Journal of
Clinical & Cellular Immunology
ISSN: 2155-9899

González, J Clin Cell Immunol 2013, S13
DOI: 10.4172/2155-9899.S13-001

Review Article
Open Access

Innate Immune Response to the Dimorphic Fungal Pathogen *Coccidioides*: Molecular and Cellular Mechanisms

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Abstract

Coccidioides spp is considered to be one of the most important fungal pathogen of humans. It is the causal agent of coccidioidomycosis, a systemic and endemic mycosis with a significant impact on public health, mainly in the United States, Central and South America. The host innate immune system appears to play an important role in the initial interaction and recognition of *Coccidioides* infection and the subsequent development of adaptive immunity. In this review article, I focus on the interaction between the innate immune response and *Coccidioides* in an attempt to increase our knowledge of the pathogenesis of this fungus.

Keywords: *Coccidioides* spp; Coccidioidomycosis; Innate immune response; *Toll*-like receptor (TLR)

Introduction

Coccidioidomycosis, commonly known as San Joaquin Valley fever, is a systemic and endemic mycosis caused by the dimorphic fungal pathogen *Coccidioides* spp. It is acquired by the inhalation of airborne fungal propagules (arthroconidia; spores) produced by the fungus saprobic phase, followed by the initiation of an elaborated parasitic cycle unique among the medically important fungi [1]. The spores undergo isotropic growth, giving rise to large multinucleate cells or "spherules" which typically range from 40 to 120 µm in diameter [2,3]. The genus *Coccidioides* includes two species (*C. posadasii* and *C. immitis*), distinguished on the basis of molecular and biogeographical differences [4]. Coccidioidomycosis is endemic in certain desertic and semiarid regions of the southwestern US, northern Mexico and Central and South America, including Guatemala, Honduras, Venezuela, Paraguay, Argentina, northern Colombia and northeast Brazil [5,6]. It is estimated that 100 000 new cases occur in the US each year [7]. Human infection occurs after inhalation of fungal spores (arthroconidia). The majority of *Coccidioides* infections in people either produce no symptoms or a self-limited pneumonia. Although this mycosis is rarely life-threatening, most patients who do not recover spontaneously develop extrapulmonary infections [7].

Host immune responses can be divided into two phases, the innate and the adaptive. The innate immune response is represented by host cells with the capability to recognize foreign molecules through the expression of pattern recognition receptors (PRR) whose activation is triggered by interaction with pathogen-associated molecular patterns (PAMPs); the adaptive immune response is characterized by the participation of different T lymphocyte subsets that recognize specific antigens. Recent studies have shown that in mice vaccinated with a live attenuated strain of *Coccidioides*, the adaptive immune response is directed by an increase in macrophage and dendritic cell numbers and activation of lymphocytes, resulting in the production of a mixed T-helper (Th) 1-, 2- and 17-type immune response [8]. Thus, it is suggested that the adaptive immune response is partly controlled by the initial recognition of fungal cells and subsequent activation of the innate immune response. However, this immune response and its regulation during the coccidioidal infection process, which may contribute to resistance or susceptibility to the mycosis, is not yet fully understood. Understanding the interaction between the host and *Coccidioides* spp, as well as the mechanisms of the host immune responses to coccidioidal infection are consequently essential prerequisites for development of new therapeutic strategies and the design of vaccines against coccidioidomycosis. In this review, we will focus on recent observations of the role played by the innate immune response during coccidioidal infection.

Innate Immune Cells Involved in the Host Defences Against *Coccidioides*

Professional phagocytes such as neutrophils (polymorphonuclear leukocytes [PMN]), monocyte/macrophages and dendritic cells (DC), work together with epithelial and endothelial cells to provide the first line of defence against microbial pathogens. Phagocytes are believed to be the most effective cell type involved in the control of coccidioidal infection. PMN are an important component of the inflammatory response and are the first cells recruited to the site of infection, where they participate in the host defence by killing microbes through oxidative and non-oxidative mechanisms. Several studies have shown that PMN play an important role in host defence against a wide range of microbes. Depletion of these cells increases host susceptibility to medically important fungi including *Candida albicans* [9-12], *Aspergillus fumigatus* [13,14], *Paracoccidioides brasiliensis* [15] and *Histoplasma capsulatum* [16]. However, in other studies the opposite effect has been observed. Thus, mice depleted of PMN and infected with *Cryptococcus neoformans* showed smaller fungal burdens and survived longer than controls [17], while in mice infected with *C. albicans*, neutrophil depletion did not alter fungal burden or caused systemic dissemination [18]. This illustrates the complex role played by these phagocytic cells. *In vitro* studies have shown that human PMN exert phagocytic and fungicidal activity against *C. immitis*; however this depends of both the strain and fungal morphotype involved. Thus, arthroconidia and endospores are more susceptible

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Received February 13, 2013; **Accepted** March 04, 2013; **Published** March 11, 2013

Citation: González A (2013) Innate Immune Response to the Dimorphic Fungal Pathogen *Coccidioides*: Molecular and Cellular Mechanisms. J Clin Cell Immunol S13: 001. doi:10.4172/2155-9899.S13-001

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than mature spherules [19]. Histopathological analyses of lungs of infected mice during the first 2 weeks post-challenge revealed an infiltration of higher numbers of neutrophils surrounding the mature spherules, which ruptured and released their endospores [20]. More recently, flow cytometry analysis was used to confirm neutrophils as the major cells involved in this response, their being rapidly recruited to the lung in response to experimental pulmonary infection with *C. posadasii* [21,22]. Nevertheless, the contribution of neutrophils to early defence against *Coccidioides* remains incompletely defined. We have hypothesized that neutrophils respond to the fungal insult and that this mechanism could be associated with the contents released by these parasitic cells; furthermore, the higher numbers of neutrophils observed in the lungs can be correlated to the fungal burden in this organ [21-23]. This intense inflammatory response at infection sites may contribute to lung tissue damage, possibly exacerbating the course of fungal disease.

In addition to their phagocytic role, macrophages also have the ability to mediate antimicrobial effects against several pathogens; thus, the mechanisms involved in the recognition, activation and regulations of these antimicrobial and phagocytic effects are pivotal to understanding the innate immune response developed against microbial pathogens. Studies have been made *in vitro* of the interaction of murine peritoneal and alveolar macrophages, nonhuman primate alveolar macrophages and human peripheral blood monocytes with coccidioidal arthroconidia, endospores or initial spherules [22,24-30]. The phagocytic cells were able to engulf the fungal propagules but not to kill them without being activated or stimulated [24-27,29]. However, the addition of recombinant gamma interferon (IFN-γ) or tumour necrosis factor alpha (TNF-α) appeared to activate the fungicidal capability of murine alveolar and peritoneal macrophages and human mononuclear phagocytes, as demonstrated both by reduced recovery and inhibited development of the fungus [28,31]. Controversially, it was demonstrated that peritoneal macrophages challenged with initial spherules of *C. posadasii* and activated with IFN-γ and lipopolysaccharide (LPS) showed a similar fungicidal effect to that observed in non-stimulated macrophages [22,30]. These results may suggest that the fungicidal/fungistatic effect exerted by macrophages against *Coccidioides* depends on the fungal morphotype, indicating that arthroconidia and endospores are more susceptible to these mechanisms than initial or mature spherules.

DC are considered to be professional antigen-presenting cells which reside in and patrol the skin and mucosal surfaces, playing an important role in mediation of the innate immune system with subsequent activation of T cell responses to provide a cell-mediated immunity against microbial pathogens [32]. *In vitro* studies have shown that human immature DC have the ability to bind and internalize *C. posadasii* spherules in a time- and temperature-dependent manner, an interaction that induces the maturation and activation of these phagocytic cells in a similar way to TNF-α [33]. In a further study, it was observed that bone marrow-derived DC (BMDC) from DBA/2 mice (a strain relatively resistant to coccidioidal infection) showed a significant up-regulation of *toll*-like receptor (TLR)-2 and TLR4 gene expression, secretion of IL-12 and a modest increase in T cell co-stimulatory molecule production compared with BMDC from BALB/c mice (which are highly susceptible to coccidioidal infection) [34]. These results indicate that DC may play a critical role in the initial recognition of this fungal pathogen and subsequent formation of a cellular immune response [33].

Interaction of this fungal pathogen with epithelial and endothelial cells has not been studied. It may be that after interaction with *Coccidioides* and their subsequent activation of dendritic cells, as well as macrophages and neutrophils, act as a bridge to the adaptive immune response in this fungal infection.

Toll-like Receptors (TLRs) in the Recognition of *Coccidioides* Infection

The majority of the interactions described above are mediated by a cluster of molecules called pattern recognition receptors (PRRs), located on the plasma or endoplasmic membranes of virtually all nucleated cells. PRRs recognize pathogen-associated molecular patterns (PAMPs), which are shared among groups of pathogens. Toll-like receptors (TLRs) have been the best characterized of PRR so far [35]. TLRs recognize several microbial cell wall components (lipids, carbohydrates, structural proteins) as well as nucleic acid structures that are broadly expressed by several microorganisms [36]. To date 10 TLRs have been identified in humans (TLR1-10) and 12 in mice (TLR1-9 and TLR11-13) [37]. These TLRs have a cytoplasmic domain known as the Toll/interleukin-1 receptor (TIR). Once a TLR binds to its ligand, an activation process is initiated with a signalling pathway via TIR domain-containing adaptor proteins. Several adaptor proteins that participate in TLR-mediated mechanisms have been described; these molecules include the myeloid differentiation primary-response protein 88 (MyD88), Toll/interleukin-1 receptor (TIR) domain-containing adaptor protein (TIRAP), MyD88-adaptor-like protein (Mal), TIR domain-containing adaptor-including interferon-β (TRIF), and TRIF-related adaptor molecule (TRAM). These adaptors mediate the activation of transcription factors such as the nuclear factor-κB (NF-κB) and the interferon regulatory factor (IRF), which in turn induce the expression of inflammatory and anti-inflammatory cytokine and chemokine genes [38,39]. Thus, several fungal components or PAMPs (mainly of *Aspergillus*, *Candida* and *Cryptococcus*) are recognized by a number of TLRs; i.e,. TLR2/1, TLR4, TLR3, TLR2/6, TLR7, and TLR9 [40]. Although BMDC from a mouse strain (DBA/2) resistant to coccidioidal infection showed a high expression of TLR2 and TLR4 after infection with *C. posadasii* arthroconidia [34], Viriyakosol et al. [41] reported that peritoneal macrophages from TLR4 knockout mice ($TLR4^{-/-}$) as well as phagocytic cells from C3H/HeJ mice which had a point mutation in TLR4 exhibited no defect in cytokine production compared to control mice after stimulation with formalin-killed spherules (FKS). By contrast, macrophages from $TLR2^{-/-}$ and $MyD88^{-/-}$ mice made less TNF-α, MIP-2 and IL-6 than did macrophages from wild type animals [41]. When TLR4-defective C3H/HeJ mice were infected with a sublethal dose of *C. posadasii* they were as susceptible to fungal infection as C3H/OuJ mice which had intact TLR4 [42]. Moreover, blockade of TLR4 using a specific antibody did not affect IL-12 secretion by DC infected with *C. posadasii* arthroconidia [42]. Interestingly, TLR4 defective mice had a significant lower fungal burden in spleen [42]. Taken together, the above results suggest that TLR2 signalling via MyD88, but not TLR4, could be involved in the initial inflammatory response against coccidioidal infection. Additional TLRs could also be activated by this fungal pathogen.

Other PRR Involved in the Recognition of *Coccidioides* Infection

The other major PRR family is that of the C-type lectin receptors (CLRs), including the following: Dectin-1 which recognizes β-glucans [43]; Dectin-2 which recognizes both high-mannose structures and α-mannan [44,45]; mannose receptor (MR) which recognizes N-linked mannan [46]; DC-SIGN (a receptor on the dendritic cells) which also

recognizes mannan [47]; galectin-3 which recognizes β-mannosides [48]; and the soluble mannose-binding lectin (MBL) which recognizes mannan and acts as an opsonin [49]. It is noteworthy that various CLRs (including Dectin-1, DC-SIGN and galectin-3) have been identified as TLR2 co-receptors [40]. Several of these CLRs appear to be involved in the recognition of *Candida albicans* [50]. In the case of *Coccidioides*, it has been reported that RAW 264.7 macrophages overexpressing Dectin-1 produced more cytokines when challenged with FKS, live spherules or purified β-glucan than control RAW cells; in addition, blockade of Dectin-1 with a specific antibody inhibited cytokine production in murine peritoneal macrophages [41]. In another study, DC from C57BL/6 mice (a susceptible strain for coccidioidal infection) made more IL-10 and less IL-23 and IL-12p70 than DC from DBA/2 resistant mice; interestingly, this response was inhibited when an anti-Dectin-1 antibody was employed [51]. This response was attributed to the expression of a truncated splice variant of Dectin-1 in susceptible mice; moreover, RAW cells transduced to express the full-length Dectin-1 responded better to *Coccidioides* than cells expressing truncated Dectin-1 [51]. These results indicate that the susceptibility observed in mice could be partially attributed to a process of alternative splicing in the Dectin-1 gene [51].

MR has been involved in the recognition and internalization of medically important fungi [46,52]. Thus, DC exhibited the capability to bind *C. posadasii* spherules through a MR-dependent mechanism, based on the observation that addition of mannan to co-cultures of these cells inhibited this binding process [33].

Pulmonary surfactant proteins belong to the C-type lectins or C-type collectins; these glycoproteins are secreted by alveolar type II cells or airway Clara cells [53,54]. Surfactant proteins-A (SPA) and D (SPD) appear to play an important role in the innate host defence mechanism against several clinically important fungal pathogens [55-59]. In an *in vivo* model of coccidioidomycosis, it was found that levels of SPA and SPD were altered in the lungs of *C. posadasii*-infected mice, but not in those of immunized infected animals [60]. In addition, it was observed that SPA and SPD could bind to antigens obtained from lysate or culture filtrate of *C. posadasii* [60]. These results indicate that pulmonary surfactant proteins may be involved in the initial recognition of *Coccidioides* and subsequent activation and regulation of the immune response.

Fungal Components of *Coccidioides* that Interact with PRRs

The fungal cell wall is a complex structure that comprises mannan, glucans, and chitin which are covalently cross-linked in a network [61]. The fungal components or PAMPs that interact with host cells through different PRRs have been well characterized for other fungi, particularly *C. albicans* [50]. The major component of the spherule cell wall of *Coccidioides* is 1,3-β-glucan [41], whose recognition is mediated through an interaction with Dectin-1 present on both DC and macrophage surfaces [41,51], while the MR present on DC recognize fungal mannan in the coccidioidal cell wall [33]. SPA and SPD bind to unidentified molecules present in lysate or culture filtrate antigens of *C. posadasii* [60]. The fungal components of *Coccidioides* that are recognized by TLR2 and TLR4 remain unknown. A schematic representation of the possible coccidioidal fungal components activating the different PRRs is shown in Figure 1. However, it is important to note that several TLR could cooperate with each other in recognition of fungal components; furthermore, other molecules including C-type lectin or other carbohydrate-binding proteins could act as co-receptors of TLR, especially TLR2. The mechanisms of this cooperation need to be elucidated in order to understand the interaction between *Coccidioides* and host cells. The PRR, fungal components and effect of the interaction of *Coccidioides* and host cells are described in Table 1.

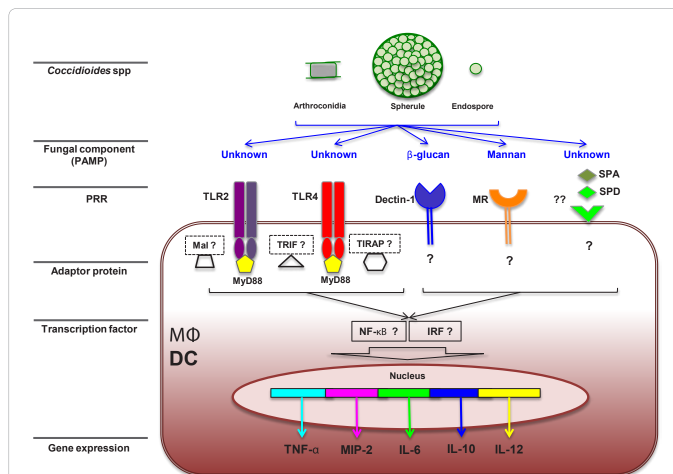

Figure 1: Interaction of PRRs and coccidioidal components.

Surface *Toll*-like receptors (TLRs) as well as other C-type lectins [e.g. Dectin-1 and mannose receptor (MR) and pulmonary surfactant proteins (SP)-A and –D (SPD)] participate in the recognition of coccidioidal components or PAMPs (e.g. β-glucan, mannan and other unknown components). In coccidioidal infection, interaction of fungal PAMPs with PRRs activates a signalling pathway which occurs at the level of the intracellular adaptor molecule myeloid differentiation primary-response protein 88 (MyD88). The participations of other adaptor molecules such as Toll/interleukin-1 receptor (TIR) domain-containing adaptor protein (TIRAP), MyD88-adaptor-like protein (Mal), TIR domain-containing adaptor-including interferon-β (TRIF) and transcription factors including nuclear factor-κB (NF-κB) and interferon regulatory factor (IRF) have not been studied and remain to be confirmed. TLR-mediated MyD88 signalling and Dectin-1 activation induce the expression of pro-inflammatory cytokines including TNF-α, MIP-2, IL-6, IL-10 and IL-12, thus driving the immune response.

PRR	Coccidioidal component	Effect	References
TLR2	Unidentified	Low TNF-α, MIP-2 and IL-6 levels	[41]
TLR4	Unidentified	Low fungal burden in spleen	[42]
Dectin-1	β-glucans	High TNF-α, MIP-2, IL-12 and IL-6 levels	[41,51]
MR	Mannan	Spherule binding to DC	[33]
SP-A	Unidentified	uptake/phagocytosis ?	[60]
SP-D	Unidentified	uptake/phagocytosis ?	[60]

PRR: Pattern Recognition Receptors; PAMP: Pathogen-Associated Molecular Patterns; TLR: Toll-like Receptor; MR: Mannose Receptor; SP: Surfactant Protein; DC: Dendritic Cell

Table 1: Interaction between PRRs and coccidioidal PAMP components, and its effect.

Evasion Mechanisms of *Coccidioides* from the Host Defence

Several strategies have been developed by various fungal pathogens to escape or evade the host immune system. These mechanisms involve interaction with PRRs including TLRs [62], as well as morphological changes, especially in dimorphic fungi [40]. In the case of *Coccidioides*, the infectious particles or arthroconidia (barrel-shaped cells measuring 2-6 µm in diameter) undergo isotropic growth, giving rise to large multinucleated cells (spherules) that range from 40 to 120 µm in diameter [2,3], and thus hamper phagocytosis. Arthroconidia also possess an anti-phagocytic surface derived from the original

hyphal outer wall layer [63]. It has also been demonstrated that the spherule produces an extracellular fibrillar matrix based on a complex glycoprotein which interferes with the PMN-spherule interaction [19]. Once arthroconidia and endospores are phagocytized, they appear to inhibit the fusion of phagosomes [24,26,27], a mechanism that can be reversed by prior activation of phagocytes with lymphokine to enhance phagosome-lysosome fusion and subsequently kill the fungus [25].

Several other virulence factors have been described to account for host evasion in *Coccidioides*. Thus during parasitic fungal growth, *Coccidioides* spherules release an outer wall (SOW) material which is engulfed by phagocytic cells at the infection site [64,65]. A glycoprotein component of this SOW (SOWgp) is specifically recognized by serum from patients with coccidioidomycosis [66]. SOWgp is produced during the isotropic growth of the spherules and decreases during endospore formation [67]. It is noteworthy that SOWgp is undetectable during the endosporulating process in culture, when a metalloproteinase (Mep1) is produced [68]. Studies *in vitro* have shown that the recombinant Mep1 enzyme digests the purified SOWgp [65]. Additionally, it was shown that a murine alveolar macrophage cell line infected with SOWgp-coated parasitic cells enchanced phagocytosis and killing of this fungal pathogen in the presence of anti-SOWgp antibody [68]. These results may suggest that the SOWgp degradation observed during endosporulation could interfere with endospore recognition by specific antibodies, evading the opsonization and phagocytosis processes and subsequent elimination of the fungal pathogen.

Hydrolysis of urea by coccidioidal urease [69] yields carbonic acid and ammonia, a process that accounts for microenvironment alkalinization [70]. Urease has been identified as an important virulence factor in *Cryptoccocus* [71]. In a series of elegant experiments, Mirbod-Donovan et al. [72], deleted the URE gene in *C. posadassi*, resulting in a significant reduction in virulence when this mutant strain was used to infect mice. These results allow it to suggest that urease produced by spherules during the parasitic cycle of *Coccidioides* could account for: (i) tissue damage observed during infection, (ii) alkalinization of the microenvironment including that within phagosomes containing endospores, and (iii) induction of high expression levels of arginase I [65]. The latter process is described below.

Reactive oxygen species (ROS) and reactive oxygen intermediates (ROI) are produced by mammalian cells (particularly phagocytes), against several microbial pathogens [73-75]. These molecules are generated by activation of the enzymatic complex nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2) and include superoxide anion (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical OH), peroxynitrite (ONOO-), and hypochlorous acid (-OCl) among others [73-75]. *In vitro* studies have shown that exogenous hydrogen peroxide (H_2O_2) affects the arthoconidia but not spherule viability in the same way as PMN [76]; more recently, Margolis et al. [77] also showed that *C. immitis* arthroconidia and spherules were significantly more resistant to H_2O_2 treatment than *Aspergillus fumigatus* spores. These results clearly indicate that fungal morphotype is at least one of the characteristics that allow *Coccidioides* to evade natural antimicrobial mechanisms exerted by PMN. Furthermore, IFN-γ- and LPS-activated and non-activated macrophages isolated from either NOX2 knockout ($NOX2^{-/-}$) or wild type (WT) mice showed comparable ROS production and killing efficiency when infected with *Coccidioides* spherule initial morphotype [22]. Interestingly, *in vivo* studies showed that $NOX2^{-/-}$ mice infected i.n. with *C. posadasii* arthroconidia showed an equivalent fungal burden to WT mice; nevertheless, infected $NOX^{-/-}$ mice died earlier and showed an exuberant inflammatory response compared to infected WT mice [22]. These results indicate that ROS may to be dispensable for innate immunity to coccidioidal infection [22,77].

Nitric oxide (NO) is considered to be one of the most important reactive nitrogen intermediates and is produced by an oxidative mechanism involving the catabolism of L-arginine [78]. NO production by enzymatic action of inducible nitric oxide synthase (iNOS) represents one of the major microbicidal mechanisms of phagocytic cells against several pathogens [79]. NO synthesis by iNOS can be induced by several stimuli, including IFN-γ, TNF-α and LPS, and is expressed by immune cells such as macrophages, neutrophils, dendritic cells and NK cells [78]. In a previous study using a macrophage-free system and a NO generator (3-morpholinosydnonimine [SIN-1]), *C. posadasii* arthroconidia were observed to be more sensitive to low concentrations of SIN-1 than either initials or segmented/endosporulating spherules, indicating that the later forms of *C. posadasii* could have mechanisms capable of detoxifying NO [3]. More recently, it was demonstrated that initials spherule of *Coccidioides* spp. have the ability to suppress both NO production and *iNOS* expression by murine primary macrophages previously activated with IFN-γ+LPS, through the secretion of an unknown soluble factor [30]. However, peritoneal macrophages from $iNOS^{-/-}$ mice were able to phagocytize the fungal cells and showed similar fungicidal activity against *Coccidioides* initial spherules to macrophages from WT mice [30]. In additional *in vivo* studies, it was observed that both $iNOS^{-/-}$ and WT mice infected i.n. with *C. posadasii* arthroconidia showed similar survival rates and fungal burden in lungs [21]. Nevertheless, iNOS-deficient mice showed a significantly higher fungal burden in the spleen than that observed in WT mice. In summary, the above studies suggest that although both NOX2 and iNOS activity are not essential for killing of *Coccidioides* they may play a pivotal role in regulation of the innate inflammatory response against this fungal pathogen, and that some other undefined mechanism of host protection against coccidioidomycosis is involved. On the other hand, a microarray approach allowed an upregulation of arginase I expression to be identified in mice infected i.n. with *Coccidioides* arthroconidia [65]. Arginase I competes with iNOS for the common substrate L-arginine [80]. The former is able to hydrolyze L-arginine to L-ornithine, providing a substrate for the enzyme ornithine decarboxylase (ODC). ODC has been cloned, sequenced and expressed in *E. coli* where it was observed that this enzyme was only present during the growth phase [81]; this enzyme is a key component of the polyamine biosynthetic pathway and apparently accounts for growth and proliferation of this fungal pathogen [65]. In concurrence with the above results, low *iNOS* gene expression has been reported in the lungs of mice infected with *Coccidioides* [3]. Thus, upregulation of arginase I may decrease levels of NO production allowing survival of the fungal pathogen. A physiological inhibitor of arginase [N $^{\omega}$-hydrohy-nor-L-arginine (nor-LOHA)] was employed to determine the contribution of NO to this coccidioidomycosis model. The i.p. treatment with nor-LOHA significantly increased survival of infected mice compared with that of untreated animals [3]. These data indicate that arginase I induction plays a pivotal role in coccidioidal infection.

Concluding Remarks

During the process of compiling this review, it was observed rapid progress in the understanding of the mechanisms involved in innate immunity for several fungal models, particularly those of *Candida, Aspergillus* and *Cryptoccocus*. The studies cited have provided pivotal insights into the interactions between TLRs and other PRRs with fungal pathogens. In the case of *Coccidioides*, data about innate immune response remain scarce. Few research groups currently work with this

pathogen, whose classification as a class III bioterrorist agent further restricts investigations into its model of infection; this could explain the few data found. We observed that some TLR and other PRR are involved in recognition of this dimorphic fungal pathogen, and some virulence factors that have already been identified contribute to pathogenesis of infection. Several points remain to be elucidated however, including: (a) the involvement of TLRs other than TLR2 and TLR4, as well as that of other PRRs such as Dectin-2, DC-SIGN, galectin-3 and MBL; (b) the participation of other adaptor molecules and transcription factors; and (c) identification of the specific fungal components that interact with these host receptors. Coccidioidomycosis could thus provide an exciting model for investigation of the innate immune system's role in host defence against infection. Understanding the nature of the interactions between this fungal pathogen and innate immune system is crucial to the development of vaccines and other immunomodulatory strategies against coccidioidal infection.

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This article was originally published in a special issue, entitled: "**Innate Response to Infectious Diseases**", Edited by Dr. Anshu Agrawal, University of California Irvine, USA