of the signaling pathway for CLRs and Toll-like receptors (TLRs), and card9 were unable to acquire protective immunity against coccidioidal challenge after vaccination of C57BL/6 mice [27]. These results emphasize the importance of signaling pathways on inducing protective coccidioidal immunity.

Human Studies

When compared to murine experiments, human studies are restricted in the type and scope of their immunological intervention, the relatively low number of subjects studied, and the lack of control over the genetic background of the subjects. Despite these constraints, these studies have offered insights into the host response to coccidioidomycosis. Moreover, the results are more directly applicable to patient care than murine experiments.

Several studies have examined ex vivo the cytokine response to coccidioidal antigens among patients with various forms of coccidioidomycosis. Nesbit and coworkers [28] used multiparametric flow cytometry of peripheral blood mononuclear cells (PBMC) incubated with T27K, a preparation containing multiple antigens derived from *C. posadasii* spherules, to ascertain whether the response was polyfunctional, where a single immune cell produces multiple Th1 cytokines. Such responses are considered indicative of a robust and protective cellular immune response [29]. The frequency of polyfunctional T cells, both CD4+ and CD8+, was significantly higher in PBMC from healthy donors with known coccidioidal immunity than in a group of donors without immunity. Incubation with macrophage-derived mature dendritic cells loaded with T27K did not increase this frequency.

This work was extended to examining the ex vivo cytokine response of bronchoalveolar cells from patients with pulmonary coccidioidomycosis [30]. To do this, mononuclear cells from bronchoalveolar lavage (BAL) fluid were incubated with T27K and the cytokine release pattern compared to that of PBMC from the same subjects. There were significantly more CD8+ polyfunctional T cells in the BAL fluid compartment among donors with a diagnosis of pulmonary coccidioidomycosis compared to subjects with other pulmonary diagnoses. Moreover, in cells collected from BAL fluid and from PBMCs, the concentrations of IFN-γ, tumor necrosis factor-α (TNF-α), and IL-17 were all significantly increased in samples from those with acute pulmonary coccidioidomycosis compared with the other subjects.

The finding of IL-17 led to a further study in which whole blood samples were obtained from patients with either pulmonary or non-meningeal disseminated coccidioidomycosis and incubated with T27K [31]. In addition to measurement of the release of IL-2, IFN-γ, and TNF-α, a highly sensitive assay for IL-17A was employed. While virtually no IL-17A was detected in asymptomatic control subjects, including those with prior coccidioidal immunity, it was routinely detected in samples both from those with pulmonary and disseminated coccidioidomycosis, even years after their initial diagnosis.

These data suggest that IL-17A is a marker for those with symptomatic coccidioidomycosis. Because IL-17A release was not seen in subjects who were asymptomatic and coccidioidal immune, it suggests that this cytokine could be a marker for a failure to develop a fully protective cellular immune response. This finding presents a possible contrast to the mouse model, in which IL-17 was required for the development of vaccine immunity.

The cellular immune system is not the only response in play during coccidioidomycosis. Lee and coworkers [32•] used a single-live-cell:single-target system to mimic, visualize, and analyze encounters of human neutrophils with *C. posadasii* endospores and spherules. Quiescent neutrophils were found to readily recognize *C. posadasii* particles without physical contact. Subsequent contact usually led to cell-to-target adhesion, followed by phagocytosis of the coccidioidal particle. Although the neutrophil response was vigorous, single neutrophils could not completely surround large spherules of *C. posadasii*. Neutrophils from patients with chronic coccidioidomycosis responded as strongly to *C. posadasii* endospores as those from healthy donors. These results are in contrast to earlier studies and suggest that neutrophils may play a role in the inflammatory response in coccidioidomycosis. The authors speculate that avoidance of long-range neutrophil recruitment is a key evasive strategy of *C. posadasii*.

Lessons from Human Immune Defects

Natural and iatrogenic immune defects in humans have provided insight into the pathogenesis of coccidioidomycosis. Examples include organ transplantation, use of tumor necrosis factor inhibitors and other biologic response modifiers, and genetic defects in interferon response pathways.

Organ transplantation requires administration of agents that suppress cell-mediated immunity, so it would be expected to impair host defense against *Coccidioides*. Transplant centers located in the endemic area have reported an incidence in solid organ transplant recipients of 1.4 to 6.9 % [33]. Some of the cases represent active (usually unrecognized) infection at the time of transplantation, and some represent reactivation of old disease, but a significant number are due to de novo acquisition of infection in the post-transplantation period. Acquisition of coccidioidomycosis via the donated organ is well documented, although rare [34]. Rates of disseminated infection and death are higher in transplant recipients than in the general population [33]. Attempts to identify specific risk factors (aside from prior infection) within the group of transplant recipients have found no relationship with age, sex, underlying organ disease, presence of acute rejection, or cytomegalovirus mismatch. The type of immunosuppressive regimen (most commonly tacrolimus, corticosteroids, and/or mycophenolate, with occasional use of cyclosporine, sirolimus, antithymocyte globulin, daclizumab, and/or basiliximab) has not been correlated with development of coccidioidomycosis [33, 35]. Accordingly, one experienced transplant infectious disease group in the endemic area has recently switched from a strategy of targeted antifungal prophylaxis to universal prophylaxis for liver transplant recipients. This strategy appears to be effective thus far in preventing new infections, although 9 % of patients experienced antifungal drug toxicity [36••].

Fewer data exist on coccidioidomycosis in hematopoietic stem cell transplantation. A recent retrospective study from the endemic area identified 11 cases among 426 allogenic transplant recipients (2.6 %) over a 10-year period. At the time of coccidioidomycosis diagnosis, 7 of 11 patients were on some type of immunosuppressive medication, including tacrolimus, mycophenolate, and/or prednisone. All but one patient had pulmonary coccidioidomycosis and the mortality rate was 55 % [37•].

Biologic response modifiers (BRM) are agents derived from biologic production systems that target and modify key components of the immune system. These include tumor necrosis factor-α (TNF) antagonists, anti-B cell therapy (rituximab), IL-1 receptor antagonists (anakinra), IL-6 antibody (tocilizumab), and soluble inhibitors of T cell activation, such as abatacept. Treatment with BRM is beneficial in rheumatologic and other autoimmune diseases but is associated with an increased risk of infection including endemic fungal infection. Three retrospective studies have reviewed coccidioidomycosis in patients with inflammatory arthritis. In the first cohort, 11 of 985 (1 %) patients developed symptomatic coccidioidomycosis; the risk of symptomatic coccidioidomycosis in patients treated with infliximab, a monoclonal antibody TNF antagonist, was higher compared to those without infliximab (relative risk 5.23, 95 % confidence interval 1.54–17.71; $p<0.01$) [38]. In the second cohort, 16 of 854 (1.9 %) patients developed symptomatic coccidioidomycosis; among 121 infliximab patients, the incidence of coccidioidomycosis was 2 and 12 %, at 1 and 5 years, respectively [39]. The third study addressed management of patients who developed coccidioidomycosis while taking disease-modifying antirheumatic drugs (methotrexate, azathioprine, or leflunomide) and/or BRM. Twenty-nine patients had pulmonary coccidioidomycosis, 9 had disseminated disease, and 6 had positive serologic tests but no symptoms. Most patients had their immunosuppressive medication discontinued at least temporarily, and almost all were treated with antifungal therapy. After a median of 30 months of follow-up, 33 patients had continued or resumed their immunosuppressive therapy, and half of them were no longer taking antifungal therapy. There were no cases of subsequent dissemination or development of severe coccidioidomycosis [40•]. These results suggest that some patients control coccidioidomycosis despite BRM use.

Until recently, specific genetic mutations had not been associated with an increased susceptibility to

coccidioidomycosis [41]. In 2009, a patient with widespread *Mycobacterium kansasii* infection and disseminated coccidioidomycosis was described to have an autosomal dominant mutation (818del4) in the gene for interferon (IFN)-γ receptor 1, leading to overaccumulation of truncated, nonfunctional receptors on the cell surface of monocytes [42]. Subsequently, two siblings with disseminated coccidioidomycosis were found to have a novel missense mutation in the interleukin (IL)-12 receptor resulting in a lack of receptor on the cell surface [43]. Finally, two patients with severe, progressive, non-cavitary pulmonary coccidioidomycosis as well as extrapulmonary disease were demonstrated to have gain-of-function mutations in STAT1, a downstream regulator of IFN-γ signaling, leading to hyperphosphorylation of STAT1, lower STAT1 methylation, and an impaired response to IFN-γ restimulation [44•]. These reports establish the importance of the IFN-γ/IL-12 axis in control of coccidioidomycosis, in addition to its previously known role in control of bacterial infections including nontuberculous mycobacteria and *Salmonella*.

Conclusions

Data continue to accumulate supporting the idea that *Coccidioides* pathogenesis depends upon both induction and avoidance of host immune responses [45]. Virulence factors of the fungus itself include the spherule outer wall glycoprotein, which stimulates host immune response, and also an enzyme responsible for reducing this stimulation. Host control of coccidioidomycosis requires cell-mediated immune responses. In mice, the innate immune response involves lectin receptors and the adaptive immune response involves both Th1 and Th17 cell types, although the precise contributions of each pathway are still being elucidated. In humans, the IL-17, TNF-α, and IFN-γ pathways are all important for control of infection. Patients with defects in their cellular immune response, either because of pharmacologic therapy or because of a gene mutation, appear to be at higher risk for developing symptomatic and severe coccidioidomycosis. These observations emphasize the role of the cellular immune response in controlling coccidioidal infection.

Compliance with Ethics Guidelines

Conflict of Interest Neil M. Ampel and Susan E. Hoover declare that they have no conflict of interest.

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.

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