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Host Immune Responses Against Pulmonary Fungal Pathogens

Karen L. Wozniak^{1,2}, Michal Olszewski^{3,4} and Floyd L. Wormley Jr.^{1,2,*}

¹Department of Biology, The University of Texas at San Antonio,
San Antonio, TX

²South Texas Center for Emerging Infectious Diseases,
The University of Texas at San Antonio, San Antonio, TX

³Veterans Affairs Ann Arbor Health System, Ann Arbor, MI

⁴University of Michigan Medical School, Ann Arbor, MI
USA

1. Introduction

The lungs are a gateway for numerous airborne pathogens that are ubiquitous in our environment. Among these potential pathogens are fungi that can be found in the soil, bird excreta, air ducts, and many other places where their contact is unavoidable. Exposure to these fungal pathogens oftentimes goes unnoticed due to the activation of our robust immune systems which sequester and control these microbes before significant damage occurs. Still, there are many situations in which host immunity becomes compromised providing an opportunity for typically innocuous fungal organisms to become established and cause disease or for dormant infections to reawaken. Also, in certain cases disease may be exacerbated due to an over exuberant immune response. In this chapter, we will review the main aspects of innate and adaptive immune responses against pulmonary fungal pathogens. We will also discuss the potential for vaccines to prevent pulmonary fungal infections.

2. Introduction to pulmonary fungal infections

Pulmonary fungal infections can be grouped into primary fungal pathogens and opportunistic fungal pathogens. Those organisms that can cause disease in immune competent hosts are considered primary pathogens including *Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, and *Blastomyces dermatitidis*. All of the primary pulmonary fungal pathogens are endemic to the United States and/or Central & South America. *Histoplasma* and *Blastomyces* are endemic to the Ohio River & Mississippi River Valleys of the United States and also to certain regions of Central and South America (Klein et al., 1986; Deepe, 2000). *Coccidioides* is prevalent in the desert southwest United States (Fisher et al., 2007), and *Paracoccidioides* is endemic in Central and South America, particularly in Brazil (Franco, 1987; Franco et al., 1989; Brummer et al., 1993). These

* Corresponding Author

infections are acquired by inhalation of fungi from contaminated soil, and severity of disease generally correlates with the amount of exposure to the pathogen.

Examples of organisms that are opportunistic pulmonary fungal pathogens include *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Pneumocystis*, and *Rhizopus*. *C. neoformans* is found ubiquitously in the soil, usually in soil contaminated with pigeon guano (Perfect and Casadevall, 2002). These fungi primarily cause disease in individuals with compromised immune systems. Most cryptococcal infections are asymptomatic, and the organism typically causes disease in immune compromised patients, such as AIDS patients, solid organ transplant patients on immune-suppressive drugs, or patients receiving chemotherapy (Levitz, 1991; Mitchell and Perfect, 1995; Singh et al., 1997; Shoham and Levitz, 2005). *A. fumigatus* is ubiquitously found in the environment, and is normally found in association with decaying wood and plant matter (Deacon et al., 2009). However, *A. fumigatus* can cause severe respiratory infections in cases of massive exposure or immune deficiency, such as neutropenia, due to chemotherapy, AIDS, or bone marrow transplant therapy (Denning, 1996; Almyroutdis et al., 2005; Magill et al., 2008). *Pneumocystis* infection is acquired by inhalation of organisms from a yet unknown source (Keely et al., 1995; reviewed in Kelly and Shellito, 2010). Most *Pneumocystis* infections occur in immunosuppressed individuals due to either HIV or chronic obstructive pulmonary disease (Leigh et al., 1993; Nevez et al., 1999; Huang et al., 2003; Calderon et al., 1996; Morris et al., 2004; Norris et al., 2006; Davis et al., 2008; Morris et al., 2008a; Morris et al., 2008b; Kling et al., 2009). Similarly, infection with *Rhizopus* typically occurs in individuals who are immune compromised, such as organ transplant recipients (Kontoyiannis, 2010; Pappas et al., 2010).

3. Innate immune responses against pulmonary fungal pathogens

3.1 Phagocyte interactions with pulmonary fungal pathogens

Cells of the innate immune system such as dendritic cells (DCs) and macrophages residing in the lungs/airways are the first line of defense against pulmonary fungal pathogens. Although these innate cells cannot completely eliminate many fungal pathogens, they are involved in uptake and degradation of fungi and processing of antigens derived from these pathogens. In contrast, neutrophils which are also phagocytic and can be fungistatic are unable to present antigen. Based on the subset of receptors involved and signaling pathways triggered by these receptors, the innate immune system will trigger different types of early responses and subsequently translate these signals to mount different types of adaptive responses.

H. capsulatum can initially be engulfed by macrophages, DCs, and neutrophils (reviewed in (Deepe, 2005)), however, *H. capsulatum* recognition by different receptors results in different fates (Gomez et al., 2008). DCs recognize *H. capsulatum* by VLA-5, by interaction with an unknown receptor, which results in uptake, killing, and antigen presentation (Gildea et al., 2001; Gomez et al., 2008). Human DCs exert their antifungal activity via phagolysosomal fusion. The addition of suramin (which blocks phagolysosomal fusion) inhibits DC fungicidal activity, but inhibition of lysosomal acidification and inhibition of respiratory burst has no effect (Gildea et al., 2005). In contrast to DCs, macrophages recognize the *H. capsulatum* surface molecule heat-shock protein 60 (HSP 60) by LFA-1 (CD11a/CD18), complement receptor 3 (CD11b/CD18), and complement receptor 4 (CD11c/CD18) and this recognition leads to uptake and intracellular replication (Kimberlin et al., 1981; Bullock and Wright, 1987; Long et al., 2003; Gomez et al., 2008; Lin et al., 2010). However, activated

macrophages can halt intracellular replication (Wu-Hsieh and Howard, 1984; Wu-Hsieh et al., 1984). *H. capsulatum* can avoid the macrophage lysosomal environment by preventing phagolysosomal fusion (Newman et al., 1997; Strasser et al., 1999) or by alkalinizing the pH of the phagolysosome (Eissenberg and Goldman, 1988; Eissenberg et al., 1988; Eissenberg et al., 1993). Macrophages infected with *H. capsulatum* and activated with GM-CSF decrease available iron and zinc, while infected macrophages without GM-CSF do not. Further, chelation of zinc inhibits yeast replication; therefore zinc deprivation may be used by macrophages in host defense against *H. capsulatum* (Winters et al., 2010). Neutrophil phagocytosis of *H. capsulatum* requires opsonization with either antibody or complement (Brummer et al., 1991; Kurita et al., 1991a; Kurita et al., 1991b; Newman et al., 1993). Neutrophil uptake of *H. capsulatum* is fungistatic, as opposed to macrophages (permissive growth & replication) and DCs (fungicidal) (reviewed in Deepe, 2005). A lack of neutrophils causes a non-lethal infection to become a lethal infection (Zhou et al., 1998).

Immature DCs bind spherules of *Coccidioides* in a time and temperature-dependent manner, and binding is blocked by mannan, suggesting that mannose receptor (MR) is involved in this interaction (Dionne et al., 2006). Spherules of *Coccidioides* stimulate DC functional maturation, evidenced by decreased endocytic capacity and stimulation of allogeneic peripheral blood mononuclear cell activation (Dionne et al., 2006). Further studies showed that a DC-based *Coccidioides* vaccine had adjuvant properties and activated protective immune responses in mice (Awasthi, 2007). Although macrophages can ingest *Coccidioides*; earlier studies suggested that they are not able to kill the arthroconidia (Kashkin et al., 1977; Beaman et al., 1981, 1983; Beaman and Holmberg, 1980b, 1980a). Studies demonstrated that monocytes derived from human peripheral blood were able to kill *Coccidioides* (Ampel and Galgiani, 1991). Neutrophils are the earliest cell type to infiltrate upon pulmonary infection with *Coccidioides* arthroconidia (Savage and Madin, 1968). Phagocytosis by neutrophils is enhanced by the addition of immune serum (Drutz and Huppert, 1983; Wegner et al., 1972; Frey and Drutz, 1986). Uptake of *Coccidioides* arthroconidia by neutrophils induces a respiratory burst (Frey and Drutz, 1986), but less than 20% of the arthroconidia are killed (Frey and Drutz, 1986; Beaman and Holmberg, 1980b; Drutz and Huppert, 1983). The spherule form of *Coccidioides* cannot be phagocytosed by or killed by neutrophils (Frey and Drutz, 1986; Galgiani, 1986), but rupture of the spherule leads to an influx of neutrophils (Frey and Drutz, 1986).

P. brasiliensis can be phagocytosed by immature DCs, and uptake is significantly decreased with the addition of mannan, suggesting that MR is the primary receptor for *P. brasiliensis* on DCs (Ferreira et al., 2004). After DC uptake of *P. brasiliensis*, the fungal organisms survive and multiply intracellularly rather than being killed (Ferreira et al., 2004). Following *in vitro* culture of *P. brasiliensis* or the major surface antigen gp43 with DCs, major histocompatibility complex (MHC) II is downregulated as is the production of interleukin (IL)-12 and tumor necrosis factor (TNF)- α (Ferreira et al., 2004). However, *in vivo* studies showed that DC interaction with *P. brasiliensis* results in modification of DC receptor expression, including upregulation of CCR7, CD103, and MHC II and also induces migration of both pulmonary and bone marrow-derived DCs. DCs are also able to activate T helper cell responses in the draining lymph nodes following interaction with *P. brasiliensis* (Silvana dos Santos et al., 2011). Alveolar macrophages adhere to and internalize *Paracoccidioides* using the organism's phospholipase B, which also serves to downregulate macrophage activation (Soares et al., 2010). During pulmonary infection with *P. brasiliensis*, a shift in macrophage activation occurs, which is characterized by an increase in IL-1, TNF- α ,

and IL-6 (Silva et al., 2011). *P. brasiliensis* can proliferate within macrophages, but macrophage activation inhibits its growth (Brummer et al., 1988; Cano et al., 1994). Further, macrophages activated by interferon (IFN)- γ can kill *P. brasiliensis* (Cano et al., 1994; Gonzalez et al., 2000). *In vitro* stimulation of human monocytes and neutrophils with *Paracoccidioides* yeast showed downregulation of toll-like receptor (TLR)2, TLR4, and dectin-1 on the surface of these cells. In addition, yeast cells induced the production of pro-inflammatory cytokines such as TNF- α (Bonfim et al., 2009). Mice lacking TLR2 had a less severe pulmonary infection than wild-type (WT) mice and had decreased nitric oxide (NO) production. However, despite the differences in infection, both TLR2^{-/-} mice and WT mice had similar rates of survival and similar pulmonary inflammatory responses (Loures et al., 2009). Further, TLR2 deficiency skewed the adaptive response towards a T helper (Th)17 phenotype and caused a decrease in T regulatory cells. Increased neutrophils and eosinophils migrate to the lungs of mice susceptible to *P. brasiliensis*, (Cano et al., 1995), and this influx affects the disease outcome and the adaptive response induced to infection. In susceptible individuals recovered from *Paracoccidioides*, neutrophils are able to phagocytose the organism, but this leads to degeneration of the neutrophils. These data suggest that susceptible individuals have an inherent neutrophil deficiency (Dias et al., 2008). Further, neutrophils from patients with *P. brasiliensis* have a digestive defect against the fungus (Goihman-Yahr et al., 1980), and also have a killing defect against the fungus (Goihman-Yahr et al., 1985; Goihman-Yahr et al., 1992).

B. dermatiditis interaction with DCs causes efficient upregulation of antigen presentation and costimulatory molecules and induces production of IL-12 and TNF- α (Wuthrich et al., 2006). DCs can activate CD8⁺ T cells in the absence of CD4⁺ T cells, and the yeast alone is a sufficient inflammatory stimulus that can directly induce maturation of DCs and can induce production of TNF- α , IL-1 β , and IL-12 (Wuthrich et al., 2006). Monocyte-derived dendritic cells can associate with yeast in the lung and transport them to the draining lymph nodes, but fail to present antigen to CD4⁺ T cells, however dermal DCs are capable of antigen presentation (Ersland et al., 2010). During *B. dermatiditis* infection, alveolar macrophages are only modestly able to ingest and kill the yeast form of the organism (Bradsher et al., 1987). Murine macrophages are only able to kill less than 5% of yeast (Brummer and Stevens, 1987; Brummer et al., 1988), and had a 25-30% reduction in respiratory burst compared to the respiratory burst induced by zymosan. The *Blastomyces* adhesion 1 (*BAD1*) molecule on the *Blastomyces* yeast surface is responsible for binding to CD11b/CD18 and CD14 on the macrophage surface and subsequent entry (Klein et al., 1993; Newman et al., 1995). Neutrophils rapidly infiltrate to pulmonary tissues following infection, and are responsible for the formation of pyogranulomatous lesions. Conidia are rapidly phagocytosed by neutrophils, but killing of conidia is inefficient. Similar to macrophages, the neutrophil respiratory burst induced by conidia is only 70% of that induced by zymosan (Drutz and Frey, 1985). In addition, yeasts are even more difficult for the neutrophils to phagocytose & kill than conidia (Drutz and Frey, 1985).

Pneumocystis interacts with DCs *in vitro* by MR, (Kobayashi et al., 2007) but the interaction does not lead to an increase in maturation markers such as MHC II, CD40, CD54, CD80, or CD86. Additionally, this interaction induces the production of IL-4 but not IL-12p40, IL-10, TNF- α , or IL-6 (Kobayashi et al., 2007). However, *Pneumocystis* cell wall β -glucans have the ability to induce costimulatory molecule upregulation on DCs, such as MHC II, CD80, CD86, and CD40. These DCs interacted with β -glucans from *Pneumocystis* via dectin-1, and

co-stimulatory molecule expression and Th1-type cytokine secretion by β -glucan stimulated DCs was regulated by Fas-Fas ligand interaction (Carmona et al., 2006). *In vivo* administration of DCs pulsed with *Pneumocystis* induced specific T cell responses and release of IL-4 as well as specific IgG₁, IgG_{2a}, and IgG_{2b} production (Kobayashi et al., 2007). Alveolar macrophages have been shown to directly kill both *Pneumocystis* trophozoites and cysts (Fleury et al., 1985; reviewed in Kelly and Shellito, 2010). Specifically, alternatively-activated macrophages (aaMac) are important effector cells against *Pneumocystis*, and aaMac is enhanced by IL-33 (Nelson et al., 2011). In addition, *Pneumocystis* infection causes changes in gene expression of alveolar macrophages that included upregulation of genes involved in antigen presentation and antimicrobial peptides, but downregulation of genes involved in phagocytosis and uptake (Cheng et al., 2010). *Pneumocystis* major surface glycoprotein (MSG), which is a heavily glycosylated surface antigen, is recognized by MR on alveolar macrophages (Ezekowitz et al., 1991). *Pneumocystis* infection in HIV⁺ patients induces shedding of the MR, which results in reduced alveolar macrophage phagocytosis of the microbe (Koziel et al., 1998; Fraser et al., 2000). Neutrophils can also interact with *Pneumocystis*, but the presence of neutrophils is correlated with inflammation and increased severity of disease (reviewed in Kelly and Shellito, 2010).

Inhaled *A. fumigatus* conidia are first encountered by alveolar macrophages and neutrophils (reviewed in Hasenberg et al., 2011). Following uptake of *Aspergillus* by phagocytes, the organism enters the phagosome and killing occurs following phagosomal fusion with lysosomes, (Ibrahim-Granet et al., 2003). In the absence or impairment of phagocytic cells, there are dramatic increases in invasive *Aspergillus* infections (Latge, 1999). β -1,3 glucans of *Aspergillus* swollen conidia and hyphae are recognized by dectin-1 on the surface of alveolar macrophages, monocytes, and neutrophils (Taylor et al., 2002; Taylor et al., 2007). This recognition of *Aspergillus* leads to phagocytosis and the production of cytokines such as TNF- α , IL-6, and IL-18 (Gersuk et al., 2006). In addition, *Aspergillus* can be recognized by TLRs, predominantly TLR2 and TLR4 (Wang et al., 2001; Mambula et al., 2002; Netea et al., 2002; Meier et al., 2003; Netea et al., 2003; Bellocchio et al., 2004; Bochud et al., 2008), but phagocytosis and uptake are not due to recognition by TLR2, TLR4, TLR9, or MyD88 (Bellocchio et al., 2004). More recent data also points to recognition of *Aspergillus* unmethylated DNA by TLR9 (Ramirez-Ortiz et al., 2008; Ramaprakash et al., 2009). Further, TLR9 is actively recruited to the *Aspergillus* phagosome and requires the N-terminal proteolytic cleavage domain for proper intracellular trafficking (Kasperkovitz et al., 2010).

DCs bind and internalize *A. fumigatus* through DC-SIGN, and this binding triggers DC maturation (Serrano-Gomez et al., 2004). Mouse DCs can internalize conidia of *A. fumigatus* using MR and a C-type lectin receptor as well as Fc γ R (Bozza et al., 2002). Upon exposure of DCs to *A. fumigatus*, DCs upregulate HLA-DR, CD80 and CD86 (Grazziutti et al., 2001; Bozza et al., 2002). Following *A. fumigatus* infection, DCs can release the chemokine CXCL8, which promotes migration of PMNs, can upregulate CCL19, which is important in migration of CCR7⁺ naïve T cells and mature DCs to lymph nodes, and can release soluble factors that increase CD11b and CD18 on PMNs (Gafa et al., 2007). DC phagocytosis of *A. fumigatus* conidia and hyphae occur by different means and through different receptors; conidia are phagocytosed by coiling phagocytosis and hyphae are phagocytosed by zipper-type phagocytosis (Bozza et al., 2002). *A. fumigatus* killing by DCs is dependent on phagolysosomal fusion and a reduction in pH (Ibrahim-Granet et al., 2003). Plasmacytoid DCs (pDCs) have the ability to spread over *A. fumigatus* hyphae and inhibit their growth

(Ramirez-Ortiz et al., 2011), and antifungal activity does not require direct cell contact. Following interaction of pDCs with *Aspergillus*, pDCs release pro-inflammatory cytokines, such as IFN- α and TNF- α , and these are produced via a TLR9-independent mechanism (Ramirez-Ortiz et al., 2011). During the early stages of *Aspergillus* infection, alternatively activated macrophages are recruited to the lung and are important in host defense (Bhatia et al., 2011). Studies examining the interaction of *Aspergillus* conidia with alveolar macrophages showed that infectivity and inhibition of macrophage killing by the fungus were due to the presence of a siderophore system that allows the fungus to acquire iron (Schrettl et al., 2010). In neutropenic mice, inflammatory DCs are recruited to the lungs during *Aspergillus* infection, and this recruitment is dependent on the absence of neutrophils (Park et al., 2010). This accumulation led to increased TNF- α , CCL2, and CCL20, which resulted in further recruitment of inflammatory DCs. Neutrophils, when incubated with *A. fumigatus* hyphae, form neutrophil extracellular traps (NETs), which are antifungal, but mostly act in a fungistatic manner to limit spread of the hyphae (Bruns et al., 2010; Hasenberg et al., 2011).

In vitro studies of DCs with *C. neoformans* have shown that DCs are involved in detection, binding, phagocytosis, processing, antigen presentation, T cell activation, and killing of the organism (Bauman et al., 2000; Bauman et al., 2003; Wozniak et al., 2006; Wozniak and Levitz, 2008). DCs isolated from infected lungs presented cryptococcal mannoprotein (MP) to MP-specific T cells and induced T cell activation ex vivo (Wozniak et al., 2006). Depletion of DCs abrogated the T cell response (Mansour et al., 2006). Furthermore, DC phagocytosis of mannoprotein (MP) in the presence of the appropriate adjuvant induces production of Th1-type cytokines (Dan et al., 2008). Additional studies revealed that the interaction of *C. neoformans* with DCs, but not macrophages, induced the production of IL-12 and IL-23, two cytokines associated with protection against cryptococcosis (Kleinschek et al., 2010). Phagocytosis of encapsulated *C. neoformans* by DCs requires opsonization with either anti-capsular antibody or complement, and the combination of these has an additive effect (Kelly et al., 2005). Also, both murine and human DCs are able to kill *C. neoformans*, by both oxidative and non-oxidative mechanisms (Kelly et al., 2005). Recognition and uptake of acapsular *C. neoformans* strains by DCs requires MR and Fc γ R II (Syme et al., 2002). TLR2 and TLR4 are not important in uptake of *C. neoformans* or activation of DCs by the fungus (Nakamura et al., 2006). DCs stimulated with DNA from *C. neoformans* release IL-12p40 and express CD40, a costimulatory molecule associated with DC maturation, and thus was tied to recognition by TLR9 (Nakamura et al., 2008). Upon infection with *C. neoformans*, CCR2-deficient mice, which are impaired in trafficking of monocyte-derived DCs, developed a non-protective Th2-type immune response and persistent infection, and had reduced DC recruitment, bronchovascular collagen deposition, and increased IL-4 production (Osterholzer et al., 2008). *C. neoformans* can also be phagocytosed by macrophages (Levitz et al., 1999; Del Poeta, 2004). Macrophage phenotypes are associated with differential immune responses against *C. neoformans*. Protection against infection is associated with the presence of classically-activated macrophages (caMac) (Zhang et al., 2009; Hardison et al., 2010a; Hardison et al., 2010b), while disease progression is associated with the presence of alternatively activated macrophages (aaMac) (Arora et al., 2005; Muller et al., 2007; Arora et al., 2011; Chen et al., 2007; Guerrero et al., 2010). Also, macrophages can serve as a site of replication of *C. neoformans* (Tucker and Casadevall, 2002). Intracellular replication rates within macrophages correlated to virulence for *C. neoformans* strains (Voelz et al., 2009). In addition to replication, yeasts can be expelled from macrophages by a non-lytic mechanism

that leaves both *C. neoformans* and macrophages intact and capable of replication and growth (Alvarez and Casadevall, 2006; Ma et al., 2006; Alvarez and Casadevall, 2007; Johnston and May, 2010). *C. neoformans* can also be phagocytosed by activated neutrophils (Kozel et al., 1987). The capsule of *C. neoformans* induces neutrophils to release proinflammatory cytokines, such as IL-1 β , IL-6, IL-8 and TNF- α (Retini et al., 1996). Neutrophils can kill *C. neoformans* by non-oxidative mechanisms, including neutrophil defensins and calprotectin (Mambula et al., 2000). Interestingly, induction of neutropenia in mouse models of infection reduces their susceptibility to infection (Mednick et al., 2003).

Although innate immune responses against *Rhizopus*, the main causative agent of mucormycosis, have not yet been fully characterized, recent work has shown that *Rhizopus* can trigger a common innate sensing pathway in DCs that leads to the production of IL-23 and drives Th17-type responses (Chamilos et al., 2010). This is due to interaction of dectin-1 with β -glucans on the surface of *Rhizopus* hyphae.

3.2 NK cell activity

Another innate immune response to pulmonary fungal pathogens is due to recognition and action by natural killer (NK) cells. NK cells were thought to act primarily against viruses and tumors, but more recent studies have shown that NK cells have a wide variety of functions against bacteria, fungi, and parasites (Newman and Riley, 2007).

In *H. capsulatum* infection, there is little evidence of a protective role for NK cells. While beige mice (lacking functional NK cells) are more susceptible to *H. capsulatum* infection, T cells play a greater role in controlling infection (Patino et al., 1987). In studies evaluating both beige mice and mice depleted of NK cells, beige mice were still more susceptible to infection, while mice depleted of NK cells were no more susceptible to infection than WT mice, therefore indicating no major role for NK cells in protection (Suchyta et al., 1988). However, mice deficient in perforin, a major component of NK cell anti-microbial activity, had accelerated mortality and increased fungal burden (Zhou et al., 2001). Infection with *Coccidioides* during depletion of NK cells leads to increased susceptibility to infection (Petkus and Baum, 1987). Furthermore, NK cells have a direct cytotoxic effect on *Coccidioides* young spherule and endospore cells (Petkus and Baum, 1987). In *Paracoccidioides*, studies have shown increased NK cell activity in infected hamsters compared to uninfected controls. Impaired NK cell activity was associated with a decrease in cell-mediated immunity (CMI) and an increase in histopathologic lesions. However, after initial activation, NK cells alone were not able to control dissemination of *Paracoccidioides* (Peracoli et al., 1995). *In vitro* NK cell activity correlated with growth inhibition of *Paracoccidioides* yeast (Jimenez and Murphy, 1984).

In neutropenic mice with *A. fumigatus* infection, NK cells are the major cell type responsible for the production of IFN- γ early in the infection. Additionally, depletion of NK cells reduces IFN- γ levels and caused increased pulmonary fungal load (Park et al., 2009). NK cells have direct anti-fungal activity against hyphae but not against resting conidia (Schmidt et al., 2011). Killing is due to production of mediators by NK cells, including perforin. However, *A. fumigatus* can also down-regulate some cytokines induced by the NK cells, including IFN- γ and GM-CSF (Schmidt et al., 2011). In addition, recruitment of NK cells to the lung during *A. fumigatus* infection by the chemokine MCP-1 is required for optimal clearance of the organism from the lungs (Morrison et al., 2003). During *Pneumocystis* infection in SCID mice (lacking T and B cells), NK cells were responsible for production of

cytokines such as IFN- γ , TNF- α , TNF- β , IL-10, and IL-12 (Warschkau et al., 1998). Recent studies have shown that NK cells are recruited to the lung during *Pneumocystis* infection and are important in fungal clearance of murine PCP (M. Kelly and J. Shellito, personal communication). Further, combined depletion of NK and CD4⁺ T cells resulted in increased pulmonary fungal burden compared to individual depletion of each subset. In vitro, NK cells have direct microbicidal activity against *Pneumocystis*, and this anti-fungal activity is significantly enhanced in the presence of CD4⁺ T cells, suggesting that both cell types are necessary for a protective response against *Pneumocystis* infection (M. Kelly and J. Shellito, personal communication). Early studies showed that NK cells can directly kill *C. neoformans* (Murphy and McDaniel, 1982). Further, IFN- γ production by NK cells enhances elimination of the fungus in murine models (Kawakami et al., 2001a; Kawakami et al., 2001b; Kawakami et al., 2001c). Depletion of NK cells using anti-asialo GM antibody resulted in increased fungal burden in mice (Hidore et al., 1991a; Hidore et al., 1991b). Increased fungal burden was seen in beige mice compared to wild-type mice, and in mice depleted of NK1.1⁺ NK cells, fungal burden was also increased compared to controls (Lipscomb et al., 1987; Salkowski and Balish, 1991). Human NK cells kill *C. neoformans* (Levitz and Dupont, 1993), and this killing is enhanced in the presence of anti-cryptococcal antibodies (Miller et al., 1990). Binding of NK cells is required for cryptococcal killing, and requires disulfide bonds and is dependent on magnesium (Nabavi and Murphy, 1985; Hidore and Murphy, 1989; Murphy et al., 1991). Killing of *C. neoformans* is due to perforin interaction with the organism (Ma et al., 2004; Marr et al., 2009). In summary, NK cells act as accessory cells in antifungal host defenses contributing to clearance of fungi by a variety of mechanisms.

3.3 Gamma/delta T cell activity

The role of gamma delta ($\gamma\delta$) T cells during the immune response to pulmonary fungal pathogens is diverse. During infection with *Cryptococcus*, mice genetically deficient or depleted in $\gamma\delta$ T cells have reduced fungal burden compared to controls. Further, mice lacking $\gamma\delta$ T cells had increased levels of IFN- γ and decreased levels of TGF- β compared to controls, therefore suggesting that $\gamma\delta$ T cells are detrimental to protective immunity during cryptococcal infection (Uezu et al., 2004). In *Pneumocystis* pneumonia, CD4⁺ T cells are necessary for protection against infection, but $\gamma\delta$ cells are known to infiltrate into the lung during pneumonia (Kagi et al., 1993; Agostini et al., 1995; Steele et al., 2002). However, resolution of pulmonary *Pneumocystis* infection is augmented in $\gamma\delta$ T cell-deficient mice, (Steele et al., 2002), suggesting that these cells are detrimental to clearance of the organism. Further, the absence of $\gamma\delta$ T cells led to an increase in recruitment of CD8⁺ T cells and production of cytokines such as IFN- γ . Complete lack of all T cell subsets ($\alpha\beta$ and $\gamma\delta$) during *Pneumocystis* infection led to lethal consequences (Hanano and Kaufmann, 1999). Thus, $\gamma\delta$ T cells have either a limited role in antifungal protection or are detrimental to antifungal host defenses.

3.4 Innate anti-fungal defenses by non-immune cells

While innate immune cells and components of the innate immune system are the predominant innate immune defenses, it has also been shown that unconventional cells, such as epithelial cells can also play a role in anti-fungal innate host responses. Airway epithelial cells are capable of uptake and processing of antigens and initiation of Th-type

immune responses (Gereke et al., 2009). *P. brasiliensis* interacts with and can be internalized by bronchial epithelial cells (Mendes-Giannini et al., 1994, and this internalization is due to activation of a tyrosine kinase pathway (Monteiro da Silva et al., 2007; Hanna et al., 2000). In addition, uptake of *P. brasiliensis* causes both cytoskeletal rearrangements as well as apoptosis of the epithelial cells (Mendes-Giannini et al., 2004). *C. neoformans* can bind to pulmonary epithelial cells by a mechanism believed to be due to carbohydrate moieties that can be a ligand for the yeast (Merkel and Scofield, 1997). *C. neoformans* interaction with bronchial epithelial cells causes the production of IL-8, but epithelial cells are also susceptible to damage by the organism (Guillot et al., 2008a). In *A. fumigatus* infection, conidia can be taken up by tracheal epithelial cells, alveolar type II cells, and endothelial cells (Paris et al., 1997). Further, cytokines such as IL-6 and IL-8 are released by epithelial cells *in vitro* following stimulation with *A. fumigatus* proteases (Borger et al., 1999) or by *A. fumigatus* hyphal fragments (Zhang et al., 2005) and nasal epithelium. And nasal epithelium can engulf *A. fumigatus* conidia (Botterel et al., 2008). Epithelial cells can also release antimicrobial peptides following stimulation with fungal organisms. Epithelial cells *in vitro* cultured with *A. fumigatus* conidia, swollen conidia, or hyphae produced large amounts of beta defensins (Alekseeva et al., 2009). Airway epithelial cells internalize *A. fumigatus* conidia, and a genome-wide analysis revealed differential gene expression in epithelial cells with conidia compared to cells without conidia. Genes that were upregulated with conidia included genes involved in repair and inflammation, such as matrix metalloproteinases and chemokines (Gomez et al., 2010). In *Pneumocystis*, several studies have shown that the organism interacts with pulmonary epithelial cells. The interaction of *Pneumocystis* with epithelial cells was shown to be one of the initial steps in infection (Lanken et al., 1980; Yoneda and Walzer, 1980; Long et al., 1986; Millard et al., 1990). The β -glucan from the *Pneumocystis* cell wall can stimulate pulmonary epithelial cells to produce IL-8, and the organism can induce the production of MCP-1 and ICAM -1 (Yu and Limper, 1997; Evans et al., 2005; Wang et al., 2007; Carmona et al., 2010). Interaction of *Pneumocystis* and alveolar epithelial cells also leads to the production of the chemokine MIP-2 following NF- κ B signaling (Evans et al., 2005; Wang et al., 2005). These studies show that non-immune cells, such as epithelial cells, play a role in pulmonary anti-fungal immunity.

4. T cell and antibody mediated immune responses to fungal infections

4.1 Adaptive responses against pulmonary fungal pathogens

When challenged with pathogenic fungi, the adaptive immune system is capable of mounting an effective response against most fungal species to eliminate fungal infections and maintain immunological memory that prevents their reoccurrence. However, fungi are ubiquitous in the host's environment including the saprophytes and opportunists that survive on the host's body surfaces and thus, the adaptive immune system is constantly challenged by fungal antigens. Excessive response to these antigens could lead to allergic responses or other types of immunopathological reactions. The balance between day-to-day fungal antigen exposure and the immune system is thought to lead to a homeostatic state defined as protective tolerance. Protective tolerance allows the host to keep possible fungal pathogens "in check" while preserving integrity of the natural barriers, which are potential portals for fungal infections (Romani and Puccetti, 2008; de Luca et al., 2010a; Littman and Rudensky, 2010).

T cells are responsible for orchestration of adaptive immune responses and T cell derived signals produced in response to specific antigens lead to targeted expansion, recruitment, activation of leukocytes, and regulation of B cell antibody responses. T cells also serve as a pool of immunological memory. Additionally, T cells have been shown to directly act as the fungicidal effector cells and serve as regulators of inflammatory responses, contributing to the development and maintenance of the protective tolerance. These regulatory mechanisms are designed to limit the damage that the host immune system can inflict on host tissues during incorrect and/or excessive host responses. Thus, properly functioning T cells are responsible for building up protective immunity against fungal pathogens and play an essential role in maintaining normal homeostasis of the immune system in the context of normal presence of fungal antigens.

4.2 CD4⁺ and CD8⁺ T cell mediated immunity

The importance of T cells in antifungal protection is well documented. T-cell deficient individuals show diminished resistance to fungal infections including coccidiomycosis (Kappe et al., 1998) cryptococcosis (Kovacs et al., 1985; Chuck and Sande, 1989; Spitzer et al., 1993; Jarvis and Harrison, 2007), histoplasmosis (Odio et al., 1999), pneumocystis pneumonia (Kelly and Shellito), *Paracoccidioides* (Bava et al., 1991; Brummer et al., 1993), as well as pulmonary aspergillosis (Mylonakis et al., 1998). Likewise, laboratory studies have shown a strong contribution and/or requirement of T cells for protection against most pathogenic fungi such as *Coccidioides* (Fierer et al., 2006), *Cryptococcus* (Lim and Murphy, 1980; Mody et al., 1990; Huffnagle et al., 1991; Huffnagle and Lipscomb, 1992; Mody et al., 1994), *Pneumocystis* (Harmsen and Stankiewicz, 1990), *Histoplasma* (Deepe et al., 1984), *Paracoccidioides* (Cano et al., 2000) and *Aspergillus* (Cenci et al., 1997). These epidemiological and experimental studies have established that T cells are an important component of the antifungal host resistance.

Both subsets of T lymphocytes, CD4⁺ and CD8⁺ cells, are involved in antifungal host defenses. CD4⁺ T cells classically represent the T helper cell population. The T helper function was defined by MHC II restricted antigen specific activation of B-cell clones needed for the generation of specific antibodies. The CD4⁺ cell function in cell-mediated immunity (CMI) likewise requires antigen presenting cells and MHC II restricted antigen presentation. Presentation of antigen to the reactive T cells by dendritic cells and/or macrophages results in cytokine production. Through generation of different cytokine spectra, CD4⁺ T cells orchestrate recruitment and activation of various leukocyte subsets. The cytokines produced by the effector T cells are essential for macrophage fungicidal function and granuloma formation, but also may support chronic inflammation and immunopathology (Arora et al., 2005; Chen et al., 2008; Jain et al., 2009; Zhang et al., 2009). Thus, cytokine induction by differentially polarized T-cell lineages is the major determinant for fungicidal potential of distal effector cells. Although the effector CD4⁺ cell function relies predominantly on cytokine production, CD4⁺ T-cells are capable of fungal killing via direct cell contact. At least in some biological circumstances, the direct fungicidal effect of CD4⁺ T cells relies on granulysin as the fungicidal mediator (Zheng et al., 2007; Zheng et al., 2008).

In contrast with CD4⁺ T cells, CD8⁺ T cells are classically viewed as cytotoxic lymphocytes. These cells respond to antigen presentation in the context of MHC I, to enable their cytotoxic machinery. Such cytotoxic responses are particularly crucial in responses to viral infection and tumor cells, leading to elimination of the virally infected or tumor-transformed cells by

cytotoxic lymphocytes. CD8⁺ cells also play an important role in host defenses to bacterial, parasitic and fungal infections (Oykhman and Mody, 2010). Numerous studies showed that CD8⁺ T cells significantly contribute to protection against *Cryptococcus*, *Pneumocystis*, *Histoplasma* and *Blastomyces*, even in the absence of CD4⁺ T cells. Depending on the type and virulence of the fungal pathogen, CD8⁺ cells could afford either partial or a complete protection against the major fungal pathogens in experimental models. In this context, CD8⁺ T cells could induce all the protective effector functions of CD4⁺ T cells including production of protective cytokines. Another important aspect of CD8⁺ T cell effector function is the direct fungicidal effect of CD8⁺ T cells. Such direct fungicidal activity of CD8⁺ T cells have been demonstrated for *C. neoformans* (Ma et al., 2002). The killing of *C. neoformans* requires direct cell contact; it is enhanced by IL-15 and is thought to be mediated by granulysin. The direct cytotoxic effects are most pronounced when lymphocytes from fungus-immunized mice are used, however, a relatively high rate of binding of T cells to the fungus suggests that these cytotoxic mechanisms are innate rather than adaptive.

4.3 Immune polarization in antifungal host defenses

T helper cell subsets characterized by differential cytokine production by differentially programmed T-cell lineages were initially defined as Th1 and Th2 (Mosmann et al., 1986; Cherwinski et al., 1987). The types of immune responses driven by each of these cell lineages are described as Th1 and Th2 immune responses, generate different types of immune effector responses, and show different spectra of effectiveness against different classes of pathogens. For effective control/clearance of the majority of fungal pathogens, Th1 is the required type of the immune response. The Th1 response is promoted by IL-12, IFN- γ , and TNF- α . The two latter cytokines are also the major products of Th1 helper T cells (Cherwinski et al., 1987). Th1-type T-cells are responsible for the delayed-type hypersensitivity (DTH) reactions and CMI associated with vigorous proinflammatory responses and granuloma formation (Cher and Mosmann, 1987) and induction of IgG2a class antibodies in B cells (Stevens et al., 1988). The Th2 immune response is characterized by T-cell production of IL-4, IL-5, IL-9, IL-10, and IL-13 (Cherwinski et al., 1987), IgG1 and IgE antibody production by B cells (Stevens et al., 1988) and the presence of eosinophilic inflammation (Huffnagle et al., 1994; Cenci et al., 1999; Olszewski et al., 2001). The Th1 and Th2 responses counter-regulate each other predominantly via an IL-4/IFN- γ negative feedback loop (Fernandez-Botran et al., 1988; Gajewski and Fitch, 1988); however other cytokines can be also involved in Th1/Th2 regulation. The oversimplified Th1/Th2 paradigm has further evolved as new T cell lineages were defined. Th17 and regulatory type T cells (Treg), are T-cell lineages that are distinct from Th1 and Th2 cells that possess distinct functions in host defenses. Th17 cells are generated following the priming with IL-6 and TGF- β and sustained by the presence of IL-23. Th17 cells classically produce IL-17 and IL-22, however, a subset of Th17 cells can produce IFN- γ . Regulatory T-cells are thought to be responsible for tolerance that prevents autoimmune diseases and to contribute to resolution of inflammatory responses. These effects of Tregs are thought to be mediated by anti-inflammatory cytokines IL-10 and TGF- β , which are signature cytokines for Treg cells. New Th-cell lineages continue to be described including Th22 (Eyerich et al., 2009; Fujita et al., 2009) and Th9 (Soroosh and Doherty, 2009). Just like CD4⁺ effector T-cells, CD8⁺ T cells can also display a polarization pattern and thus can be an important source of the polarizing cytokines. Thus, both CD4⁺ and CD8⁺ T cells contribute to the cytokine balance during the immune response (Huffnagle et al., 1994).

4.4 Th1/2/17/22 cytokine responses

The protective role of Th1 along with the requirement of type 1 cytokines for fungal clearance have been demonstrated in models of cryptococcosis (Huffnagle et al., 1994; Kawakami et al., 1997; Blackstock et al., 1999; Abe et al., 2000; Traynor et al., 2000; Olszewski et al., 2001; Herring et al., 2002; Arora et al., 2005; Hernandez et al., 2005; Lindell et al., 2006; Wormley et al., 2007; Chen et al., 2008; Guillot et al., 2008b; Jain et al., 2009; Wozniak et al., 2009; Zhang et al., 2009), *Coccidioides* (Silva and Benitez, 2005), *Paracoccidioides* (Cano et al., 1998), *Histoplasma* (Zhou et al., 1995; Deepe and Gibbons, 2006) and *Blastomyces* (Brummer et al., 2006) infections. Th1 skewing is beneficial for clearance of *Aspergillus* (Cenci et al., 1997), although clearance of the filamentous fungi is mainly a domain of the innate immune system. The Th1 cytokine environment promotes clearance of fungi by supporting the classical activation of macrophages (Mantovani et al., 2001). Pathogenic fungi possess mechanisms that interfere with their recognition by macrophages. These fungi can survive within macrophage unless additional “external” stimulation occurs to activate fungicidal mechanisms. Such stimulation can be provided by Th1-type cytokines, especially IFN- γ (Arora et al., 2005; Hardison et al.). In the context of a Th1 immune response, macrophages become classically activated and abundantly generate fungicidal molecules such as nitric oxide produced by nitric oxide synthase, an enzyme that utilizes L-arginine. Importance of classical macrophage activation and production of nitric oxide for fungal clearance has been demonstrated for *Blastomyces* (Brummer et al., 2005; Kethineni et al., 2006), *Cryptococcus* (Granger et al., 1990; Alspaugh and Granger, 1991; Rivera et al., 2002; Arora et al., 2005; Zhang et al.; Hardison et al.), *Histoplasma* (Zhou et al., 1995; Allendoerfer and Deepe, 1998; Allen and Deepe, 2006) and *Paracoccidioides* (Moreira et al.; Pinzan et al.) infections. The deficiencies in cytokines that support classical activation of macrophages GM-CSF, IFN- γ , TNF- α , IL-12 are generally associated with the development of progressive fungal infection (Romani et al., 1994; Kawakami et al., 1999; Rayhane et al., 1999; Herring et al., 2005; Deepe and Gibbons, 2006) consistent with the general conclusion that Th1-type immune responses and type 1 cytokines are most optimal for resistance against fungal infections.

Unlike Th1-type responses, the Th2 response is non-protective and frequently results in pathological responses to fungal challenges. For most fungal species, Th2 responses and type 2 cytokines decrease clearance of fungus. This is attributed to: 1) a suppression of protective Th1 responses due to a mutual counterregulatory feedback loop (Cenci et al., 1999) and 2) a generation of alternatively activated macrophages that can harbor fungal organisms (Arora et al., 2005; Jain et al., 2009; Osterholzer et al., 2009a; Zhang et al., 2009). Th2 cytokines such as IL-4, IL-13 are the major trigger of alternative activation of macrophages (Arora et al., 2005; Jain et al., 2009; Zhang et al., 2009). These alternatively activated macrophages do not express nitric oxide synthase but induce arginase which metabolizes L-arginine without yielding fungicidal nitric oxide. In the Th2 biased experimental models of fungal infections, intracellular survival of fungus within macrophages parallels high induction of alternatively activated macrophage markers (Arora et al., 2005; Zhang et al., 2009; Hardison et al.).

Increased production of Th2-type cytokines has been associated with increased susceptibility to *Cryptococcus* (Arora et al., 2005; Zhang et al., 2009; Hardison et al.) and *Paracoccidioides* (Ruas et al., 2009) infections and to invasive pulmonary aspergillosis (Cenci et al., 1997; Cenci et al., 1999). Fungus-triggered Th2-type responses in the respiratory

system may also lead to allergic diseases such rhinitis/sinusitis, asthma, allergic bronchopulmonary mycosis. Th2 type responses are highly detrimental to the respiratory system by promoting mucus hypersecretion/goblet cell metaplasia, eosinophilic inflammation, and peribronchial fibrosis all of which contribute to impaired airway function. Cytokines IL-4, IL-5 and IL-13 are the major triggers of these pathologies as increased expression of these cytokines can be reproduced along with the allergic symptoms in the lungs challenged with fungi or their antigenic components (Blease et al., 2000; Arora et al., 2005; Jain et al., 2009; Zhang et al., 2009). Some of the fungal antigens can directly promote Th2 skewing. The secreted protein fraction from *Aspergillus fumigatus* promotes Th2 bias of the immune response (Bozza et al., 2009). Th2 pathologies are also found in mouse models of *C. neoformans* infections (Abe et al., 2000; Jain et al., 2009; Osterholzer et al., 2009b) (Figure 1). Expression of enzymes phospholipase B and urease by *C. neoformans* promote Th2 bias in the infected mice (Noverr et al., 2003; Osterholzer et al., 2009b). While Th2-biased responses are clearly undesirable in most types of fungal infections the exception is *Pneumocystis* infection, in which the Th2 response can contribute to fungal clearance (Shellito et al., 2000; McKinley et al., 2006; Hu et al., 2009).

Fig. 1. Classical versus alternative activation of macrophages during pulmonary infection with *C. neoformans*. A) Classically activated macrophages upregulate fungicidal mechanisms that eliminate ingested fungi. Note that ingested intracellular organisms show signs of degradation. B) Alternatively activated macrophages (AAM) harbor the ingested fungi. Note the abundant capsule formation (evidence of fungal metabolic activity) and dividing organisms (evidence of intracellular growth) within AAM. Alternative activation of macrophages is associated with crystallization of chitinase family proteins YM1 and YM2, a hallmark of AAM-induced pathology. V-vacuoles with the remnants of destroyed organisms, YM- YM1/YM2 crystals, C.n. – intact cryptococcal organisms.

The effects of Th17 responses and the IL-17 cytokine family in anti-fungal host responses may be protective or non-protective depending on fungal species and sites of infection (Figure 2). Thus, Th17 responses may be beneficial for some types of fungal infections or

Fig. 2. Th polarization in antifungal host defenses. The outcome of Th1, Th2, Th17, and Treg polarization results from balance between Th lineages which can mutually regulate each other via cytokine feedback loops. Resultant outcome can either promote clearance of the fungal infection or result in persistent infection and limited or severe pathology. Th1 response promotes control of most fungal infections; Th2 leads to severe pathology and fungal persistence; Th17 may support clearance or persistence of different fungal infections, but may promote chronic neutrophilic inflammation. Treg may limit pathology by promoting resolution of the inflammatory response, but may increase the risk of persistence. Correct balance between Th1 and Treg is thought to support protective tolerance.

exhibit detrimental effects. In the *H. capsulatum* infection model, IL-17 neutralization increases pulmonary fungal burden in connection with increased Treg numbers, suggesting that Th17 is beneficial for clearance of *Histoplasma* (Kroetz and Deepe, 2010). Th17 responses also contribute to anticryptococcal protection and the development of the protective inflammatory response in *C. neoformans* infected lungs (Zhang et al., 2009; Hardison et al., 2010b; Wozniak et al., 2011a).

The IL-23/IL-17 axis contributes to clearance of *Pneumocystis* (Rudner et al., 2007). However, in IFN- γ deficient mice infected with *Pneumocystis* the development of strong Th17 response is detrimental, suggesting that a balance between IFN- γ and IL-17 is needed for optimal clearance of *Pneumocystis* (Hu et al., 2009). At other mucosal sites, the effects of Th17 are variable. Th17 cells and IL-17 receptor signaling are required for mucosal host defenses in oral candidiasis (Conti et al., 2009); whereas Th17 impairs antifungal resistance and promotes inflammation in gastric infection model (Zelante et al., 2007). Th17 responses impair antifungal resistance and promotes inflammatory damage in the lungs of mice infected with *Aspergillus* (Zelante et al., 2007; Bozza et al., 2009; D'Angelo et al., 2009).

Overall, the Th17 response may have beneficial effects for clearance of some fungal pathogens; however it also has high potential to produce undesirable effects, including inflammatory damage.

Excessive immune reaction and uncontrolled inflammation can result in serious damage of the inflicted organs and tissues. Anti-inflammatory or regulatory cytokines such as IL-10 and TGF- β are an important part of the balance which prevents over exuberant inflammation during acute responses. These cytokines are also thought to be important components of resolution and tissue repair that occurs after elimination of the pathogen. Regulatory T cells are important sources of these cytokines and their role in inflammatory diseases and in the maintenance of healthy tissue homeostasis becomes increasingly appreciated (Romani and Puccetti, 2008; De Luca et al., 2010b; Littman and Rudensky, 2010). The importance of balance between pro-inflammatory processes and Treg cell regulation has recently been demonstrated in models of *Pneumocystis* (McKinley et al., 2006) and *Histoplasma* infections (Kroetz and Deepe). The excessive/damaging inflammatory reaction can be exemplified by immune reconstitution inflammatory syndrome (IRIS). IRIS is characterized by uncontrolled inflammatory responses with high induction of IFN- γ , TNF- α and other pro-inflammatory cytokines (Mori and Levin, 2009). Overproduction of these cytokines, rather than having protective effects, contributes to tissue injury that leads to worsening of the patient condition and high mortality (Mori and Levin, 2009). Interestingly, occurrence of IRIS in HIV patients who undergo antiretroviral therapy is particularly high in patients with *Cryptococcus* and *Pneumocystis* infections (Singh et al., 2005; Singh and Perfect, 2007; Murdoch et al., 2008). The mechanism of inadequate inflammatory response in IRIS is not understood, however it has been proposed that the regulatory mechanisms that control the inflammation, including Tregs are not sufficiently mobilized to put a break on this inflammatory response (McKinley et al., 2006; Shankar et al., 2008). In fact, patients with IRIS showed reduced suppressor function and diminished secretion of anti-inflammatory IL-10 by Tregs in one of the studies (Seddiki et al., 2009). Tregs are critical for maintaining the proper homeostasis in the GI track, and such mechanisms of protective tolerance are likely to be critical in the respiratory tract which is constantly exposed to inhaled fungal antigens. Insufficiency of the regulatory mechanisms most likely contributes to the development of allergic diseases. Thus, Tregs cells are important for maintaining balance between appropriate clearance rate and the inflammatory tissue damage. Such balance can be disturbed and the excessive Treg function may promote fungal persistence. A detrimental role of IL-10 has been demonstrated in cryptococcal infection models (Blackstock et al., 1999; Arora et al., 2005). Future studies will be needed to evaluate the possible role of Tregs in fungal infections, especially in the patients who develop mycoses without apparent immunodeficiency.

The polarization of T cells to Th1, Th2, Th17 and Treg lineages is important for the development of protective immunity, protective tolerance, chronic/allergic syndromes, or overwhelming allergic reactions. The proper balance maintained by the mutual regulation between these arms of the immune system is necessary to optimize clearance and minimize inflammatory damage to the infected tissues in the context of fungal infection. Our present understanding of these responses evolved from an oversimplified polarized Th1/Th2 paradigm to a broader understanding of mutual regulation ongoing during the immune process. Recent studies show that the Th1, Th2, Th17 responses co-exist in a fungus infected

lungs and the balance of cytokine production alters during different time points in a chronic fungal infection (Arora et al., 2011). Modulation of these responses can be achieved experimentally and therapeutically by use of cytokines and vaccination with different fractions of fungal antigens resulting in the induction of the proper and protective Th-cell polarization.

4.5 Vaccine-induced therapies targeting cellular mediated immunity

Currently, there are no standardized vaccines available for the prevention of fungal diseases in humans (as discussed earlier). A preponderance of evidence points to the development of cell-mediated immune responses, principally by Th1-type CD4⁺ T cells, as the predominant host defense mechanism against primary and opportunistic pulmonary fungal pathogens (Cutler et al., 2007). Further, ablation or neutralization of several Th1-type cytokines renders mice more susceptible to experimental infection with a number of fungal pathogens. Consequently, there has been great interest in identifying antigens that elicit protective CMI against fungal infections; some of which will be discussed herein.

Vaccination with native or recombinant Hsp60 from *H. capsulatum* or a domain within Hsp60 conferred protection in mice given a sub-lethal challenge with yeast cells and prolonged survival in mice given a lethal challenge (Gomez et al., 1995; Deepe and Gibbons, 2002). Protection was CD4⁺ T cell dependent and associated with the induction of IFN- γ , IL-12 and, surprisingly, the Th2-type cytokine IL-10 (Deepe and Gibbons, 2002; Scheckelhoff and Deepe, 2005). A similar vaccination strategy in mice using Hsp70 did not induce robust IL-12 or IFN- γ responses and protection against subsequent challenge with live yeast. Neutralization of IL-12 or IFN- γ abolished the protective efficacy of the Hsp60 vaccine in mice further highlighting the importance of these Th1-type cytokines in the induction of protection against *H. capsulatum*.

Similarly, vaccination of mice with recombinant Hsp60 derived from *P. brasiliensis* elicited protection against a lethal intranasal challenge with yeast (de Bastos Ascenco Soares et al., 2008). The protective effect of *P. brasiliensis* Hsp60 was abrogated following the depletion of CD4⁺ T cells or neutralization of IFN- γ ; similar to that observed for Hsp60 from *H. capsulatum* (Scheckelhoff and Deepe, 2005; de Bastos Ascenco Soares et al., 2008). However, IL-10 was not produced following antigen stimulation of splenocytes obtained from *P. brasiliensis* Hsp60 immunized mice. While the efficacy of vaccination with forms of Hsp60 from *H. capsulatum* and *P. brasiliensis* are encouraging, immunization with recombinant Hsp60 derived from *C. immitis* resulted in predominantly Th2 cytokine responses and little protection against a subsequent intraperitoneal challenge (Li et al., 2001). Thus, the induction of Th1-type immune responses in the lungs appears critical for the development of protection following immunization with Hsp60.

Evaluation of live attenuated, recombinant, and DNA vaccines of *C. immitis* in murine models have also highlighted the importance of Th1-type cytokine production, particularly IFN- γ , in protection against this microbe (reviewed in (Cole et al., 2004; Cox and Magee, 2004; Xue et al., 2009)). Mice immunized with recombinant aspartyl protease (Pep1), alpha-mannosidase (Amn1), or phospholipase B (Plb) individually or together as multivalent vaccine experienced a significant reduction in fungal burden and prolonged survival against a lethal pulmonary challenge with *C. posadasii* arthroconidia compared to controls (Tarcha et

al., 2006). Approximately 85% of mice immunized with the multivalent recombinant vaccine survived to day 90 post-inoculation. Similarly, immunization of mice with two recombinant antigens, *Coccidioides*-specific antigen (CSA) and the proline-rich cell wall protein Ag2/PRA, either as a mixture of two separately expressed proteins or as a single chimeric expression product was shown to protect mice from a lethal intranasal infection with *C. posadasii* (Shubitz et al., 2006). The protection observed with each vaccination strategy was associated with robust IFN- γ responses in protected mice, again showing the importance of Th1-type cytokines during protective host responses. Further, these studies highlighted the utility of a multivalent vaccination strategy that potentially evokes protective responses towards a broader set of T-cell epitopes.

The importance of CD4⁺ T cells and the generation of Th1-type responses towards eliciting protection against pulmonary fungal pathogens are also observed in vaccination models using a live *C. neoformans* strain engineered to express IFN- γ (Wormley et al., 2007) (Wozniak et al., 2009) (Young et al., 2009), a live attenuated strain of *B. dermatitidis* (Wuthrich et al., 2000), and recombinant *A. fumigatus* protein Asp f3 (Diaz-Arevalo et al., 2011). Immunization with recombinant Asp f3 of *A. fumigatus* protected cortisone acetate immune suppressed mice from an experimental pulmonary infection with *A. fumigatus* conidia (Diaz-Arevalo et al., 2011). The protection was dependent on CD4⁺ T cells as their depletion reduced the survival of vaccinated mice and adoptive transfer of Aspf3 primed CD4⁺ T cells into non-vaccinated mice enhanced their survival against experimentally induced pulmonary aspergillosis. Generation of sterilizing immunity in mice following pulmonary immunization with a *C. neoformans* strain engineered to express murine IFN- γ , designated H99 γ , was shown to require the induction of Th1-type cell-mediated immune responses (Wozniak et al., 2009). Interestingly, B-cell deficient mice immunized with H99 γ were protected from a subsequent lethal pulmonary challenge with WT *C. neoformans* (Wozniak et al., 2009; Young et al., 2009; Wozniak et al., 2011b). Also, vaccination of mice with an attenuated strain of *B. dermatitidis* containing a targeted deletion in the *BAD1* locus resulted in prolonged survival that was chiefly mediated by IFN- γ and TNF- α production by CD4⁺ T cells (Wuthrich et al., 2000; Wuthrich et al., 2002). Although these studies show that Th1-type CD4⁺ T cell responses are required for optimal host responses against these pulmonary pathogens, studies in *H. capsulatum*, *B. dermatitidis*, and *C. neoformans* highlight the inherent plasticity of the host response against pulmonary fungal pathogens. That is that some elements of the immune response can compensate for the loss of other components.

Vaccine-induced immunity against *B. dermatitidis* was shown to be mediated by CD4⁺ α/β T cell production of TNF- α and IFN- γ (Wuthrich et al., 2002). Moreover, the initiation, but not maintenance, of protective memory responses to *B. dermatitidis* required IL-12 production (Wuthrich et al., 2005). However, vaccine-induced immunity could be elicited and expressed in IFN- γ and TNF- α deficient mice. The reciprocal cytokine or the presence of GM-CSF was shown to compensate for the loss of IFN- γ and TNF- α showing some plasticity in the vaccine-induced host response to *Blastomyces* (Wuthrich et al., 2002). Furthermore, a role for Th17 cells in vaccine-induced protection against multiple pulmonary fungal pathogens has been shown (Wuthrich et al., 2011). Specifically, protection afforded by vaccination against *C. posadasii*, *H. capsulatum*, and *B. dermatitidis* was observed to be dependent on IL-17. In fact, IL-17 was shown to be indispensable since vaccinated IL-17A or IL-17RA deficient mice showed impaired anti-fungal resistance despite having normal Th1-type cytokine expression. In contrast, IL-17A was shown to contribute to but ultimately be dispensable for

protection against experimental pulmonary cryptococcosis in *C. neoformans* strain H99γ vaccinated mice (Hardison et al., 2010b; Wozniak et al., 2011a). Still, it appears imperative that vaccine strategies to prevent pulmonary mycoses be evaluated for their capacity to induce Th1 and Th17-type cytokine responses.

The induction of T cell-mediated immune responses is critical for optimal protection against pulmonary fungal pathogens (Cutler et al., 2007). Consequently, it may seem counterintuitive to suggest that vaccines designed to prevent fungal infections in patients with T cell deficiencies is possible. Nonetheless, vaccination studies using experimental models of *H. capsulatum* (Deepe and Gibbons, 2002), *P. brasiliensis* (de Bastos Ascenco Soares et al., 2008), *H. capsulatum* (Wuthrich et al., 2003), *B. dermatitidis* (Wuthrich et al., 2002; Wuthrich et al., 2003), *C. immitis* (Fierer et al., 2006), and *C. neoformans* (Wozniak et al., 2011b) have indicated that vaccine-induced protective immune responses can be elicited in immune deficient hosts. Cumulatively, the studies show that the presence of CD4⁺ or CD8⁺ T cells is essential for the induction (the period following vaccination) and expression (immune response following challenge) phases of the protective immune response. Protection is not induced in mice that are T cell deficient or depleted of both CD4⁺ and CD8⁺ T cell populations. Further, protection is lost in vaccinated mice following deletion of both T cell subsets. Interestingly, 80% of mice vaccinated with *C. neoformans* strain H99γ and subsequently depleted of both CD4⁺ and CD8⁺ T cells were protected from a lethal pulmonary challenge with WT *C. neoformans* (Wozniak et al., 2011b). These studies highlight dynamic compensatory mechanisms that mediate vaccine-induced protection during both the induction and expression phases of the anti-fungal immune response. Altogether, the results demonstrating the plasticity of the vaccine-induced immune response to pulmonary fungal pathogens are particularly exciting as they highlight the potential for inducing protection in immune competent and immune compromised hosts.

4.6 Antibody-mediated immunity and therapeutics

The contribution of antibody mediated immunity (AMI) towards protecting individuals against pulmonary fungal infections remains uncertain. Individuals with humoral deficiencies such as autosomal hyper-IgM syndrome and IgA deficiency do not exhibit an increased susceptibility to fungal infections (reviewed in Antachopoulos, 2007, 2010). In contrast, patients with X-linked hyper IgM syndrome and common-variable immunodeficiency which are often accompanied by defects in T CMI have a higher risk of developing pulmonary and invasive fungal infections like cryptococcosis and histoplasmosis. The efficacious role for antibodies during the host immune responses against fungi is like that observed against bacterial and viral pathogens. Antibodies produced in response to fungal infection serve as opsonins to promote phagocytosis, participate in antibody-dependent cellular cytotoxicity, augment Th1-type polarization, help to eliminate immunosuppressive polysaccharide antigen from serum and tissues, inhibit biofilm formation, have direct antifungal activity, and modulate the immune response to prevent host damage (reviewed in Alvarez and Casadevall, 2007; reviewed in Zaragoza and Casadevall, 2004).

Most studies showing the efficacy of AMI against pulmonary fungal pathogens has involved experimental models of PcP and cryptococcosis. The polysaccharide capsule of *Cryptococcus*, its main virulence determinant, is predominantly comprised of the polysaccharides glucuronoxylomannan (GXM) and galactoxylomannan (GalXM) and to a

much lesser extent, <1%, mannoproteins (MP) (reviewed in Zaragoza et al., 2009). Conjugate vaccines consisting of GXM combined to either tetanus toxoid (TT) or *Pseudomonas aeruginosa* exoprotein A (rEPA) induce high antibody titers (Devi et al., 1991; Casadevall et al., 1992), enhanced antifungal activity of murine and human phagocytes (Mukherjee et al., 1995c; Zhong and Pirofski, 1996, 1998) and conferred some protection against cryptococcosis in mice (Devi, 1996; Fleuridor et al., 1998; Nussbaum et al., 1999). Unfortunately, the profound suppressive effects on immune responses induced by cryptococcal polysaccharides and the highly variable immune responses observed in response to the intact GXM portion of the conjugate vaccine renders it an unlikely choice for future vaccine development (reviewed in Zaragoza et al., 2009; reviewed in Pirofski, 2001). A strategy using small peptide mimotopes (peptides which are able to induce antibodies that are capable of binding to the native antigen when administered as an immunogen) that mimic defined GXM epitopes was attempted to elicit protective antibody responses where using total GXM was unsuccessful. Zhang et al. described a peptide mimetic (P13) of GXM that was recognized by human anti-GXM antibodies (Zhang et al., 1997) and showed that vaccination with P13-protein conjugates in mice resulted in prolonged survival after a lethal *C. neoformans* challenge compared to controls (Fleuridor et al., 2001) or following establishment of a chronic infection (Datta et al., 2008).

Casadevall et al. developed a murine monoclonal antibody (MAb), 18B7, to *C. neoformans* polysaccharide that underwent phase I clinical studies in HIV⁺ patients with cryptococcal antigenemia (Casadevall et al., 1998). A modest reduction in serum cryptococcal antigen titers was observed in patients receiving singular doses of 1 and 2 mg/kg up to 10 weeks post-treatment before returning to baseline (Casadevall et al., 1998). To date, no follow-up clinical studies have been published. A new approach using MAb 18B7 currently being investigated in mice involves conjugation of the MAb to the therapeutic radioisotopes ¹⁸⁸Rhenium or ²¹³Bismuth (Dadachova et al., 2003; Bryan et al., 2010). Studies have shown that administration of radiolabeled MAb 18B7 to lethally infected mice results in prolonged survival, reduced organ fungal burden, and was a more effective therapy compared to mice treated with amphotericin B. Radioimmunotherapy can be applied using MAb derived against multiple pulmonary fungal pathogens and thus may evolve into an attractive option for the treatment of other pulmonary mycoses. Lastly, while most studies have examined passive administration with antibodies targeting *C. neoformans* polysaccharide, other cryptococcal targets for passive antibody therapy under experimental investigation include melanin (Rosas et al., 2001), β -glucan (Rachini et al., 2007), heat shock protein (HSP) 90 (Nooney et al., 2005) and glucosylceramide (Rodrigues et al., 2007).

Mice deficient in B cells, either due to a targeted disruption of the IgM constant region (μ MT mice) or using depletion antibodies, are more susceptible to PcP infection (Harmsen and Stankiewicz, 1991; Marcotte et al., 1996) (Lund et al., 2003; Lund et al., 2006). These studies showed that B cells were able to provide protection against PcP not only by producing Ab but also by amplifying the CD4⁺ T cell-mediated immune response. Passive administration of an IgM mAb shown to be directed against a surface antigen present on rat-, rabbit-, ferret-, and human-derived *P. carinii* induced partial protection against PcP in animal models (Gigliotti and Hughes, 1988). Subsequent studies showed that the passive administration of mAbs recognizing kexin-like molecule (KEX1) via the intranasal route prior to experimentally induced PcP resulted in a significant reduction in pulmonary fungal burden (~99%) (Gigliotti et al., 2002).

Contrasting studies have shown that B cell deficient μ MT mice have lower pulmonary fungal burden following intranasal infection with *A. fumigatus* (Montagnoli et al., 2003) or *B. dermatitidis* (Wuthrich et al., 2000) and are not more susceptible to experimental pulmonary histoplasmosis infection (Allendorfer et al., 1999) compared to WT controls. Also, passive transfer of polyclonal serum or MAbs obtained from *A. fumigatus*, *B. dermatitidis*, or *C. immitis* vaccinated mice did not enhance protection against a subsequent intranasal challenge with these pathogens (Kong et al., 1965; Beaman et al., 1977; Frosco et al., 1994; Wuthrich et al., 2000; Beaman et al., 1979). The role of antibodies in the host defense against fungal infection remains controversial because of its complexity. The current consensus is that antifungal antibodies can mediate protective, nonprotective, or disease-enhancing effects on host defenses during infection (Mukherjee et al., 1995a; Mukherjee et al., 1995b; Yuan et al., 1998a). Thus, resistance to disease may depend upon the proportion of protective antifungal antibodies produced during infection. In support of this concept, non-protective and protective MAbs to *C. neoformans* has been described (Mukherjee et al., 1995a; Maitta et al., 2004). Also, Nosanchuk et al. demonstrated that mice passively administered MAbs targeting a histone H2B-like protein on the surface of *H. capsulatum* before infection experienced a reduction in fungal burden and prolonged survival (Nosanchuk et al., 2003). These studies were somewhat surprising in light of previous studies showing no increased susceptibility to experimental histoplasmosis infection in B cell deficient mice (Allendorfer et al., 1999). Studies in *C. neoformans* has shown that the efficacy of MAbs appears to be dependent on several variables including host genetics (Rivera and Casadevall, 2005), Ab isotype (Yuan et al., 1995; Yuan et al., 1998b), T cell function (Yuan et al., 1997), and the presence of Th1- and Th2-related cytokines (Beenhouwer et al., 2001). AMI during the protective response to pulmonary fungal pathogens is broad and divergent, but it is clear that specific antibodies are efficacious for the host in the resolution of infection.

Studies also support the potential of using antibodies that target antigens common among multiple fungi to mediate cross-protection. Passive immunization using anti β -glucan MAbs or vaccination with β -glucan (laminarin) conjugated with the genetically-inactivated diphtheria toxin CRM197 (Lam-CRM vaccine) has been shown to confer protection against *C. neoformans*, *C. albicans* and *A. fumigatus* (Torosantucci et al., 2005; Rachini et al., 2007). Since β -glucans are found in the cell wall of fungi, the efficacy of anti- β -glucan antibodies can be very broad. Cenci et al. used a killer anti-idiotypic MAb reacting to a yeast killer toxin to protect mice from a lethal *A. fumigatus* challenge during experimental bone marrow transplantation (Cenci and Romani and 2375). Killer toxin is also expressed by multiple fungal species. Mycograb (NeuTec Pharman plc.), a recombinant antibody targeting an epitope within the HSP90 of *Candida albicans* that is conserved with the corresponding protein in *C. neoformans*, has been shown to act in adjunct with amphotericin B against multiple *Candida* species and *C. neoformans*. Altogether, these studies highlight the possibility that antibodies targeting “universal” antigens common to multiple fungal species such as β -glucans, killer toxins, or Hsps may extend protection to multiple disparate fungal pathogens. Casadevall and Pirofski has published an elegant commentary on the emergence of cross-protective targets for fungi (Casadevall and Pirofski, 2007).

5. Conclusion

The principal route of entry for several of the primary and opportunistic fungal pathogens is via inhalation of infectious propagules into the lungs. Consequently, exposure to these fungi

is unavoidable. Nevertheless, most encounters are asymptomatic due to the quick resolution of the fungi by resident effector cells within the lung. On those occasions that the fungal insult cannot be quickly eradicated, T cells, predominantly CD4⁺ T cells, preside over orchestrating the adaptive responses and provide help for antibody production. T cell responses are also influenced by cytokine production by innate effector cells. Nonetheless, T cells mediate various cellular responses at the sites of infection and are ultimately responsible for either resolution or pathological reactions associated with these infections. Furthermore, T cells are important players in homeostasis and protecting integrity of natural barriers. Recent advances in experimental animal models support the premise that anti-fungal vaccines may be effective in immune compromised hosts. The efficacy of anti-fungal vaccines in immune compromised populations is undoubtedly due to the inherent plasticity of host immunity. Altogether, it is clear that immune responses to pulmonary fungal infections are as diverse as the fungi themselves but that significant ground has been made towards its understanding.

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7. References

- Abe K, Kadota J, Ishimatsu Y, Iwashita T, Tomono K, Kawakami K, Kohno S. 2000. Th1-Th2 cytokine kinetics in the bronchoalveolar lavage fluid of mice infected with *Cryptococcus neoformans* of different virulences. *Microbiol Immunol* 44:849-855.
- Agostini C, Zambello R, Trentin L, Semenzato G. 1995. T lymphocytes with gamma/delta T-cell receptors in patients with AIDS and *Pneumocystis carinii* pneumonia. *Aids* 9:203-204.
- Alekseeva L, Huet D, Femenia F, Mouyna I, Abdelouahab M, Cagna A, Guerrier D, Tichanne-Seltzer V, Baeza-Squiban A, Chermette R, Latge JP, Berkova N. 2009. Inducible expression of beta defensins by human respiratory epithelial cells exposed to *Aspergillus fumigatus* organisms. *BMC Microbiol* 9:33.
- Allen HL, Deepe GS, Jr. 2006. B cells and CD4-CD8- T cells are key regulators of the severity of reactivation histoplasmosis. *J Immunol* 177:1763-1771.
- Allendoerfer R, Deepe GS, Jr. 1998. Infection with *Histoplasma capsulatum*: Host-fungus interface. *Rev Iberoam Micol* 15:256-260.
- Allendorfer R, Brunner GD, Deepe GS, Jr. 1999. Complex requirements for nascent and memory immunity in pulmonary histoplasmosis. *J Immunol* 162:7389-7396.
- Almyroutdis NG, Holland SM, Segal BH. 2005. Invasive aspergillosis in primary immunodeficiencies. *Med Mycol* 43 Suppl 1:S247-259.

- Alspaugh JA, Granger DL. 1991. Inhibition of *Cryptococcus neoformans* replication by nitrogen oxides supports the role of these molecules as effectors of macrophage-mediated cytostasis. *Infect Immun* 59:2291-2296.
- Alvarez M, Casadevall A. 2006. Phagosome extrusion and host-cell survival after *Cryptococcus neoformans* phagocytosis by macrophages. *Curr Biol* 16:2161-2165.
- Alvarez M, Casadevall A. 2007. Cell-to-cell spread and massive vacuole formation after *Cryptococcus neoformans* infection of murine macrophages. *BMC Immunol* 8:16.
- Ampel NM, Galgiani JN. 1991. Interaction of human peripheral blood mononuclear cells with *Coccidioides immitis* arthroconidia. *Cell Immunol* 133:253-262.
- Antachopoulos C. 2010. Invasive fungal infections in congenital immunodeficiencies. *Clin Microbiol Infect* 16:1335-1342.
- Antachopoulos C, Walsh T, Roilides E. 2007. Fungal infections in primary immunodeficiencies. *Eur J Pediatr* 166:1099-1117.
- Arora S, Hernandez Y, Erb-Downward JR, McDonald RA, Toews GB, Huffnagle GB. 2005. Role of IFN-gamma in regulating T2 immunity and the development of alternatively activated macrophages during allergic bronchopulmonary mycosis. *J Immunol* 174:6346-6356.
- Arora S, Olszewski MA, Tsang TM, McDonald RA, Toews GB, Huffnagle GB. 2011. Effect of cytokine interplay on macrophage polarization during chronic pulmonary infection with *Cryptococcus neoformans*. *Infect Immun* 79:1915-1926.
- Awasthi S. 2007. Dendritic cell- based vaccine against *Coccidioides* infection. *Ann N Y Acad Sci*.
- Bauman SK, Huffnagle GB, Murphy JW. 2003. Effects of tumor necrosis factor alpha on dendritic cell accumulation in lymph nodes draining the immunization site and the impact on the anticryptococcal cell-mediated immune response. *Infect Immun* 71:68-74.
- Bauman SK, Nichols KL, Murphy JW. 2000. Dendritic cells in the induction of protective and nonprotective anticryptococcal cell-mediated immune responses. *J Immunol* 165:158-167.
- Bava AJ, Mistchenko AS, Palacios MF, Estevez ME, Tiraboschi NI, Sen L, Negroni R, Diez RA. 1991. Lymphocyte subpopulations and cytokine production in paracoccidioidomycosis patients. *Microbiol Immunol* 35:167-174.
- Beaman L, Benjamini E, Pappagianis D. 1981. Role of lymphocytes in macrophage-induced killing of *Coccidioides immitis* in vitro. *Infect Immun* 34:347-353.
- Beaman L, Benjamini E, Pappagianis D. 1983. Activation of macrophages by lymphokines: enhancement of phagosome-lysosome fusion and killing of *Coccidioides immitis*. *Infect Immun* 39:1201-1207.
- Beaman L, Holmberg CA. 1980a. In vitro response of alveolar macrophages to infection with *Coccidioides immitis*. *Infect Immun* 28:594-600.
- Beaman L, Holmberg CA. 1980b. Interaction of nonhuman primate peripheral blood leukocytes and *Coccidioides immitis* in vitro. *Infection and immunity* 29:1200-1201.
- Beaman L, Pappagianis D, Benjamini E. 1977. Significance of T cells in resistance to experimental murine coccidioidomycosis. *Infect Immun* 17:580-585.
- Beaman LV, Pappagianis D, Benjamini E. 1979. Mechanisms of resistance to infection with *Coccidioides immitis* in mice. *Infect Immun* 23:681-685.

- Beenhouwer DO, Shapiro S, Feldmesser M, Casadevall A, Scharff MD. 2001. Both Th1 and Th2 cytokines affect the ability of monoclonal antibodies to protect mice against *Cryptococcus neoformans*. *Infect Immun* 69:6445-6455.
- Bellocchio S, Montagnoli C, Bozza S, Gaziano R, Rossi G, Mambula SS, Vecchi A, Mantovani A, Levitz SM, Romani L. 2004. The contribution of the Toll-like/IL-1 receptor superfamily to innate and adaptive immunity to fungal pathogens in vivo. *J Immunol* 172:3059-3069.
- Bhatia S, Fei M, Yarlagadda M, Qi Z, Akira S, Saijo S, Iwakura Y, van Rooijen N, Gibson GA, St Croix CM, Ray A, Ray P. 2011. Rapid host defense against *Aspergillus fumigatus* involves alveolar macrophages with a predominance of alternatively activated phenotype. *PLoS ONE* 6:e15943.
- Blackstock R, Buchanan KL, Adekunle M, Adesina, Murphy JW. 1999. Differential Regulation of Immune Responses by Highly and Weakly Virulent *Cryptococcus neoformans* Isolates. *Infect Immun* 67:3601-3609.
- Blease K, Mehrad B, Standiford TJ, Lukacs NW, Gosling J, Boring L, Charo IF, Kunkel SL, Hogaboam CM. 2000. Enhanced pulmonary allergic responses to *Aspergillus* in CCR2^{-/-} mice. *J Immunol* 165:2603-2611.
- Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, Rodrigues SD, Li S, Hansen JA, Zhao LP, Aderem A, Boeckh M. 2008. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. *New Eng J Med* 359:1766-1777.
- Bonfim CV, Mamoni RL, Lima Blotta MHS. 2009. TLR-2, TLR-4 and dectin-1 expression in human monocytes and neutrophils stimulated by *Paracoccidioides brasiliensis*. *Med Mycol* 47:722-733.
- Borger P, Koeter GH, Timmerman JA, Vellenga E, Tomee JF, Kauffman HF. 1999. Proteases from *Aspergillus fumigatus* induce interleukin (IL)-6 and IL-8 production in airway epithelial cell lines by transcriptional mechanisms. *J Infect Dis* 180:1267-1274.
- Botterel F, Gross K, Ibrahim-Granet O, Khoufache K, Escabasse V, Coste A, Cordonnier C, Escudier E, Bretagne S. 2008. Phagocytosis of *Aspergillus fumigatus* conidia by primary nasal epithelial cells in vitro. *BMC Microbiol* 8:97.
- Bozza S, Clavaud C, Giovannini G, Fontaine T, Beauvais A, Sarfati J, D'Angelo C, Perruccio K, Bonifazi P, Zagarella S, Moretti S, Bistoni F, Latge JP, Romani L. 2009. Immune sensing of *Aspergillus fumigatus* proteins, glycolipids, and polysaccharides and the impact on Th immunity and vaccination. *J Immunol* 183:2407-2414.
- Bozza S, Gaziano R, Spreca A, Bacci A, Montagnoli C, di Francesco P, Romani L. 2002. Dendritic cells transport conidia and hyphae of *Aspergillus fumigatus* from the airways to the draining lymph nodes and initiate disparate Th responses to the fungus. *J Immunol* 168:1362-1371.
- Bradsher RW, Balk RA, Jacobs RF. 1987. Growth inhibition of *Blastomyces dermatitidis* in alveolar and peripheral macrophages from patients with blastomycosis. *Am Rev Resp Dis* 135:412-417.
- Brummer E, Castaneda E, Restrepo A. 1993. Paracoccidioidomycosis: an update. *Clin Microbiol Rev* 6:89-117.
- Brummer E, Hanson LH, Restrepo A, Stevens DA. 1988. In vivo and in vitro activation of pulmonary macrophages by IFN-gamma for enhanced killing of *Paracoccidioides brasiliensis* or *Blastomyces dermatitidis*. *J Immunol* 140:2786-2789.

- Brummer E, Kethineni N, Stevens DA. 2005. Immunological basis for susceptibility and resistance to pulmonary blastomycosis in mouse strains. *Cytokine* 32:12-19.
- Brummer E, Kurita N, Yosihida S, Nishimura K, Miyaji M. 1991. Fungistatic activity of human neutrophils against *Histoplasma capsulatum*: correlation with phagocytosis. *J Infect Dis* 164:158-162.
- Brummer E, Stevens DA. 1987. Fungicidal mechanisms of activated macrophages: evidence for nonoxidative mechanisms for killing of *Blastomyces dermatitidis*. *Infect Immun* 55:3221-3224.
- Brummer E, Vinoda V, Stevens DA. 2006. IL-12 induction of resistance to pulmonary blastomycosis. *Cytokine* 35:221-228.
- Bruns S, Kniemeyer O, Hasenberg M, Aimaganianda V, Nietzsche S, Thywissen A, Jeron A, Latge JP, Brakhage AA, Gunzer M. 2010. Production of extracellular traps against *Aspergillus fumigatus* in vitro and in infected lung tissue is dependent on invading neutrophils and influenced by hydrophobin RodA. *PLoS Pathog* 6:e1000873.
- Bryan RA, Jiang Z, Howell RC, Morgenstern A, Bruchertseifer F, Casadevall A, Dadachova E. 2010. Radioimmunotherapy is more effective than antifungal treatment in experimental cryptococcal infection. *J Infect Dis* 202:633-637.
- Bullock WE, Wright SD. 1987. Role of the adherence-promoting receptors, CR3, LFA-1, and p150,95, in binding of *Histoplasma capsulatum* by human macrophages. *J Exp Med* 165:195-210.
- Calderon EJ, Regordan C, Medrano FJ, Ollero M, Varela JM. 1996. *Pneumocystis carinii* infection in patients with chronic bronchial disease. *Lancet* 347:977.
- Cano LE, Gomez B, Brummer E, Restrepo A, Stevens DA. 1994. Inhibitory effect of deferoxamine or macrophage activation on transformation of *Paracoccidioides brasiliensis* conidia ingested by macrophages: reversal by holotransferrin. *Infect Immun* 62:1494-1496.
- Cano LE, Kashino SS, Arruda C, Andre D, Xidieh CF, Singer-Vermes LM, Vaz CA, Burger E, Calich VL. 1998. Protective role of gamma interferon in experimental pulmonary paracoccidioidomycosis. *Infect Immun* 66:800-806.
- Cano LE, Singer-Vermes LM, Costa TA, Mengel JO, Xidieh CF, Arruda C, Andre DC, Vaz CA, Burger E, Calich VL. 2000. Depletion of CD8(+) T cells in vivo impairs host defense of mice resistant and susceptible to pulmonary paracoccidioidomycosis. *Infect Immun* 68:352-359.
- Cano LE, Singer-Vermes LM, Vaz CA, Russo M, Calich VL. 1995. Pulmonary paracoccidioidomycosis in resistant and susceptible mice: relationship among progression of infection, bronchoalveolar cell activation, cellular immune response, and specific isotype patterns. *Infect Immun* 63:1777-1783.
- Carmona EM, Lamont JD, Xue A, Wylam M, Limper AH. 2010. *Pneumocystis* cell wall beta-glucan stimulates calcium-dependent signaling of IL-8 secretion by human airway epithelial cells. *Resp Res* 11:95.
- Carmona EM, Vassallo R, Vuk-Pavlovic Z, Standing JE, Kottom TJ, Limper AH. 2006. *Pneumocystis* cell wall beta-glucans induce dendritic cell costimulatory molecule expression and inflammatory activation through a Fas-Fas ligand mechanism. *J Immunol* 177:459-467.
- Casadevall A, Cleare W, Feldmesser M, Glatman-Freedman A, Goldman DL, Kozel TR, Lendvai N, Mukherjee J, Pirofski LA, Rivera J, Rosas AL, Scharff MD, Valadon P,

- Westin K, Zhong Z. 1998. Characterization of a murine monoclonal antibody to *Cryptococcus neoformans* polysaccharide that is a candidate for human therapeutic studies. *Antimicrob Agents Chemother* 42:1437-1446.
- Casadevall A, Mukherjee J, Devi SJ, Schneerson R, Robbins JB, Scharff MD. 1992. Antibodies elicited by a *Cryptococcus neoformans*-tetanus toxoid conjugate vaccine have the same specificity as those elicited in infection. *J Infect Dis* 165:1086-1093.
- Casadevall A, Pirofski LA. 2007. Antibody-mediated protection through cross-reactivity introduces a fungal heresy into immunological dogma. *Infect Immun* 75:5074-5078.
- Cenci E, Mencacci A, Del Sero G, Bacci A, Montagnoli C, d'Ostiani CF, Mosci P, Bachmann M, Bistoni F, Kopf M, Romani L. 1999. Interleukin-4 causes susceptibility to invasive pulmonary aspergillosis through suppression of protective type I responses. *J Infect Dis* 180:1957-1968.
- Cenci E, Perito S, Enssle KH, Mosci P, Latge JP, Romani L, Bistoni F. 1997. Th1 and Th2 cytokines in mice with invasive aspergillosis. *Infect Immun* 65:564-570.
- Chamilos G, Ganguly D, Lande R, Gregorio J, Meller S, Goldman WE, Gilliet M, Kontoyiannis DP. 2010. Generation of IL-23 producing dendritic cells (DCs) by airborne fungi regulates fungal pathogenicity via the induction of T(H)-17 responses. *PLoS ONE* 5:e12955.
- Chen GH, McNamara DA, Hernandez Y, Huffnagle GB, Toews GB, Olszewski MA. 2008. Inheritance of Immune Polarization Patterns Is Linked to Resistance versus Susceptibility to *Cryptococcus neoformans* in a Mouse Model. *Infect Immun* 76:2379-2391.
- Chen GH, Olszewski MA, McDonald RA, Wells JC, Paine R, 3rd, Huffnagle GB, Toews GB. 2007. Role of granulocyte macrophage colony-stimulating factor in host defense against pulmonary *Cryptococcus neoformans* infection during murine allergic bronchopulmonary mycosis. *Am J Pathol* 170:1028-1040.
- Cheng BH, Liu Y, Xuei X, Liao CP, Lu D, Lasbury ME, Durant PJ, Lee CH. 2010. Microarray studies on effects of *Pneumocystis carinii* infection on global gene expression in alveolar macrophages. *BMC Microbiol* 10:103.
- Cher DJ, Mosmann TR. 1987. Two types of murine helper T cell clone. II. Delayed-type hypersensitivity is mediated by TH1 clones. *J Immunol* 138:3688-3694.
- Cherwinski HM, Schumacher JH, Brown KD, Mosmann TR. 1987. Two types of mouse helper T cell clone. III. Further differences in lymphokine synthesis between Th1 and Th2 clones revealed by RNA hybridization, functionally monospecific bioassays, and monoclonal antibodies. *J Exp Med* 166:1229-1244.
- Chuck SL, Sande MA. 1989. Infections with *Cryptococcus neoformans* in the Acquired Immunodeficiency Syndrome. *New Engl J Med* 321:794-799.
- Cole GT, Xue JM, Okeke CN, Tarcha EJ, Basrur V, Schaller RA, Herr RA, Yu JJ, Hung CY. 2004. A vaccine against coccidioidomycosis is justified and attainable. *Med Mycol* 42:189-216.
- Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, Filler SG, Masso-Welch P, Edgerton M, Gaffen SL. 2009. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med* 206:299-311.
- Cox RA, Magee DM. 2004. Coccidioidomycosis: host response and vaccine development. *Clin Microbiol Rev* 17:804-839.

- Cutler JE, Deepe GS, Jr., Klein BS. 2007. Advances in combating fungal diseases: vaccines on the threshold. *Nat Rev Microbiol* 5:13-28.
- D'Angelo C, De Luca A, Zelante T, Bonifazi P, Moretti S, Giovannini G, Iannitti RG, Zagarella S, Bozza S, Campo S, Salvatori G, Romani L. 2009. Exogenous pentraxin 3 restores antifungal resistance and restrains inflammation in murine chronic granulomatous disease. *J Immunol* 183:4609-4618.
- Dadachova E, Nakouzi A, Bryan RA, Casadevall A. 2003. Ionizing radiation delivered by specific antibody is therapeutic against a fungal infection. *Proc Natl Acad Sci U S A* 100:10942-10947.
- Dan JM, Wang JP, Lee CK, Levitz SM. 2008. Cooperative Stimulation of Dendritic Cells by *Cryptococcus neoformans* Mannoproteins and CpG Oligodeoxynucleotides. *PLoS ONE* 3:e2046.
- Datta K, Lees A, Pirofski LA. 2008. Therapeutic efficacy of a conjugate vaccine containing a peptide mimotope of cryptococcal capsular polysaccharide glucuronoxylomannan. *Clin Vaccine Immunol* 15:1176-1187.
- Davis JL, Welsh DA, Beard CB, Jones JL, Lawrence GG, Fox MR, Crothers K, Morris A, Charbonnet D, Swartzman A, Huang L. 2008. *Pneumocystis* colonisation is common among hospitalised HIV infected patients with non-*Pneumocystis* pneumonia. *Thorax* 63:329-334.
- de Bastos Ascenco Soares R, Gomez FJ, de Almeida Soares CM, Deepe GS, Jr. 2008. Vaccination with heat shock protein 60 induces a protective immune response against experimental *Paracoccidioides brasiliensis* pulmonary infection. *Infect Immun* 76:4214-4221.
- de Luca A, Bozza S, Zelante T, Zagarella S, D'Angelo C, Perruccio K, Vacca C, Carvalho A, Cunha C, Aversa F, Romani L. 2010a. Non-hematopoietic cells contribute to protective tolerance to *Aspergillus fumigatus* via a TRIF pathway converging on IDO. *Cell Mol Immunol* 7:459-470.
- De Luca A, Zelante T, D'Angelo C, Zagarella S, Fallarino F, Spreca A, Iannitti RG, Bonifazi P, Renauld JC, Bistoni F, Puccetti P, Romani L. 2010b. IL-22 defines a novel immune pathway of antifungal resistance. *Mucosal Immunol* 3:361-373.
- Deacon L, Pankhurst L, Liu J, Drew GH, Hayes ET, Jackson S, Longhurst J, Longhurst P, Pollard S, Tyrrel S. 2009. Endotoxin emissions from commercial composting activities. *Environ Health* 8 Suppl 1:S9.
- Deepe G. 2005. The Innate and Adaptive Immune Response to Pulmonary *Histoplasma capsulatum* Infection. In: Fidel P, Huffnagle G, editors. *Fungal Immunology*: Springer US, p 85-112.
- Deepe GS, Jr. 2000. Immune response to early and late *Histoplasma capsulatum* infections. *Curr Opin Microbiol* 3:359-362.
- Deepe GS, Jr., Gibbons RS. 2002. Cellular and molecular regulation of vaccination with heat shock protein 60 from *Histoplasma capsulatum*. *Infect Immun* 70:3759-3767.
- Deepe GS, Jr., Gibbons RS. 2006. T cells require tumor necrosis factor-alpha to provide protective immunity in mice infected with *Histoplasma capsulatum*. *J Infect Dis* 193:322-330.
- Deepe GS, Jr., Watson SR, Bullock WE. 1984. Cellular origins and target cells of immunoregulatory factors in mice with disseminated histoplasmosis. *J Immunol* 132:2064-2071.

- Del Poeta M. 2004. Role of Phagocytosis in the Virulence of *Cryptococcus neoformans*. Eukaryotic Cell 3:1067-1075.
- Denning DW. 1996. Aspergillosis: diagnosis and treatment. Int J Antimicrob Agents 6:161-168.
- Devi SJ. 1996. Preclinical efficacy of a glucuronoxylomannan-tetanus toxoid conjugate vaccine of *Cryptococcus neoformans* in a murine model. Vaccine 14:841-844.
- Devi SJ, Schneerson R, Egan W, Ulrich TJ, Bryla D, Robbins JB, Bennett JE. 1991. *Cryptococcus neoformans* serotype A glucuronoxylomannan-protein conjugate vaccines: synthesis, characterization, and immunogenicity. Infect Immun 59:3700-3707.
- Dias MF, Mesquita J, Filgueira AL, De Souza W. 2008. Human neutrophils susceptibility to *Paracoccidioides brasiliensis*: an ultrastructural and cytochemical assay. Med Mycology 46:241-249.
- Diaz-Arevalo D, Bagramyan K, Hong TB, Ito JI, Kalkum M. 2011. CD4(+) T cells mediate the protective effect of the recombinant Asp f3-based anti-aspergillosis vaccine. Infect Immun 79:2257-2266.
- Dionne SO, Podany AB, Ruiz YW, Ampel NM, Galgiani JN, Lake DF. 2006. Spherules derived from *Coccidioides posadasii* promote human dendritic cell maturation and activation. Infect Immun 74:2415-2422.
- Drutz DJ, Frey CL. 1985. Intracellular and extracellular defenses of human phagocytes against *Blastomyces dermatitidis* conidia and yeasts. J Lab Clin Med 105:737-750.
- Drutz DJ, Huppert M. 1983. Coccidioidomycosis: factors affecting the host-parasite interaction. Journal Infect Dis 147:372-390.
- Eissenberg LG, Goldman WE. 1988. Fusion of lysosomes with phagosomes containing *Histoplasma capsulatum*: use of fluoresceinated dextran. Adv Exp Med Biol 239:53-61.
- Eissenberg LG, Goldman WE, Schlesinger PH. 1993. *Histoplasma capsulatum* modulates the acidification of phagolysosomes. J Exp Med 177:1605-1611.
- Eissenberg LG, Schlesinger PH, Goldman WE. 1988. Phagosome-lysosome fusion in P388D1 macrophages infected with *Histoplasma capsulatum*. J Leuk Biol 43:483-491.
- Ersland K, Wuthrich M, Klein BS. 2010. Dynamic interplay among monocyte-derived, dermal, and resident lymph node dendritic cells during the generation of vaccine immunity to fungi. Cell Host Microbe 7:474-487.
- Evans SE, Hahn PY, McCann F, Kottom TJ, Pavlovic ZV, Limper AH. 2005. Pneumocystis cell wall beta-glucans stimulate alveolar epithelial cell chemokine generation through nuclear factor-kappaB-dependent mechanisms. Am J Resp Cell Mol Biol 32:490-497.
- Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, Cianfarani F, Odorisio T, Traidl-Hoffmann C, Behrendt H, Durham SR, Schmidt-Weber CB, Cavani A. 2009. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 119:3573-3585.
- Ezekowitz RA, Williams DJ, Koziel H, Armstrong MY, Warner A, Richards FF, Rose RM. 1991. Uptake of *Pneumocystis carinii* mediated by the macrophage mannose receptor. Nature 351:155-158.
- Fernandez-Botran R, Sanders VM, Mosmann TR, Vitetta ES. 1988. Lymphokine-mediated regulation of the proliferative response of clones of T helper 1 and T helper 2 cells. J Exp Med 168:543-558.

- Ferreira KS, Lopes JD, Almeida SR. 2004. Down-regulation of dendritic cell activation induced by *Paracoccidioides brasiliensis*. *Immunol Lett* 94:107-114.
- Fierer J, Waters C, Walls L. 2006. Both CD4+ and CD8+ T cells can mediate vaccine-induced protection against *Coccidioides immitis* infection in mice. *J Infect Dis* 193:1323-1331.
- Fisher FS, Bultman MW, Johnson SM, Pappagianis D, Zaborsky E. 2007. *Coccidioides* niches and habitat parameters in the southwestern United States: a matter of scale. *Ann N Y Acad Sci* 1111:47-72.
- Fleuridor R, Lees A, Pirofski L. 2001. A cryptococcal capsular polysaccharide mimotope prolongs the survival of mice with *Cryptococcus neoformans* infection. *J Immunol* 166:1087-1096.
- Fleuridor R, Zhong Z, Pirofski L. 1998. A human IgM monoclonal antibody prolongs survival of mice with lethal cryptococcosis. *J Infect Dis* 178:1213-1216.
- Fleury J, Escudier E, Pocholle MJ, Carre C, Bernaudin JF. 1985. Cell population obtained by bronchoalveolar lavage in *Pneumocystis carinii* pneumonitis. *Acta Cytol* 29:721-726.
- Franco M. 1987. Host-parasite relationships in paracoccidioidomycosis. *J Med Vet Mycol* 25:5-18.
- Franco M, Sano A, Kera K, Nishimura K, Takeo K, Miyaji M. 1989. Chlamydospore formation by *Paracoccidioides brasiliensis* mycelial form. *Rev Inst Med Trop Sao Paulo* 31:151-157.
- Fraser IP, Takahashi K, Koziel H, Fardin B, Harmsen A, Ezekowitz RA. 2000. *Pneumocystis carinii* enhances soluble mannose receptor production by macrophages. *Microbes Infect* 2:1305-1310.
- Frey CL, Drutz DJ. 1986. Influence of fungal surface components on the interaction of *Coccidioides immitis* with polymorphonuclear neutrophils. *The Journal of Infectious Diseases* 153:933-943.
- Frosco MB, Chase T, Jr., Macmillan JD. 1994. The effect of elastase-specific monoclonal and polyclonal antibodies on the virulence of *Aspergillus fumigatus* in immunocompromised mice. *Mycopathologia* 125:65-76.
- Fujita H, Nogales KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. 2009. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A* 106:21795-21800.
- Gafa V, Remoli ME, Giacomini E, Gagliardi MC, Lande R, Severa M, Grillot R, Coccia EM. 2007. In vitro infection of human dendritic cells by *Aspergillus fumigatus* conidia triggers the secretion of chemokines for neutrophil and Th1 lymphocyte recruitment. *Microbes Infect* 9:971-980.
- Gajewski TF, Fitch FW. 1988. Anti-proliferative effect of IFN-gamma in immune regulation. I. IFN-gamma inhibits the proliferation of Th2 but not Th1 murine helper T lymphocyte clones. *J Immunol* 140:4245-4252.
- Galgiani JN. 1986. Inhibition of Different Phases of *Coccidioides immitis* by Human Neutrophils or Hydrogen Peroxide. *Journal of Infectious Diseases* 153:217-222.
- Gereke M, Jung S, Buer J, Bruder D. 2009. Alveolar type II epithelial cells present antigen to CD4(+) T cells and induce Foxp3(+) regulatory T cells. *Am J Respir Crit Care Med* 179:344-355.
- Gersuk GM, Underhill DM, Zhu L, Marr KA. 2006. Dectin-1 and TLRs permit macrophages to distinguish between different *Aspergillus fumigatus* cellular states. *J Immunol* 176:3717-3724.

- Gigliotti F, Haidaris CG, Wright TW, Harmsen AG. 2002. Passive intranasal monoclonal antibody prophylaxis against murine *Pneumocystis carinii* pneumonia. *Infect Immun* 70:1069-1074.
- Gigliotti F, Hughes WT. 1988. Passive immunoprophylaxis with specific monoclonal antibody confers partial protection against *Pneumocystis carinii* pneumonitis in animal models. *J Clin Invest* 81:1666-1668.
- Gildea LA, Ciruolo GM, Morris RE, Newman SL. 2005. Human dendritic cell activity against *Histoplasma capsulatum* is mediated via phagolysosomal fusion. *Infect Immun* 73:6803-6811.
- Gildea LA, Morris RE, Newman SL. 2001. *Histoplasma capsulatum* yeasts are phagocytosed via very late antigen-5, killed, and processed for antigen presentation by human dendritic cells. *J Immunol* 166:1049-1056.
- Goihman-Yahr M, Essenfled-Yahr E, de Albornoz MC, Yarzabal L, de Gomez MH, San Martin B, Ocanto A, Gil F, Convit J. 1980. Defect of in vitro digestive ability of polymorphonuclear leukocytes in paracoccidioidomycosis. *Infect Immun* 28:557-566.
- Goihman-Yahr M, Pereira J, Isturiz G, Vilorio N, Carrasquero M, Saavedra N, de Gomez MH, Roman A, San Martin B, Bastardo de Albornoz MC, et al. 1992. Relationship between digestive and killing abilities of neutrophils against *Paracoccidioides brasiliensis*. *Mycoses* 35:269-274.
- Goihman-Yahr M, Rothenberg A, Rosquete R, Avila-Millan E, de Albornoz MC, de Gomez MH, San Martin B, Ocanto A, Pereira J, Molina T. 1985. A novel method for estimating killing ability and digestion of *Paracoccidioides brasiliensis* by phagocytic cells in vitro. *Sabouraudia* 23:245-251.
- Gomez FJ, Allendoerfer R, Deepe GS, Jr. 1995. Vaccination with recombinant heat shock protein 60 from *Histoplasma capsulatum* protects mice against pulmonary histoplasmosis. *Infect Immun* 63:2587-2595.
- Gomez FJ, Pilcher-Roberts R, Alborzi A, Newman SL. 2008. *Histoplasma capsulatum* cyclophilin A mediates attachment to dendritic cell VLA-5. *J Immunol* 181:7106-7114.
- Gomez P, Hackett TL, Moore MM, Knight DA, Tebbutt SJ. 2010. Functional genomics of human bronchial epithelial cells directly interacting with conidia of *Aspergillus fumigatus*. *BMC Genomics* 11:358.
- Gonzalez A, de Gregori W, Velez D, Restrepo A, Cano LE. 2000. Nitric Oxide Participation in the Fungicidal Mechanism of Gamma Interferon-Activated Murine Macrophages against *Paracoccidioides brasiliensis* Conidia. *Infect Immun* 68:2546-2552.
- Granger DL, Hibbs JB, Jr., Perfect JR, Durack DT. 1990. Metabolic fate of L-arginine in relation to microbistatic capability of murine macrophages. *J Clin Invest* 85:264-273.
- Grazziutti M, Przepiorka D, Rex JH, Braunschweig I, Vadhan-Raj S, Savary CA. 2001. Dendritic cell-mediated stimulation of the in vitro lymphocyte response to *Aspergillus*. *Bone Marrow Transplant* 27:647-652.
- Guerrero A, Jain N, Wang X, Fries BC. 2010. *Cryptococcus neoformans* variants generated by phenotypic switching differ in virulence through effects on macrophage activation. *Infect Immun* 78:1049-1057.

- Guillot L, Carroll SF, Badawy M, Qureshi ST. 2008a. *Cryptococcus neoformans* induces IL-8 secretion and CXCL1 expression by human bronchial epithelial cells. *Resp Res* 9:9.
- Guillot L, Carroll SF, Homer R, Qureshi ST. 2008b. Enhanced innate immune responsiveness to pulmonary *Cryptococcus neoformans* infection is associated with resistance to progressive infection. *Infect Immun* 76:4745-4756.
- Hanano R, Kaufmann SH. 1999. *Pneumocystis carinii* pneumonia in mutant mice deficient in both TCRalpha and TCRgamma cells: cytokine and antibody responses. *J Infect Dis* 179:455-459.
- Hanna SA, Monteiro da Silva JL, Giannini MJ. 2000. Adherence and intracellular parasitism of *Paracoccidioides brasiliensis* in Vero cells. *Microbes Infect* 2:877-884.
- Hardison SE, Ravi S, Wozniak KL, Young ML, Olszewski MA, Wormley FL, Jr. 2010a. Pulmonary Infection with an Interferon- γ -Producing *Cryptococcus neoformans* Strain Results in Classical Macrophage Activation and Protection. *Am J Pathol* 176:774-785.
- Hardison SE, Wozniak KL, Kolls JK, Wormley FL, Jr. 2010b. Interleukin-17 Is Not Required for Classical Macrophage Activation in a Pulmonary Mouse Model of *Cryptococcus neoformans* Infection. *Infect Immun* 78:5341-5351.
- Harmsen AG, Stankiewicz M. 1990. Requirement for CD4⁺ cells in resistance to *Pneumocystis carinii* pneumonia in mice. *J Exp Med* 172:937-945.
- Harmsen AG, Stankiewicz M. 1991. T cells are not sufficient for resistance to *Pneumocystis carinii* pneumonia in mice. *J Protozool* 38:44S-45S.
- Hasenberg M, A KH, Bonifatius S, Jeron A, Gunzer M. 2011. Direct Observation of Phagocytosis and NET-formation by Neutrophils in Infected Lungs using 2-photon Microscopy. *J Vis Exp*.
- Hernandez Y, Arora S, Erb-Downward JR, McDonald RA, Toews GB, Huffnagle GB. 2005. Distinct roles for IL-4 and IL-10 in regulating T2 immunity during allergic bronchopulmonary mycosis. *J Immunol* 174:1027-1036.
- Herring AC, Falkowski NR, Chen GH, McDonald RA, Toews GB, Huffnagle GB. 2005. Transient neutralization of tumor necrosis factor alpha can produce a chronic fungal infection in an immunocompetent host: Potential role of immature dendritic cells. *Infect Immun* 73:39-49.
- Herring AC, Lee J, McDonald RA, Toews GB, Huffnagle GB. 2002. Induction of interleukin-12 and gamma interferon requires tumor necrosis factor alpha for protective T1-cell-mediated immunity to pulmonary *Cryptococcus neoformans* infection. *Infect Immun* 70:2959-2964.
- Hidore MR, Mislán TW, Murphy JW. 1991a. Responses of murine natural killer cells to binding of the fungal target *Cryptococcus neoformans*. *Infect Immun* 59:1489-1499.
- Hidore MR, Murphy JW. 1989. Murine natural killer cell interactions with a fungal target, *Cryptococcus neoformans*. *Infect Immun* 57:1990-1997.
- Hidore MR, Nabavi N, Sonleitner F, Murphy JW. 1991b. Murine natural killer cells are fungicidal to *Cryptococcus neoformans*. *Infection and immunity* 59:1747-1754.
- Hu T, Takamoto M, Hida S, Tagawa Y, Sugane K. 2009. IFN-gamma deficiency worsens *Pneumocystis pneumonia* with Th17 development in nude mice. *Immunol Lett* 127:55-59.

- Huang L, Crothers K, Morris A, Groner G, Fox M, Turner JR, Merrifield C, Eiser S, Zucchi P, Beard CB. 2003. Pneumocystis colonization in HIV-infected patients. *J Eukaryot Microbiol* 50 Suppl:616-617.
- Huffnagle GB, Lipscomb MF. 1992. Pulmonary cryptococcosis. *Am J Pathol* 141:1517-1520.
- Huffnagle GB, Lipscomb MF, Lovchik JA, Hoag KA, Street NE. 1994. The role of CD4(+) and CD8(+) T-Cells in the protective inflammatory response to a pulmonary cryptococcal infection. *J Leukoc Biol* 55:35-42.
- Huffnagle GB, Yates JL, Lipscomb MF. 1991. T-cell-mediated immunity in the lung - a *Cryptococcus neoformans* pulmonary infection model using SCID and athymic nude-mice. *Infect Immun* 59:1423-1433.
- Ibrahim-Granet O, Philippe B, Boleti H, Boisvieux-Ulrich E, Grenet D, Stern M, Latge JP. 2003. Phagocytosis and Intracellular Fate of *Aspergillus fumigatus* Conidia in Alveolar Macrophages. *Infect Immun* 71:891-903.
- Jain AV, Zhang Y, Fields WB, McNamara DA, Choe MY, Chen GH, Erb-Downward J, Osterholzer JJ, Toews GB, Huffnagle GB, Olszewski MA. 2009. Th2 but not Th1 immune bias results in altered lung functions in a murine model of pulmonary *Cryptococcus neoformans* infection. *Infect Immun* 77:5389-5399.
- Jarvis JN, Harrison TS. 2007. HIV-associated cryptococcal meningitis. *AIDS* 21:2119-2129.
- Jimenez BE, Murphy JW. 1984. In vitro effects of natural killer cells against *Paracoccidioides brasiliensis* yeast phase. *Infect Immun* 46:552-558.
- Johnston SA, May RC. 2010. The human fungal pathogen *Cryptococcus neoformans* escapes macrophages by a phagosome emptying mechanism that is inhibited by Arp2/3 complex-mediated actin polymerisation. *PLoS Pathog* 6.
- Kagi MK, Fierz W, Grob PJ, Russi EW. 1993. High proportion of gamma-delta T cell receptor positive T cells in bronchoalveolar lavage and peripheral blood of HIV-infected patients with *Pneumocystis carinii* pneumonias. *Respiration* 60:170-177.
- Kappe R, Levitz S, Harrison TS, Ruhnke M, Ampel NM, Just-Nubling G. 1998. Recent advances in cryptococcosis, candidiasis and coccidioidomycosis complicating HIV infection. *Med Mycol* 36:207-215.
- Kashkin KP, Likholetov SM, Lipnitsky AV. 1977. Studies on mediators of cellular immunity in experimental coccidioidomycosis. *Sabouraudia* 15:59-68.
- Kasperkovitz PV, Cardenas ML, Vyas JM. 2010. TLR9 is actively recruited to *Aspergillus fumigatus* phagosomes and requires the N-terminal proteolytic cleavage domain for proper intracellular trafficking. *J Immunol* 185:7614-7622.
- Kawakami K, Kinjo Y, Uezu K, Yara S, Miyagi K, Koguchi Y, Nakayama T, Taniguchi M, Saito A. 2001a. Monocyte chemoattractant protein-1-dependent increase of V alpha 14 NKT cells in lungs and their roles in Th1 response and host defense in cryptococcal infection. *J Immunol* 167:6525-6532.
- Kawakami K, Kinjo Y, Yara S, Koguchi Y, Uezu K, Nakayama T, Taniguchi M, Saito A. 2001b. Activation of Valpha14(+) natural killer T cells by alpha-galactosylceramide results in development of Th1 response and local host resistance in mice infected with *Cryptococcus neoformans*. *Infect Immun* 69:213-220.
- Kawakami K, Kinjo Y, Yara S, Uezu K, Koguchi Y, Tohyama M, Azuma M, Takeda K, Akira S, Saito A. 2001c. Enhanced gamma interferon production through activation of Valpha14(+) natural killer T cells by alpha-galactosylceramide in interleukin-18-deficient mice with systemic cryptococcosis. *Infect Immun* 69:6643-6650.

- Kawakami K, Qureshi MH, Zhang T, Okamura H, Kurimoto M, Saito A. 1997. IL-18 protects mice against pulmonary and disseminated infection with *Cryptococcus neoformans* by inducing IFN-gamma production. *J Immunol* 159:5528-5534.
- Kawakami K, Shibuya K, Qureshi MH, Zhang TT, Koguchi Y, Tohyama M, Xie QF, Naoe S, Saito A. 1999. Chemokine responses and accumulation of inflammatory cells in the lungs of mice infected with highly virulent *Cryptococcus neoformans*: effects of interleukin-12. *FEMS Immunol Med Microbiol* 25:391-402.
- Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. 1995. Genetic variation among *Pneumocystis carinii* hominis isolates in recurrent pneumocystosis. *J Infect Dis* 172:595-598.
- Kelly MN, Shellito JE. 2010. Current understanding of *Pneumocystis* immunology. *Future Microbiol* 5:43-65.
- Kelly RM, Chen JM, Yauch LE, Levitz SM. 2005. Opsonic requirements for dendritic cell-mediated responses to *Cryptococcus neoformans*. *Infect Immun* 73:592-598.
- Kethineni N, Brummer E, Stevens DA. 2006. Susceptibility to pulmonary blastomycosis in young compared to adult mice: immune deficiencies in young mice. *Med Mycol* 44:51-60.
- Kimberlin CL, Hariri AR, Hempel HO, Goodman NL. 1981. Interactions between *Histoplasma capsulatum* and macrophages from normal and treated mice: comparison of the mycelial and yeast phases in alveolar and peritoneal macrophages. *Infect Immun* 34:6-10.
- Klein BS, Hogan LH, Jones JM. 1993. Immunologic recognition of a 25-amino acid repeat arrayed in tandem on a major antigen of *Blastomyces dermatitidis*. *J Clin Invest* 92:330-337.
- Klein BS, Vergeront JM, Weeks RJ, Kumar UN, Mathai G, Varkey B, Kaufman L, Bradsher RW, Stoebig JF, Davis JP. 1986. Isolation of *Blastomyces dermatitidis* in soil associated with a large outbreak of blastomycosis in Wisconsin. *New Engl J Med* 314:529-534.
- Kleinschek MA, Muller U, Schutze N, Sabat R, Straubinger RK, Blumenschein WM, McClanahan T, Kastelein RA, Alber G. 2010. Administration of IL-23 engages innate and adaptive immune mechanisms during fungal infection. *Int Immunol* 22:81-90.
- Kling HM, Shipley TW, Patil S, Morris A, Norris KA. 2009. *Pneumocystis* colonization in immunocompetent and simian immunodeficiency virus-infected cynomolgus macaques. *J Infect Dis* 199:89-96.
- Kobayashi H, Worgall S, O'Connor TP, Crystal RG. 2007. Interaction of *Pneumocystis carinii* with dendritic cells and resulting host responses to *P. carinii*. *J Immunother* (1997) 30:54-63.
- Kong YM, Savage DC, Levine HB. 1965. Enhancement of immune responses in mice by a booster injection of *Coccidioides* spherules. *J Immunol* 95:1048-1056.
- Kontoyiannis DP. 2010. Manipulation of host angiogenesis: A critical link for understanding the pathogenesis of invasive mold infections? *Virulence* 1:192-196.
- Kovacs JA, Kovacs AA, Polis M, Wright WC, Gill VJ, Tuazon CU, Gelmann EP, Lane HC, Longfield R, Overturf G, Macher AM, Fauci AS, Parrillo JE, Bennett JE, Masur H. 1985. Cryptococcosis in the Acquired Immunodeficiency Syndrome. *Ann Intern Med* 103:533-538.

- Kozel TR, Pfrommer GS, Redelman D. 1987. Activated neutrophils exhibit enhanced phagocytosis of *Cryptococcus neoformans* opsonized with normal human serum. Clin Exp Immunol 70:238-246.
- Koziel H, Eichbaum Q, Kruskal BA, Pinkston P, Rogers RA, Armstrong MY, Richards FF, Rose RM, Ezekowitz RA. 1998. Reduced binding and phagocytosis of *Pneumocystis carinii* by alveolar macrophages from persons infected with HIV-1 correlates with mannose receptor downregulation. J Clin Invest 102:1332-1344.
- Kroetz DN, Deepe GS, Jr. 2010. CCR5 dictates the equilibrium of proinflammatory IL-17+ and regulatory Foxp3+ T cells in fungal infection. J Immunol 184:5224-5231.
- Kurita N, Brummer E, Yoshida S, Nishimura K, Miyaji M. 1991a. Antifungal activity of murine polymorphonuclear neutrophils against *Histoplasma capsulatum*. J Med Vet Mycol 29:133-143.
- Kurita N, Terao K, Brummer E, Ito E, Nishimura K, Miyaji M. 1991b. Resistance of *Histoplasma capsulatum* to killing by human neutrophils. Evasion of oxidative burst and lysosomal-fusion products. Mycopathologia 115:207-213.
- Lanken PN, Minda M, Pietra GG, Fishman AP. 1980. Alveolar response to experimental *Pneumocystis carinii* pneumonia in the rat. Am J Pathol 99:561-588.
- Latge JP. 1999. *Aspergillus fumigatus* and aspergillosis. Clin Microbiol Rev 12:310-350.
- Leigh TR, Millett MJ, Jameson B, Collins JV. 1993. Serum titres of *Pneumocystis carinii* antibody in health care workers caring for patients with AIDS. Thorax 48:619-621.
- Levitz SM. 1991. The ecology of *Cryptococcus neoformans* and the epidemiology of cryptococcosis. Rev Infect Dis 13:1163-1169.
- Levitz SM, Dupont MP. 1993. Phenotypic and functional characterization of human lymphocytes activated by interleukin-2 to directly inhibit growth of *Cryptococcus neoformans* in vitro. Journal Clin Invest 91:1490-1498.
- Levitz SM, Nong SH, Seetoo KF, Harrison TS, Speizer RA, Simons ER. 1999. *Cryptococcus neoformans* resides in an acidic phagolysosome of human macrophages. Infect Immun 67:885-890.
- Li K, Yu JJ, Hung CY, Lehmann PF, Cole GT. 2001. Recombinant urease and urease DNA of *Coccidioides immitis* elicit an immunoprotective response against coccidioidomycosis in mice. Infect Immun 69:2878-2887.
- Lim TS, Murphy JW. 1980. Transfer of immunity to cryptococcosis by T-enriched splenic lymphocytes from *Cryptococcus neoformans*-sensitized mice. Infect Immun 30:5-11.
- Lin JS, Huang JH, Hung LY, Wu SY, Wu-Hsieh BA. 2010. Distinct roles of complement receptor 3, Dectin-1, and sialic acids in murine macrophage interaction with *Histoplasma* yeast. J Leuk Biol 88:95-106.
- Lindell DM, Moore TA, McDonald RA, Toews GB, Huffnagle GB. 2006. Distinct compartmentalization of CD4+ T-cell effector function versus proliferative capacity during pulmonary cryptococcosis. Am J Pathol 168:847-855.
- Lipscomb MF, Alvarellos T, Toews GB, Tompkins R, Evans Z, Koo G, Kumar V. 1987. Role of natural killer cells in resistance to *Cryptococcus neoformans* infections in mice. Am J Pathol 128:354-361.
- Littman DR, Rudensky AY. 2010. Th17 and regulatory T cells in mediating and restraining inflammation. Cell 140:845-858.
- Long EG, Smith JS, Meier JL. 1986. Attachment of *Pneumocystis carinii* to rat pneumocytes. Laboratory investigation; a journal of technical methods and pathology 54:609-615.

- Long KH, Gomez FJ, Morris RE, Newman SL. 2003. Identification of heat shock protein 60 as the ligand on *Histoplasma capsulatum* that mediates binding to CD18 receptors on human macrophages. *J Immunol* 170:487-494.
- Loures FV, Pina A, Felonato M, Calich VL. 2009. TLR2 is a negative regulator of Th17 cells and tissue pathology in a pulmonary model of fungal infection. *J Immunol* 183:1279-1290.
- Lund FE, Hollifield M, Schuer K, Lines JL, Randall TD, Garvy BA. 2006. B cells are required for generation of protective effector and memory CD4 cells in response to *Pneumocystis* lung infection. *J Immunol* 176:6147-6154.
- Lund FE, Schuer K, Hollifield M, Randall TD, Garvy BA. 2003. Clearance of *Pneumocystis carinii* in mice is dependent on B cells but not on *P. carinii*-specific antibody. *J Immunol* 171:1423-1430.
- Ma H, Croudace JE, Lammas DA, May RC. 2006. Expulsion of live pathogenic yeast by macrophages. *Curr Biol* 16:2156-2160.
- Ma LL, Spurrell JC, Wang JF, Neely GG, Epelman S, Krensky AM, Mody CH. 2002. CD8 T cell-mediated killing of *Cryptococcus neoformans* requires granulysin and is dependent on CD4 T cells and IL-15. *J Immunol* 169:5787-5795.
- Ma LL, Wang CL, Neely GG, Epelman S, Krensky AM, Mody CH. 2004. NK cells use perforin rather than granulysin for anticryptococcal activity. *J Immunol* 173:3357-3365.
- Magill SS, Chiller TM, Warnock DW. 2008. Evolving strategies in the management of aspergillosis. *Expert Opin Pharmacother* 9:193-209.
- Maitta RW, Datta K, Chang Q, Luo RX, Witover B, Subramaniam K, Pirofski LA. 2004. Protective and nonprotective human immunoglobulin M monoclonal antibodies to *Cryptococcus neoformans* glucuronoxylomannan manifest different specificities and gene use profiles. *Infect Immun* 72:4810-4818.
- Mambula SS, Sau K, Henneke P, Golenbock DT, Levitz SM. 2002. Toll-like receptor (TLR) signaling in response to *Aspergillus fumigatus*. *J Biol Chem* 277:39320-39326.
- Mambula SS, Simons ER, Hastey R, Selsted ME, Levitz SM. 2000. Human neutrophil-mediated nonoxidative antifungal activity against *Cryptococcus neoformans*. *Infect Immun* 68:6257-6264.
- Mansour MK, Latz E, Levitz SM. 2006. *Cryptococcus neoformans* glycoantigens are captured by multiple lectin receptors and presented by dendritic cells. *J Immunol* 176:3053-3061.
- Mantovani A, Muzio M, Garlanda C, Sozzani S, Allavena P. 2001. Macrophage control of inflammation: negative pathways of regulation of inflammatory cytokines. *Novartis Found Symp* 234:120-131.
- Marcotte H, Levesque D, Delanay K, Bourgeault A, de la Durantaye R, Brochu S, Lavoie MC. 1996. *Pneumocystis carinii* infection in transgenic B cell-deficient mice. *J Infect Dis* 173:1034-1037.
- Marr KJ, Jones GJ, Zheng C, Huston SM, Timm-McCann M, Islam A, Berenger BM, Ma LL, Wiseman JC, Mody CH. 2009. *Cryptococcus neoformans* directly stimulates perforin production and rearms NK cells for enhanced anticryptococcal microbicidal activity. *Infect Immun* 77:2436-2446.

- McKinley L, Logar AJ, McAllister F, Zheng M, Steele C, Kolls JK. 2006. Regulatory T cells dampen pulmonary inflammation and lung injury in an animal model of *Pneumocystis pneumonia*. *J Immunol* 177:6215-6226.
- Mednick AJ, Feldmesser M, Rivera J, Casadevall A. 2003. Neutropenia alters lung cytokine production in mice and reduces their susceptibility to pulmonary cryptococcosis. *Eur J Immunol* 33:1744-1753.
- Meier A, Kirschning CJ, Nikolaus T, Wagner H, Heesemann J, Ebel F. 2003. Toll-like receptor (TLR) 2 and TLR4 are essential for *Aspergillus*-induced activation of murine macrophages. *Cell Microbiol* 5:561-570.
- Mendes-Giannini MJ, Hanna SA, da Silva JL, Andreotti PF, Vincenzi LR, Benard G, Lenzi HL, Soares CP. 2004. Invasion of epithelial mammalian cells by *Paracoccidioides brasiliensis* leads to cytoskeletal rearrangement and apoptosis of the host cell. *Microbes Infect* 6:882-891.
- Mendes-Giannini MJ, Ricci LC, Uemura MA, Toscano E, Arns CW. 1994. Infection and apparent invasion of Vero cells by *Paracoccidioides brasiliensis*. *J Med Vet Mycol* 32:189-197.
- Merkel GJ, Scofield BA. 1997. The in vitro interaction of *Cryptococcus neoformans* with human lung epithelial cells. *FEMS Immunol Med Microbiol* 19:203-213.
- Millard PR, Wakefield AE, Hopkin JM. 1990. A sequential ultrastructural study of rat lungs infected with *Pneumocystis carinii* to investigate the appearances of the organism, its relationships and its effects on pneumocytes. *Int J Exp Pathol* 71:895-904.
- Miller MF, Mitchell TG, Storkus WJ, Dawson JR. 1990. Human natural killer cells do not inhibit growth of *Cryptococcus neoformans* in the absence of antibody. *Infect Immun* 58:639-645.
- Mitchell TG, Perfect JR. 1995. Cryptococcosis in the era of AIDS--100 years after the discovery of *Cryptococcus neoformans*. *Clin Microbiol Rev* 8:515-548.
- Mody CH, Chen GH, Jackson C, Curtis JL, Toews GB. 1994. In vivo depletion of murine CD8 positive T cells impairs survival during infection with a highly virulent strain of *Cryptococcus neoformans*. *Mycopathologia* 125:7-17.
- Mody CH, Lipscomb MF, Street NE, Toews GB. 1990. Depletion of CD4+ (L3T4+) lymphocytes in vivo impairs murine host defense to *Cryptococcus neoformans*. *J Immunol* 144:1472-1477.
- Montagnoli C, Bozza S, Bacci A, Gaziano R, Mosci P, Morschhauser J, Pitzurra L, Kopf M, Cutler J, Romani L. 2003. A role for antibodies in the generation of memory antifungal immunity. *Eur J Immunol* 33:1193-1204.
- Monteiro da Silva J, Andreotti P, Benard G, Soares C, Miranda E, Mendes-Giannini M. 2007. Epithelial cells treated with genistein inhibit adhesion and endocytosis of *Paracoccidioides brasiliensis*. *Antonie Van Leeuwenhoek* 92: 129-135.
- Moreira AP, Dias-Melicio LA, Soares AM. 2010. Interleukin-10 but not Transforming Growth Factor beta inhibits murine activated macrophages *Paracoccidioides brasiliensis* killing: effect on H₂O₂ and NO production. *Cell Immunol* 263:196-203.
- Mori S, Levin P. 2009. A brief review of potential mechanisms of immune reconstitution inflammatory syndrome in HIV following antiretroviral therapy. *Int J STD AIDS* 20:447-452.

- Morris A, Sciurba FC, Lebedeva IP, Githaiga A, Elliott WM, Hogg JC, Huang L, Norris KA. 2004. Association of chronic obstructive pulmonary disease severity and *Pneumocystis* colonization. *Am J Respir Crit Care Med* 170:408-413.
- Morris A, Sciurba FC, Norris KA. 2008a. *Pneumocystis*: a novel pathogen in chronic obstructive pulmonary disease? *Copd* 5:43-51.
- Morris A, Wei K, Afshar K, Huang L. 2008b. Epidemiology and clinical significance of *Pneumocystis* colonization. *J Infect Dis* 197:10-17.
- Morrison BE, Park SJ, Mooney JM, Mehrad B. 2003. Chemokine-mediated recruitment of NK cells is a critical host defense mechanism in invasive aspergillosis. *J Clin Invest* 112:1862-1870.
- Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 136:2348-2357.
- Mukherjee J, Nussbaum G, Scharff MD, Casadevall A. 1995a. Protective and nonprotective monoclonal antibodies to *Cryptococcus neoformans* originating from one B cell. *J Exp Med* 181:405-409.
- Mukherjee J, Scharff MD, Casadevall A. 1995b. Variable efficacy of passive antibody administration against diverse *Cryptococcus neoformans* strains. *Infect Immun* 63:3353-3359.
- Mukherjee S, Lee SC, Casadevall A. 1995c. Antibodies to *Cryptococcus neoformans* glucuronoxylomannan enhance antifungal activity of murine macrophages. *Infect Immun* 63:573-579.
- Muller U, Stenzel W, Kohler G, Werner C, Polte T, Hansen G, Schutze N, Straubinger RK, Blessing M, McKenzie AN, Brombacher F, Alber G. 2007. IL-13 induces disease-promoting type 2 cytokines, alternatively activated macrophages and allergic inflammation during pulmonary infection of mice with *Cryptococcus neoformans*. *J Immunol* 179:5367-5377.
- Murdoch DM, Venter WD, Feldman C, Van Rie A. 2008. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS* 22:601-610.
- Murphy JW, Hidore MR, Nabavi N. 1991. Binding interactions of murine natural killer cells with the fungal target *Cryptococcus neoformans*. *Infect Immun* 59:1476-1488.
- Murphy JW, McDaniel DO. 1982. In vitro reactivity of natural killer (NK) cells against *Cryptococcus neoformans*. *J Immunol* 128:1577-1583.
- Mylonakis E, Barlam TF, Flanigan T, Rich JD. 1998. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest* 114:251-262.
- Nabavi N, Murphy JW. 1985. In vitro binding of natural killer cells to *Cryptococcus neoformans* targets. *Infect Immun* 50:50-57.
- Nakamura K, Miyagi K, Koguchi Y, Kinjo Y, Uezu K, Kinjo T, Akamine M, Fujita J, Kawamura I, Mitsuyama M, Adachi Y, Ohno N, Takeda K, Akira S, Miyazato A, Kaku M, Kawakami K. 2006. Limited contribution of Toll-like receptor 2 and 4 to the host response to a fungal infectious pathogen, *Cryptococcus neoformans*. *FEMS Immunol Med Microbiol* 47:148-154.
- Nakamura K, Miyazato A, Xiao G, Hatta M, Inden K, Aoyagi T, Shiratori K, Takeda K, Akira S, Saijo S, Iwakura Y, Adachi Y, Ohno N, Suzuki K, Fujita J, Kaku M, Kawakami K.

2008. Deoxynucleic Acids from *Cryptococcus neoformans* Activate Myeloid Dendritic Cells via a TLR9-Dependent Pathway. *J Immunol* 180:4067-4074.
- Nelson MP, Christmann BS, Werner JL, Metz AE, Trevor JL, Lowell CA, Steele C. 2011. IL-33 and M2a alveolar macrophages promote lung defense against the atypical fungal pathogen *Pneumocystis murina*. *J Immunol* 186:2372-2381.
- Netea MG, Van Der Graaf CA, Vonk AG, Verschuieren I, Van Der Meer JW, Kullberg BJ. 2002. The role of toll-like receptor (TLR) 2 and TLR4 in the host defense against disseminated candidiasis. *J Infect Dis* 185:1483-1489.
- Netea MG, Warris A, Van der Meer JW, Fenton MJ, Verver-Janssen TJ, Jacobs LE, Andresen T, Verweij PE, Kullberg BJ. 2003. *Aspergillus fumigatus* evades immune recognition during germination through loss of toll-like receptor-4-mediated signal transduction. *J Infect Dis* 188:320-326.
- Nevez G, Raccurt C, Jounieaux V, Dei-Cas E, Mazars E. 1999. Pneumocystosis versus pulmonary *Pneumocystis carinii* colonization in HIV-negative and HIV-positive patients. *AIDS* 13:535-536.
- Newman KC, Riley EM. 2007. Whatever turns you on: accessory-cell-dependent activation of NK cells by pathogens. *Nat Rev Immunol* 7:279-291.
- Newman S, Chaturvedi S, Klein B. 1995. The WI-1 antigen of *Blastomyces dermatitidis* yeasts mediates binding to human macrophage CD11b/CD18 (CR3) and CD14. *J Immunol* 154:753-761.
- Newman SL, Gootee L, Gabay JE. 1993. Human neutrophil-mediated fungistasis against *Histoplasma capsulatum*. Localization of fungistatic activity to the azurophil granules. *Journal Clin Invest* 92:624-631.
- Newman SL, Gootee L, Kidd C, Ciralo GM, Morris R. 1997. Activation of human macrophage fungistatic activity against *Histoplasma capsulatum* upon adherence to type 1 collagen matrices. *J Immunol* 158:1779-1786.
- Nooney L, Matthews RC, Burnie JP. 2005. Evaluation of Mycograb, amphotericin B, caspofungin, and fluconazole in combination against *Cryptococcus neoformans* by checkerboard and time-kill methodologies. *Diagn Microbiol Infect Dis* 51:19-29.
- Norris KA, Morris A, Patil S, Fernandes E. 2006. *Pneumocystis* colonization, airway inflammation, and pulmonary function decline in acquired immunodeficiency syndrome. *Immunol Res* 36:175-187.
- Nosanchuk JD, Steenbergen JN, Shi L, Deepe GS, Jr., Casadevall A. 2003. Antibodies to a cell surface histone-like protein protect against *Histoplasma capsulatum*. *J Clin Invest* 112:1164-1175.
- Noverr MC, Cox GM, Perfect JR, Huffnagle GB. 2003. Role of PLB1 in pulmonary inflammation and cryptococcal eicosanoid production. *Infect Immun* 71:1538-1547.
- Nussbaum G, Anandasabapathy S, Mukherjee J, Fan M, Casadevall A, Scharff MD. 1999. Molecular and idiotypic analyses of the antibody response to *Cryptococcus neoformans* glucuronoxylomannan-protein conjugate vaccine in autoimmune and nonautoimmune mice. *Infect Immun* 67:4469-4476.
- Odio CM, Navarrete M, Carrillo JM, Mora L, Carranza A. 1999. Disseminated histoplasmosis in infants. *Pediatr Infect Dis J* 18:1065-1068.
- Olszewski MA, Huffnagle GB, Traynor TR, McDonald RA, Cook DN, Toews GB. 2001. Regulatory effects of macrophage inflammatory protein 1alpha/CCL3 on the

- development of immunity to *Cryptococcus neoformans* depend on expression of early inflammatory cytokines. *Infect Immun* 69:6256-6263.
- Osterholzer JJ, Curtis JL, Polak T, Ames T, Chen G-H, McDonald R, Huffnagle GB, Toews GB. 2008. CCR2 Mediates Conventional Dendritic Cell Recruitment and the Formation of Bronchovascular Mononuclear Cell Infiltrates in the Lungs of Mice Infected with *Cryptococcus neoformans*. *J Immunol* 181:610-620.
- Osterholzer JJ, Milam JE, Chen GH, Toews GB, Huffnagle GB, Olszewski MA. 2009a. Role of dendritic cells and alveolar macrophages in regulating early host defense against pulmonary infection with *Cryptococcus neoformans*. *Infect Immun* 77:3749-3758.
- Osterholzer JJ, Surana R, Milam JE, Montano GT, Chen GH, Sonstein J, Curtis JL, Huffnagle GB, Toews GB, Olszewski MA. 2009b. Cryptococcal urease promotes the accumulation of immature dendritic cells and a non-protective T2 immune response within the lung. *Am J Pathol* 174:932-943.
- Oykhman P, Mody CH. 2010. Direct microbicidal activity of cytotoxic T-lymphocytes. *J Biomed Biotechnol* 2010:249482.
- Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM. 2010. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis* 50:1101-1111.
- Paris S, Boisvieux-Ulrich E, Crestani B, Houcine O, Taramelli D, Lombardi L, Latge JP. 1997. Internalization of *Aspergillus fumigatus* conidia by epithelial and endothelial cells. *Infect Immun* 65:1510-1514.
- Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. 2009. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 23:525-530.
- Park SJ, Burdick MD, Brix WK, Stoler MH, Askew DS, Strieter RM, Mehrad B. 2010. Neutropenia enhances lung dendritic cell recruitment in response to *Aspergillus* via a cytokine-to-chemokine amplification loop. *J Immunol* 185:6190-6197.
- Patino MM, Williams D, Ahrens J, Graybill JR. 1987. Experimental histoplasmosis in the beige mouse. *J Leuk Biol* 41:228-235.
- Peracoli MT, Fortes MR, Da Silva MF, Montenegro MR. 1995. Natural killer cell activity in experimental paracoccidioidomycosis of the Syrian hamster. *Rev Inst Med Trop Sao Paulo* 37:129-136.
- Perfect JR, Casadevall A. 2002. Cryptococcosis. *Infect Dis Clin N Am* 16:837-874.
- Petkus AF, Baum LL. 1987. Natural killer cell inhibition of young spherules and endospores of *Coccidioides immitis*. *J Immunol* 139:3107-3111.
- Pinzan CF, Ruas LP, Casabona-Fortunato AS, Carvalho FC, Roque-Barreira MC. 2010. Immunological basis for the gender differences in murine *Paracoccidioides brasiliensis* infection. *PLoS One* 5:e10757.
- Pirofski LA. 2001. Polysaccharides, mimotopes and vaccines for fungal and encapsulated pathogens. *Trends Microbiol* 9:445-451.
- Rachini A, Pietrella D, Lupo P, Torosantucci A, Chiani P, Bromuro C, Proietti C, Bistoni F, Cassone A, Vecchiarelli A. 2007. An anti-beta-glucan monoclonal antibody inhibits

- growth and capsule formation of *Cryptococcus neoformans* in vitro and exerts therapeutic, anticryptococcal activity in vivo. *Infect Immun* 75:5085-5094.
- Ramaprakash H, Ito T, Standiford TJ, Kunkel SL, Hogaboam CM. 2009. Toll-like receptor 9 modulates immune responses to *Aspergillus fumigatus* conidia in immunodeficient and allergic mice. *Infect Immun* 77:108-119.
- Ramirez-Ortiz ZG, Lee CK, Wang JP, Boon L, Specht CA, Levitz SM. 2011. A Nonredundant Role for Plasmacytoid Dendritic Cells in Host Defense against the Human Fungal Pathogen *Aspergillus fumigatus*. *Cell Host Microbe* 9:415-424.
- Ramirez-Ortiz ZG, Specht CA, Wang JP, Lee CK, Bartholomeu DC, Gazzinelli RT, Levitz SM. 2008. Toll-like receptor 9-dependent immune activation by unmethylated CpG motifs in *Aspergillus fumigatus* DNA. *Infect Immun* 76:2123-2129.
- Rayhane N, Lortholary O, Fitting C, Callebort J, Huerre M, Dromer F, Cavaillon JM. 1999. Enhanced sensitivity of tumor necrosis factor/lymphotoxin-alpha-deficient mice to *Cryptococcus neoformans* infection despite increased levels of nitrite/nitrate, interferon-gamma, and interleukin-12. *J Infect Dis* 180:1637-1647.
- Retini C, Vecchiarelli A, Monari C, Tascini C, Bistoni F, Kozel TR. 1996. Capsular polysaccharide of *Cryptococcus neoformans* induces proinflammatory cytokine release by human neutrophils. *Infect Immun* 64:2897-2903.
- Rivera J, Casadevall A. 2005. Mouse genetic background is a major determinant of isotype-related differences for antibody-mediated protective efficacy against *Cryptococcus neoformans*. *J Immunol* 174:8017-8026.
- Rivera J, Mukherjee J, Weiss LM, Casadevall A. 2002. Antibody efficacy in murine pulmonary *Cryptococcus neoformans* infection: a role for nitric oxide. *J Immunol* 168:3419-3427.
- Rodrigues ML, Shi L, Barreto-Bergter E, Nimrichter L, Farias SE, Rodrigues EG, Travassos LR, Nosanchuk JD. 2007. Monoclonal antibody to fungal glucosylceramide protects mice against lethal *Cryptococcus neoformans* infection. *Clin Vaccine Immunol* 14:1372-1376.
- Romani L, Mencacci A, Tonnetti L, Spaccapelo R, Cenci E, Puccetti P, Wolf SF, Bistoni F. 1994. IL-12 is both required and prognostic in vivo for T helper type 1 differentiation in murine candidiasis. *J Immunol* 153:5167-5175.
- Romani L, Puccetti P. 2008. Immune regulation and tolerance to fungi in the lungs and skin. *Chem Immunol Allergy* 94:124-137.
- Rosas AL, Nosanchuk JD, Casadevall A. 2001. Passive immunization with melanin-binding monoclonal antibodies prolongs survival of mice with lethal *Cryptococcus neoformans* infection. *Infect Immun* 69:3410-3412.
- Ruas LP, Bernardes ES, Fermino ML, de Oliveira LL, Hsu DK, Liu FT, Chammas R, Roque-Barreira MC. 2009. Lack of galectin-3 drives response to *Paracoccidioides brasiliensis* toward a Th2-biased immunity. *PLoS One* 4:e4519.
- Rudner XL, Happel KI, Young EA, Shellito JE. 2007. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine *Pneumocystis carinii* infection. *Infect Immun* 75:3055-3061.
- Salkowski CA, Balish E. 1991. Role of natural killer cells in resistance to systemic cryptococcosis. *J Leuk Biol* 50:151-159.
- Savage DC, Madin SH. 1968. Cellular responses in lungs of immunized mice to intranasal infection with *Coccidioides immitis*. *Sabouraudia* 6:94-102.

- Scheckelhoff M, Deepe GS, Jr. 2005. A deficiency in gamma interferon or interleukin-10 modulates T-Cell-dependent responses to heat shock protein 60 from *Histoplasma capsulatum*. *Infect Immun* 73:2129-2134.
- Schmidt S, Tramsen L, Hanisch M, Latge JP, Huenecke S, Koehl U, Lehrnbecher T. 2011. Human natural killer cells exhibit direct activity against *Aspergillus fumigatus* hyphae, but not against resting conidia. *J Infect Dis* 203:430-435.
- Schrettl M, Ibrahim-Granet O, Droin S, Huerre M, Latge JP, Haas H. 2010. The crucial role of the *Aspergillus fumigatus* siderophore system in interaction with alveolar macrophages. *Microbes Infect* 12:1035-1041.
- Seddiki N, Sasson SC, Santner-Nanan B, Munier M, van Bockel D, Ip S, Marriott D, Pett S, Nanan R, Cooper DA, Zaunders JJ, Kelleher AD. 2009. Proliferation of weakly suppressive regulatory CD4⁺ T cells is associated with over-active CD4⁺ T-cell responses in HIV-positive patients with mycobacterial immune restoration disease. *Eur J Immunol* 39:391-403.
- Serrano-Gomez D, Dominguez-Soto A, Ancochea J, Jimenez-Heffernan JA, Leal JA, Corbi AL. 2004. Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin mediates binding and internalization of *Aspergillus fumigatus* conidia by dendritic cells and macrophages. *J Immunol* 173:5635-5643.
- Shankar EM, Vignesh R, Velu V, Murugavel KG, Sekar R, Balakrishnan P, Lloyd CA, Saravanan S, Solomon S, Kumarasamy N. 2008. Does CD4⁺CD25⁺foxp3⁺ cell (Treg) and IL-10 profile determine susceptibility to immune reconstitution inflammatory syndrome (IRIS) in HIV disease? *J Inflamm (Lond)* 5:2.
- Shellito JE, Tate C, Ruan S, Kolls J. 2000. Murine CD4⁺ T lymphocyte subsets and host defense against *Pneumocystis carinii*. *J Infect Dis* 181:2011-2017.
- Shoham S, Levitz SM. 2005. The immune response to fungal infections. *Br J Haematol* 129:569-582.
- Shubitz LF, Yu JJ, Hung CY, Kirkland TN, Peng T, Perrill R, Simons J, Xue J, Herr RA, Cole GT, Galgiani JN. 2006. Improved protection of mice against lethal respiratory infection with *Coccidioides posadasii* using two recombinant antigens expressed as a single protein. *Vaccine* 24:5904-5911.
- Silva AJ, Benitez JA. 2005. Th1-type immune response to a *Coccidioides immitis* antigen delivered by an attenuated strain of the non-invasive enteropathogen *Vibrio cholerae*. *FEMS Immunol Med Microbiol* 43:393-398.
- Silva MFd, Napimoga MH, Rodrigues DBR, Pereira SAL, Silva CL. 2011. Phenotypic and functional characterization of pulmonary macrophages subpopulations after intratracheal injection of *Paracoccidioides brasiliensis* cell wall components. *Immunobiol* 216:821-831.
- Silvana dos Santos S, Ferreira KS, Almeida SR. 2011. *Paracoccidioides brasiliensis*-Induced Migration of Dendritic Cells and Subsequent T-Cell Activation in the Lung-Draining Lymph Nodes. *PLoS ONE* 6:e19690.
- Singh N, Gayowski T, Wagener MM, Marino IR. 1997. Clinical spectrum of invasive cryptococcosis in liver transplant recipients receiving tacrolimus. *Clin Transplant* 11:66-70.
- Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, Munoz P, Klintmalm GB, Stosor V, del Busto R, Limaye AP, Somani J, Lyon M, Houston S, House AA, Pruett TL, Orloff S, Humar A, Dowdy L, Garcia-Diaz J, Kalil AC, Fisher RA, Husain

- S. 2005. An immune reconstitution syndrome-like illness associated with *Cryptococcus neoformans* infection in organ transplant recipients. *Clin Infect Dis* 40:1756-1761.
- Singh N, Perfect JR. 2007. Immune reconstitution syndrome associated with opportunistic mycoses. *Lancet Infect Dis* 7:395-401.
- Soares DA, de Andrade RV, Silva SS, Bocca AL, Soares Felipe SM, Petrofeza S. 2010. Extracellular *Paracoccidioides brasiliensis* phospholipase B involvement in alveolar macrophage interaction. *BMC Microbiol* 10:241.
- Soroosh P, Doherty TA. 2009. Th9 and allergic disease. *Immunology* 127:450-458.
- Spitzer ED, Spitzer SG, Freundlich LF, Casadevall A. 1993. Persistence of initial infection in recurrent *Cryptococcus neoformans* meningitis. *Lancet* 341:595-596.
- Steele C, Zheng M, Young E, Marrero L, Shellito JE, Kolls JK. 2002. Increased host resistance against *Pneumocystis carinii* pneumonia in gammadelta T-cell-deficient mice: protective role of gamma interferon and CD8(+) T cells. *Infect Immun* 70:5208-5215.
- Stevens TL, Bossie A, Sanders VM, Fernandez-Botran R, Coffman RL, Mosmann TR, Vitetta ES. 1988. Regulation of antibody isotype secretion by subsets of antigen-specific helper T cells. *Nature* 334:255-258.
- Strasser JE, Newman SL, Ciraolo GM, Morris RE, Howell ML, Dean GE. 1999. Regulation of the macrophage vacuolar ATPase and phagosome-lysosome fusion by *Histoplasma capsulatum*. *J Immunol* 162:6148-6154.
- Suchyta MR, Smith JG, Graybill JR. 1988. The role of natural killer cells in histoplasmosis. *Am Rev Resp Dis* 138:578-582.
- Syme RM, Spurrell JCL, Amankwah EK, Green FHY, Mody CH. 2002. Primary dendritic cells phagocytose *Cryptococcus neoformans* via mannose receptors and Fc gamma receptor II for presentation to T lymphocytes. *Infect Immun* 70:5972-5981.
- Tarcha EJ, Basrur V, Hung CY, Gardner MJ, Cole GT. 2006. A recombinant aspartyl protease of *Coccidioides posadasii* induces protection against pulmonary coccidioidomycosis in mice. *Infect Immun* 74:516-527.
- Taylor PR, Brown GD, Reid DM, Willment JA, Martinez-Pomares L, Gordon S, Wong SYC. 2002. The β -Glucan Receptor, Dectin-1, Is Predominantly Expressed on the Surface of Cells of the Monocyte/Macrophage and Neutrophil Lineages. *J Immunol* 169:3876-3882.
- Taylor PR, Tsoni SV, Willment JA, Dennehy KM, Rosas M, Findon H, Haynes K, Steele C, Botto M, Gordon S, Brown GD. 2007. Dectin-1 is required for beta-glucan recognition and control of fungal infection. *Nat Immunol* 8:31-38.
- Torosantucci A, Bromuro C, Chiani P, De Bernardis F, Berti F, Galli C, Norelli F, Bellucci C, Polonelli L, Costantino P, Rappuoli R, Cassone A. 2005. A novel glyco-conjugate vaccine against fungal pathogens. *J Exp Med* 202:597-606.
- Traynor TR, Kuziel WA, Toews GB, Huffnagle GB. 2000. CCR2 Expression Determines T1 Versus T2 Polarization During Pulmonary *Cryptococcus neoformans* Infection. *J Immunol* 164:2021-2027.
- Tucker SC, Casadevall A. 2002. Replication of *Cryptococcus neoformans* in macrophages is accompanied by phagosomal permeabilization and accumulation of vesicles containing polysaccharide in the cytoplasm. *Proc Natl Acad Sci USA* 99:3165-3170.
- Uezu K, Kawakami K, Miyagi K, Kinjo Y, Kinjo T, Ishikawa H, Saito A. 2004. Accumulation of gammadelta T cells in the lungs and their regulatory roles in Th1 response and

- host defense against pulmonary infection with *Cryptococcus neoformans*. J Immunol 172:7629-7634.
- Voelz K, Lammas DA, May RC. 2009. Cytokine signaling regulates the outcome of intracellular macrophage parasitism by *Cryptococcus neoformans*. Infect Immun.
- Wang J, Gigliotti F, Bhagwat SP, Maggirwar SB, Wright TW. 2007. Pneumocystis stimulates MCP-1 production by alveolar epithelial cells through a JNK-dependent mechanism. Am J Phys Lung Cell Mol Phys 292:L1495-1505.
- Wang J, Gigliotti F, Maggirwar S, Johnston C, Finkelstein JN, Wright TW. 2005. *Pneumocystis carinii* activates the NF-kappaB signaling pathway in alveolar epithelial cells. Infect Immun 73:2766-2777.
- Wang JE, Warris A, Ellingsen EA, Jorgensen PF, Flo TH, Espevik T, Solberg R, Verweij PE, Aasen AO. 2001. Involvement of CD14 and toll-like receptors in activation of human monocytes by *Aspergillus fumigatus* hyphae. Infect Immun 69:2402-2406.
- Warschkau H, Yu H, Kiderlen AF. 1998. Activation and suppression of natural cellular immune functions by *Pneumocystis carinii*. Immunobiol 198:343-360.
- Wegner TN, Reed RE, Trautman RJ, Beavers CD. 1972. Some evidence for the development of a phagocytic response by polymorphonuclear leukocytes recovered from the venous blood of dogs inoculated with *Coccidioides immitis* or vaccinated with an irradiated spherule vaccine. Am Rev Resp Dis 105:845-849.
- Winters MS, Chan Q, Caruso JA, Deepe GS, Jr. 2010. Metallomic analysis of macrophages infected with *Histoplasma capsulatum* reveals a fundamental role for zinc in host defenses. J Infect Dis 202:1136-1145.
- Wormley FL, Jr., Perfect JR, Steele C, Cox GM. 2007. Protection Against Cryptococcosis using a Murine Interferon-gamma Producing *Cryptococcus neoformans* Strain. Infect Immun 75:1453-1462.
- Wozniak KL, Hardison SE, Kolls JK, Wormley FL. 2011a. Role of IL-17A on resolution of pulmonary *C. neoformans* infection. PLoS One 6:e17204.
- Wozniak KL, Levitz SM. 2008. *Cryptococcus neoformans* enters the endolysosomal pathway of dendritic cells and is killed by lysosomal components. Infect Immun 76:4764-4771.
- Wozniak KL, Ravi S, Macias S, Young ML, Olszewski MA, Steele C, Wormley FL. 2009. Insights into the mechanisms of protective immunity against *Cryptococcus neoformans* infection using a mouse model of pulmonary cryptococcosis. PLoS ONE 4:e6854.
- Wozniak KL, Vyas JM, Levitz SM. 2006. In Vivo Role of Dendritic Cells in a Murine Model of Pulmonary Cryptococcosis. Infect Immun 74:3817-3824.
- Wozniak KL, Young ML, Wormley FL, Jr. 2011b. Protective immunity against experimental pulmonary cryptococcosis in T cell-depleted mice. Clin Vaccine Immunol 18:717-723.
- Wu-Hsieh B, Howard DH. 1984. Inhibition of growth of *Histoplasma capsulatum* by lymphokine-stimulated macrophages. J Immunol 132:2593-2597.
- Wu-Hsieh B, Zlotnik A, Howard DH. 1984. T-cell hybridoma-produced lymphokine that activates macrophages to suppress intracellular growth of *Histoplasma capsulatum*. Infect Immun 43:380-385.
- Wuthrich M, Filutowicz HI, Klein BS. 2000. Mutation of the WI-1 gene yields an attenuated *Blastomyces dermatitidis* strain that induces host resistance. J Clin Invest 106:1381-1389.

- Wuthrich M, Filutowicz HI, Warner T, Deepe GS, Jr., Klein BS. 2003. Vaccine immunity to pathogenic fungi overcomes the requirement for CD4 help in exogenous antigen presentation to CD8⁺ T cells: implications for vaccine development in immune-deficient hosts. *J Exp Med* 197:1405-1416.
- Wuthrich M, Filutowicz HI, Warner T, Klein BS. 2002. Requisite elements in vaccine immunity to *Blastomyces dermatitidis*: plasticity uncovers vaccine potential in immune-deficient hosts. *J Immunol* 169:6969-6976.
- Wuthrich M, Fiset PL, Filutowicz HI, Klein BS. 2006. Differential requirements of T cell subsets for CD40 costimulation in immunity to *Blastomyces dermatitidis*. *J Immunol* 176:5538-5547.
- Wuthrich M, Gern B, Hung CY, Ersland K, Rocco N, Pick-Jacobs J, Galles K, Filutowicz H, Warner T, Evans M, Cole G, Klein B. 2011. Vaccine-induced protection against 3 systemic mycoses endemic to North America requires Th17 cells in mice. *J Clin Invest* 121:554-568.
- Wuthrich M, Warner T, Klein BS. 2005. IL-12 is required for induction but not maintenance of protective, memory responses to *Blastomyces dermatitidis*: implications for vaccine development in immune-deficient hosts. *J Immunol* 175:5288-5297.
- Xue J, Chen X, Selby D, Hung CY, Yu JJ, Cole GT. 2009. A genetically engineered live attenuated vaccine of *Coccidioides posadasii* protects BALB/c mice against coccidioidomycosis. *Infect Immun* 77:3196-3208.
- Yoneda K, Walzer PD. 1980. Interaction of *Pneumocystis carinii* with host lungs: an ultrastructural study. *Infect Immun* 29:692-703.
- Young M, Macias S, Thomas D, Wormley FL, Jr. 2009. A proteomic-based approach for the identification of immunodominant *Cryptococcus neoformans* proteins. *Proteomics* 9:2578-2588.
- Yu ML, Limper AH. 1997. *Pneumocystis carinii* induces ICAM-1 expression in lung epithelial cells through a TNF- α -mediated mechanism. *Am J Physiol* 273:L1103-1111.
- Yuan R, Casadevall A, Spira G, Scharff MD. 1995. Isotype switching from IgG3 to IgG1 converts a nonprotective murine antibody to *Cryptococcus neoformans* into a protective antibody. *J Immunol* 154:1810-1816.
- Yuan RR, Casadevall A, Oh J, Scharff MD. 1997. T cells cooperate with passive antibody to modify *Cryptococcus neoformans* infection in mice. *Proc Natl Acad Sci USA* 94:2483-2488.
- Yuan RR, Clynes R, Oh J, Ravetch JV, Scharff MD. 1998a. Antibody-mediated modulation of *Cryptococcus neoformans* infections is dependent on distinct Fc receptor functions and IgG subclasses. *J Exp Med* 187:641-648.
- Yuan RR, Spira G, Oh J, Paizi M, Casadevall A, Scharff MD. 1998b. Isotype switching increases efficacy of antibody protection against *Cryptococcus neoformans* infection in mice. *Infect Immun* 66:1057-1062.
- Zaragoza O, Casadevall A. 2004. Antibodies produced in response to *Cryptococcus neoformans* pulmonary infection in mice have characteristics of nonprotective antibodies. *Infect Immun* 72:4271-4274.
- Zaragoza O, Rodrigues ML, De Jesus M, Frases S, Dadachova E, Casadevall A. 2009. The capsule of the fungal pathogen *Cryptococcus neoformans*. *Adv Appl Microbiol* 68:133-216.

- Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, Belladonna ML, Vacca C, Conte C, Mosci P, Bistoni F, Puccetti P, Kastelein RA, Kopf M, Romani L. 2007. IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol* 37:2695-2706.
- Zhang H, Zhong Z, Pirofski LA. 1997. Peptide epitopes recognized by a human anti-cryptococcal glucuronoxylomannan antibody. *Infect Immun* 65:1158-1164.
- Zhang Y, Wang F, Tompkins KC, McNamara A, Jain AV, Moore BB, Toews GB, Huffnagle GB, Olszewski MA. 2009. Robust Th1 and Th17 immunity supports pulmonary clearance but cannot prevent systemic dissemination of highly virulent *Cryptococcus neoformans* H99. *Am J Pathol* 175:2489-2500.
- Zhang Z, Liu R, Noordhoek JA, Kauffman HF. 2005. Interaction of airway epithelial cells (A549) with spores and mycelium of *Aspergillus fumigatus*. *J Infect* 51:375-382.
- Zheng CF, Jones GJ, Shi M, Wiseman JC, Marr KJ, Berenger BM, Huston SM, Gill MJ, Krensky AM, Kubes P, Mody CH. 2008. Late expression of granulysin by microbicidal CD4+ T cells requires PI3K- and STAT5-dependent expression of IL-2Rbeta that is defective in HIV-infected patients. *J Immunol* 180:7221-7229.
- Zheng CF, Ma LL, Jones GJ, Gill MJ, Krensky AM, Kubes P, Mody CH. 2007. Cytotoxic CD4+ T cells use granulysin to kill *Cryptococcus neoformans*, and activation of this pathway is defective in HIV patients. *Blood* 109:2049-2057.
- Zhong Z, Pirofski LA. 1996. Opsonization of *Cryptococcus neoformans* by human anticryptococcal glucuronoxylomannan antibodies. *Infect Immun* 64:3446-3450.
- Zhong Z, Pirofski LA. 1998. Antifungal activity of a human antiglucuronoxylomannan antibody. *Clin Diagn Lab Immunol* 5:58-64.
- Zhou P, Freidag BL, Caldwell CC, Seder RA. 2001. Perforin is required for primary immunity to *Histoplasma capsulatum*. *Journal of immunology* 166:1968-1974.
- Zhou P, Miller G, Seder RA. 1998. Factors involved in regulating primary and secondary immunity to infection with *Histoplasma capsulatum*: TNF-alpha plays a critical role in maintaining secondary immunity in the absence of IFN-gamma. *J Immunol* 160:1359-1368.
- Zhou P, Sieve MC, Bennett J, Kwon-Chung KJ, Tewari RP, Gazzinelli RT, Sher A, Seder RA. 1995. IL-12 prevents mortality in mice infected with *Histoplasma capsulatum* through induction of IFN-gamma. *J Immunol* 155:785-795.

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Pulmonary infections are notorious in causing considerable morbidity and mortality. Caused by bacteria, viruses or fungi, respiratory infections require distinct knowledge of recent advances in pathogenesis. Progress in the understanding of immunopathogenesis of *Acinetobacter baumannii* infection will explain how an atypical organism establishes infection. The chapter regarding pulmonary nontuberculous mycobacterial infections in the State of Para depicts a unique study in an endemic region for tuberculosis in North of Brazil. The diagnosis and treatment of latent tuberculosis is a formidable challenge. Thus, new developments in diagnosis and treatment of latent tuberculosis are included in this book. Challenging in their diagnosis, nontuberculous mycobacterial pulmonary diseases require special education for management. The problems of respiratory infections in the immunocompromised host are increasing in numbers and in resilience to treatment. Therefore, the chapter describing the host immune responses against pulmonary fungal pathogens comes as a necessary section in this book. The insight brought forth from this book can be valuable for both clinicians and scientists.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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