Modulation of host-cell MAP-kinase signaling during fungal infection

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Abstract

Fungal infections contribute substantially to human suffering and mortality. The interaction between fungal pathogens and their host involves the invasion and penetration of the surface epithelium, activation of cells of the innate immune system and the generation of an effective response to block infection. Numerous host-cell signaling pathways are activated during fungal infection. This review will focus on the main fungal pathogens *Aspergillus fumigatus*, *Candida albicans* and *Cryptococcus neoformans* and their ability to activate the host MAP-kinase signaling pathways leading to cytokine secretion, increased cell motility and killing of the pathogen. Both epithelial and innate immune cells specifically recognize fungal antigens and in particular cell surface polysaccharides such as β-glucans and react to them by activating multiple signaling pathways, including those containing MAP-kinase modules. Recent findings suggest that the host response to fungal infection utilizes the MAP-kinase pathway to differentiate between commensal and pathogenic fungi to selectively react only to the pathogenic forms. However, the paucity of relevant publications strongly emphasize that our understanding of host MAP-kinase signaling in response to fungal infection is still at a very early stage. It is clear, based on studies of host MAP-kinase signaling during viral and bacterial infections, that in fungi as well, a wealth of exciting findings await us.

Introduction

The MAPKs JNK, ERK1/2 and p38 are activated by phosphorylation induced by various mitogens and cell stressors, including heat shock, osmotic stress and proinflammatory cytokines. They regulate diverse cellular activities, such as gene expression, mitosis, cytoskeletal rearrangement, differentiation, proliferation and apoptosis.[1] Less well known is the fact that MAPK activation also occurs in cells infected by various pathogens, including viruses,[2-4] bacteria[5] and some fungi. In fact, some bacteria such as *Yersinia* and *Bacillus anthracis* produce proteins that hijack the MAPK pathway of the infected cell, modulating the immune response and enabling more efficient infection.[5] Interestingly, specific MAPK inhibitors can, in some cases, block the entry or proliferation of the infecting virus or bacteria in infected cells,[6] or dampen an exaggerated immune response,[7] suggesting a novel therapeutic approach of blocking infection by modulating the host MAPK-mediated response.

While fungal MAPKs and their involvement in infection has been extensively described and reviewed,[8] the other side of the coin-the MAPK mediated responses of the fungal-infected cell have received little attention and have not been reviewed, despite their importance. This essay will focus on MAPK activation of host cells by fungal pathogens. The impact of fungal pathogens on human health is not widely appreciated. Over 1.5 billion people worldwide are infected by superficial fungal infections, over 600,000 die each year of cryptococcal meningitis, and ~600,000 are infected each year with life threatening *Candida* and *Aspergillus* spp. with an associated mortality approaching 40%.[9] It is estimated that more people die each year from fungal infection than from tuberculosis and malaria. Because fungi are eukaryotes and therefore more closely related to humans than other pathogens, there is a limited armamentarium of drugs available to treat fungal infections. Most antifungal drugs have serious side effects and resistance is on the rise.[10] To identify new therapeutic avenues, it is essential to better understand at the molecular level the interaction between the infecting fungus and the human host. An important aspect of this interaction is the response of infected host cells and in particular the signaling pathways activated.

In general, fungal-infected cells undergo two broad responses: i) activation of inflammatory gene expression and the secretion of cytokines that orchestrate an effective immune response. This occurs in both epithelial, endothelial and innate immune cells and utilizes the NFκB and MAPK pathways; ii) physical interaction with the fungus that includes adhesion, recognition, internalization and destruction of either the fungus or the host. This often involves the identification of fungal pathogen associated molecular patterns (PAMPs, including polysaccharides such as glucan and mannan) by host pattern recognition receptors and the activation of various intracellular signaling pathways. Here I will describe how host MAPK signaling in epithelial, endothelial and immune cells infected by the main fungal pathogens (*Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*) affects the outcome of infection. The possibility of modulating the host MAPK response to treat infection will also be discussed.

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Key words: *Aspergillus fumigatus; Candida albicans; Cryptococcus neoformans*; ERK1/2; JNK; p38; Dectin-1; cytokine response; phagocytosis; secreted proteases.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 22 June 2015
Revision received: 19 August 2015.
Accepted for publication: 22 August 2015.

Licensee PAGEPress, Italy
MAP Kinase 2015; 4:5389
doi:10.4081/mk.2015.5389

Activation of host cell MAPK signaling by the pathogenic mold *Aspergillus fumigatus*

The environmental mold *A. fumigatus* is a ubiquitous saprophyte that produces huge amounts of minute (2-3 μm) aerosolized spores (conidia). Conidial inhalation can result in a wide spectrum of diseases ranging from deadly invasive lung infection (invasive pulmonary aspergillosis) in the immunocompromised host to acute allergic reactions and lung damage in the hypersensitive host (allergic bronchopulmonary aspergillosis).[11] Initial contact between inhaled fungal spores and the host occurs in the epithelial cell layer lining the airways and alveoli. The molecular details of this interaction have been primarily analyzed in cell culture. Epithelial cell lines of nasal, bronchial or alveolar origin are co-incubated with germinating *A. fumigatus* conidia or fungal culture extracts. Microscopy of GFP-expressing *A. fumigatus* and infected labeled cells is used to follow the physical course of infection while extraction and Western blotting is used to identify and analyze the cellular signaling events taking place. Microscopy reveals that approximately 1/3 of adherent conidia are internalized into cellular endosomes and then phagosomes by actin-depen-

dent endocytosis, where they are destroyed after ~24 h.[12] Most conidia germinate externally, forming a dense web of hyphae that gradually (1-2 days) penetrate and destroy the cells. The cells undergo actin fiber rearrangement, loss of focal adhesions, rounding and detachment followed by either necrotic or apoptotic cell death.[12]

The effect of *A. fumigatus* infection on host MAP-kinase signaling was analyzed in bronchial epithelial (BEAS-2B) and alveolar epithelial (A549) cells. In the former, germinating but not resting conidia of *A. fumigatus* activated phosphatidylinositol 3-kinase (PI3K), p38 and ERK1/2 phosphorylation leading to interleukin (IL)-8 pro-inflammatory cytokine secretion.[13] Fekkar *et al*.,[14] showed that bronchial cells react to fungal infection by lysosomal degranulation and the release of proteins belonging to the redox detoxification system. The release of lysosomal enzymes was only activated by live conidia and was partly dependent on the PI3K and p38-MAPK pathways. These studies suggest that airway epithelial cells are not a passive barrier to conidial infection: they activate signaling pathways including MAP-kinases to respond offensively by secreting lysosomal enzymes, and cytokines that alert and activate the immune system (Figure 1A).

In A549 alveolar epithelial cells the central signaling kinases JNK and p38 are not phosphorylated in response to conidial infection, whereas ERK1/2 phosphorylation is only weakly activated, suggesting that these kinases are not involved in responding to infection.[15] In contrast, culture filtrate from a growing *A. fumigatus* mycelium induces rapid phosphorylation and activation of the MAPKs ERK1/2, JNK, and p38. Activation depends on the protease activity of the culture filtrate, and does not occur in the presence of culture filtrate from a protease deficient strain of *A. fumigatus*. Strikingly, specific inhibition of ERK1/2 or JNK kinase activity strongly delays epithelial actin depolymerization, cell peeling and necrosis.[15] Together, these results suggest that secreted fungal proteases, through an unknown mechanism, activate MAPK signaling in culture-filtrate-treated A549 cells, leading to actin depolymerization, cell peeling, and death, allowing the fungus to penetrate the disrupted tissue (Figure 1B). In addition, these findings suggest that inhibition of the MAPK-mediated host response can decrease cellular damage, a finding with possible clinical implications. Further research using existing *in vivo* models of *A. fumigatus* lung infection is needed to analyze the extent of MAP-kinase activation in the epithelial layers, and its role in the response to infection.

The interaction of *A. fumigatus* with cells of the innate immune system and in particular macrophages and neutrophils has been studied in detail.[16] In immunocompetent individuals, resident alveolar macrophages normally ingest and destroy inhaled *A. fumigatus* conidia. If the fungal inoculum is large, they secrete chemokines to recruit circulating neutrophils that can destroy both conidia and growing hyphae. Neutrophils destroy germinating conidia by engulfment and hyphae by degranulation and formation of mesh-like neutrophilic extracellular traps (NETs) that trap the pathogen and inhibit its growth. However, the connection between NET-formation and activation of MAP-kinase signaling in neutrophils infected with *A. fumigatus* has not been shown. In contrast, when macrophages encounter *A. fumigatus* conidia ERK1/2 and p38 signaling is rapidly and sustainably activated and if this signaling is blocked, the cells do not release pro-inflammatory cytokines.[17] Most interestingly, both epithelial and immune cells can differentiate between benign ungerminated conidia and pathogenic growing fungus via dectin-1 receptors that identify exposed β-glucans on the surface of the growing fungus. Numerous pathways are known to be activated by dectin-1 signaling including the ERK1/2 and JNK MAPK pathways associated with NFAT activation and cytokine production.[18] However, a direct link between β-glucan activation of dectin-1 receptor and MAP-kinase activation in response to *A. fumigatus* has not yet been shown.

Activation of host cell MAPK signaling by *Candida albicans*

C. albicans is usually a benign commensal inhabitant of the human skin and mucosa. It can exist in several forms including yeast cells, chains of elongated cells called pseudohyphae and true hyphae. Candida infections most commonly occur in persons with a weakened immune system. The most severe form is called invasive candidiasis or candidemia, where the fungus enters the bloodstream and infects the internal organs. Initial contact between *C. albicans* and the host most often occurs in the epithelial cell layer lining the mucosa or skin and cells of the innate immune system. *C. albicans* hyphae invade epithelial cells by three distinct mechanisms-active hyphal penetration by physical force into the cells, penetration by hydrolytic-enzyme activity or induced endocytosis mediated by binding of fungal adhesins Als3/Ssa1 to E-Cadherin and EGF/HER2 cell surface receptors, resulting in clathrin-mediated actin-dependent endocytosis.[19,20] The molecular details of this interaction have been primarily analyzed in cell culture. Infection of oral or vaginal epithelial cells with *C. albicans* yeast cells results in weak transient activation of MAP-kinase activity and a prolonged late activation that is dependent on the formation of hyphae and dense fungal growth.[21-23] The prolonged response was hypha-specific and was associated with the activation of c-Fos (*via* the p38 pathway and MKP-1 (MAPK phosphatase-1, *via* the ERK1/2 pathway), which together with concurrent NF-κB activation, induced the release of cytokines. Importantly, this was also demonstrated *in vivo* in biopsies from orally-infected humans: activation of c-Fos and MKP-1 was evident primarily in regions of hyphal-epithelial cell contact. Taken together the results suggest the following MAP-kinase dependent model of epithelial cell infection: at low burdens, *C. albicans* avoids activating the pro-

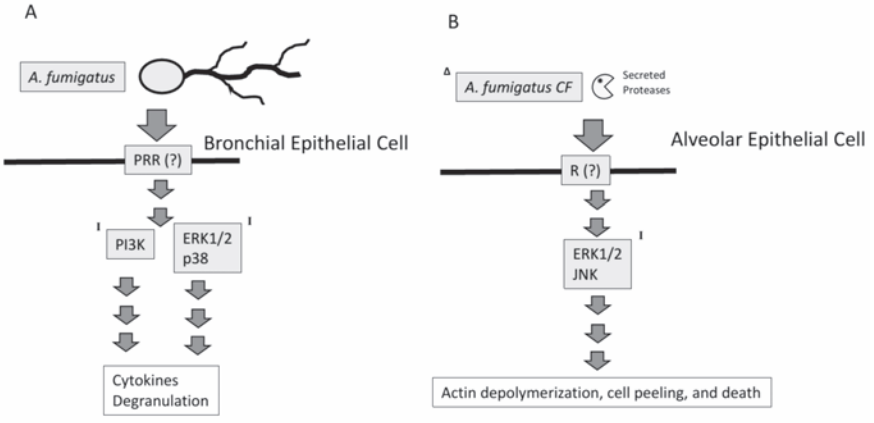

Figure 1. Interaction between the pathogenic mold *A. fumigatus* and BEAS-2B bronchial epithelial cells (A) or A549 alveolar epithelial cells (B) in culture. (A) Hyphal contact with BEAS-2B cells activates PI3K, ERK1/2 and p38 phosphorylation resulting in cytokine release and degranulation. (B) Secreted proteases in *A. fumigatus* culture filtrate activate A549 cell ERK1/2 and JNK phosphorylation through an unknown receptor (PRR?) leading to actin depolymerization, cell peeling and death. I, specific kinase inhibitor used to analyze this signaling event; Δ, protease deficient strain of *A. fumigatus* used as control.

longed MAPK-based danger response pathway, as a threshold level of activation is not reached. However, pathogenic fungal proliferation and the increased presence of hyphae causes prolonged activation of the MAP kinase pathway, activation of c-Fos and secretion of proinflammatory cytokines warning the host of the presence of a *dangerous* pathogen. This results in immune activation, neutrophil recruitment and fungal clearance (Figure 2A). The epithelial receptor eliciting prolonged MAP kinase activation and cytokine release have not been identified.

MAP-kinase pathway activation in response to *C. albicans* infection was also shown in monocytes,[24] macrophages,[25,26] neutrophils[27] and dendritic cells.[28] In monocytes, inhibition of p38, JNK or ERK1/2 reduced fungal-induced cytokine production.[24] In macrophages, both endocytosis/killing and cytokine release involve MAP-kinase activation. Ingestion of *C. albicans* by a macrophage cell line resulted in rapid phosphorylation of ERK1/2 kinases but not p38 or JNK. Phosphorylation was high after 15 min and decreased after 60 min. Killing was strongly inhibited by the addition of a MEK inhibitor, suggesting that ERK1/2 activation is crucial for killing of *C. albicans* by the macrophages.[26] A more comprehensive approach was used to link macrophage cytokine release and exposure to *C. albicans*.[25] Using a combination of dectin1/CARD9 knockout cells, H-Ras knockdowns and specific Syk and MAP-kinase inhibitors, the entire signaling pathway was delineated. The fungus binds macrophage surface dectin 1 receptors, inducing Syk-dependent phosphorylation of Ras-GRF1. Phosphorylated Ras-GRF1, in turn, forms a complex with CARD9 that further recruits H-Ras, leading to activation of H-Ras and subsequent activation of downstream ERK1/2, finally resulting in cytokine release[25] (Figure 2B). This publication is notable for using the yeast two-hybrid screen to identify in an unbiased fashion the novel physical association between the CARD9 and Ras-GRF1/H-Ras proteins, thereby linking dectin1/CARD9 activation and MAP kinase signaling.

The study of the interaction between *C. albicans* and neutrophils revealed that the latter can discriminate between the yeast and hyphal forms of this fungus. Hyphae, which are formed during invasion, specifically trigger targeted neutrophil motility and IL-8 release by activation of the ERK1/2-kinase cascade. This motility is essential for killing of *C. albicans* hyphae (Figure 2C). In contrast, killing of yeast cells does not depend on either ERK1/2 activation or motility of PMN. The fungal ligand activating ERK1/2-signaling in neutrophils has not been identified.

In dendritic cells, binding of *C. albicans* to cell surface dectin-1 receptors promotes phosphorylation of Raf-1 and ERK1/2 kinases and

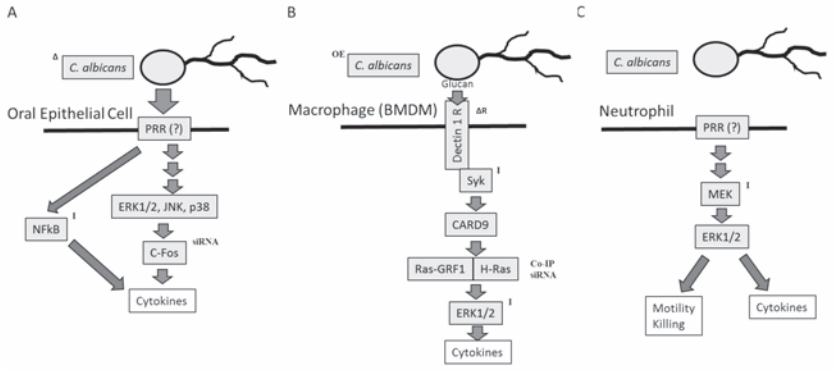

Figure 2. Pathogenic interactions between the commensal dimorphic fungus *C. albicans* and oral epithelial cells (A), macrophages (B) or neutrophils (C). Interaction between *C. albicans* hyphae and oral epithelial cells (A) leads to sustained phosphorylation of ERK1/2, JNK and p38 and activation of c-Fos. Together with concurrent activation of the NFκB pathway, this causes the release of cytokines. (B) Binding of surface *C. albicans* hyphal β-glucans to bone marrow derived macrophage dectin-1 receptors leads to the formation of a CARD9/Ras-GRF1/H-Ras signaling complex which activates ERK1/2 phosphorylation resulting in the release of cytokines. (C) Binding of *C. albicans* hyphae to neutrophils results in MEK/ERK1/2 phosphorylation, triggering targeted neutrophil motility/killing and cytokine release. Δ, strain of *C. albicans* incapable of forming hyphae used as a control, OE- strain of *C. albicans* overexpressing surface polysaccharides used; I, specific inhibitor used to analyze this signaling event; siRNA, specific siRNA used to analyze this signaling event; co-IP, co-immunoprecipitation used to show the formation of this complex.

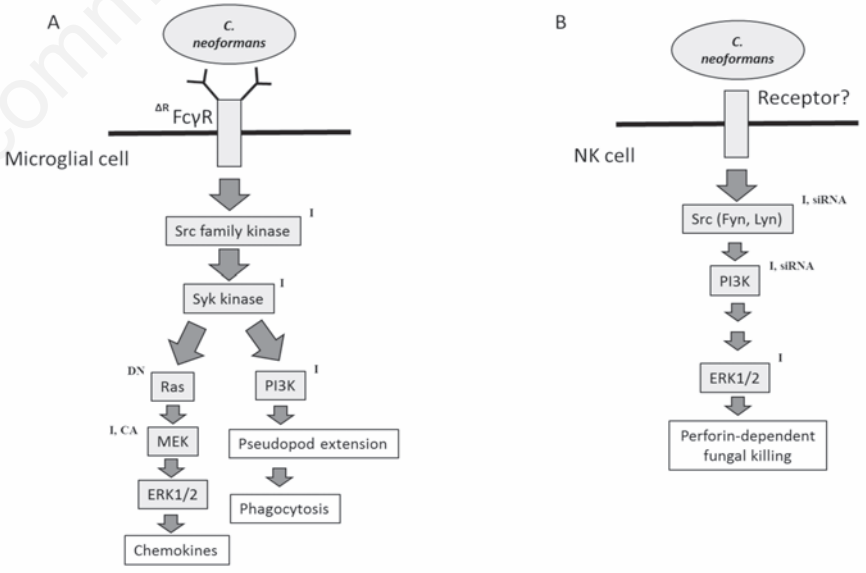

Figure 3. Interactions between the pathogenic encapsulated yeast *C. neoformans* and microglial (A) or NK (B) cells. In microglial (brain macrophage) cells interacting via FcγR receptors with *C. neoformans* (A), two signaling pathways are activated in a Src/Syk dependent manner- Ras/MEK/ERK1/2 leading to cytokine secretion and PI3K leading to phagocytosis. In NK cells (B), activation of Fyn and Lyn Src-family kinases activates PI3K, leading to ERK1/2 phosphorylation and perforin-dependent fungal killing. ΔR, microglial cell lacking the FcγR receptor used as a control; DN, dominant negative isoform of Ras used; CA, constitutively activated MEK used; I, specific inhibitor used to analyze this signaling event; siRNA, specific siRNA used to analyze this signaling event.

triggers activator protein 1 activation, leading to reactive oxygen species release and cytokine secretion. These responses are stronger and more sustained in *C. albicans* expressing high levels of surface β-glucans.[28]

Activation of host cell MAPK signaling by *Cryptococcus neoformans*

C. neoformans is an environmental encapsulated yeast often associated with soil rich in organic material such as bird droppings. Inhalation of spores or yeast cells in the immunocompromised host results in the onset of pneumonia-like symptoms and the development of cryptococcosis. Secondary and often lethal infection of the meninges and brain (cryptococcal meningitis and encephalitis) can occur, most commonly in AIDS-patients. As stated above, cryptococcal meningitis is responsible for 600,000 deaths/year in subsaharan Africa.[9] *C. neoformans* is a facultative intracellular pathogen and is highly resistant to phagocytic killing as a result of a thick protective polysaccharide capsule that surrounds its cell wall. Two factors are thought to target it to the brain- high affinity binding and enhanced endocytosis into endothelial cells of the blood-brain-barrier (BBB) and a *trojan-horse*-like ability to survive within circulating macrophages that can traverse the BBB.[29]

The interaction between *C. neoformans* and brain microvascular endothelial cells has been studied in detail. Hyaluronic acid on the fungal capsule binds the endothelial CD44 receptor, resulting in the activation of the PLB1/RhoGTPase/PKC /FAK/ezrin signaling pathway. This leads to actin-mediated endocytosis of the fungal pathogen.[29] Surprisingly, although the RhoGTPases and PKC are known activators of MAP kinase signaling, there have been no reports to date describing the involvement of MAP kinases in the process of *C. neoformans* uptake into endothelial cells.

In contrast, MAP kinases have an important role in the interaction between *C. neoformans* and microglial cells (the resident macrophages of the nervous system),[30] or NK (natural killer) cells.[31] In microglial cells, Fc R binding to *C. neoformans* cells induces Src/Syk/Ras/MEK/ERK1/2 activation resulting in chemokine release. Pseudopod extension and phagocytosis are dependent on PI3K activation (Figure 3A).[30] In NK cells, an unknown receptor activates the Src-kinases Fyn and Lyn, leading to the activation of PI3K and downstream ERK1/2. ERK1/2 phosphorylation and activation results in perforin-dependent killing of the fungus (Figure 3B). Selective inhibition of these signaling components or downregulation of their expression by siRNA blocks killing. Recent work also shows that the fungal pathogen *Histoplasma capsulatum*, upon binding to macrophage dectin 1 and CR3 receptors, activates the Syk-JNK/ERK/p38-AP1 signaling pathway to induce TNFα and IL-6 cytokine release.[32] Dectin1/CR3 null mice were significantly more susceptible to *H. capsulatum* infection. The findings in both *C. neoformans and H. capsulatum* suggest that modulation or augmentation of the host MAPK signaling response may be therapeutic in cases where the immune response is weak, for example in the immunocompromised host.

Conclusions

Several general conclusions can be drawn from the studies described above. Both epithelial and innate immune cells apparently have designated recognition and signaling pathways (NFκB, MAP-kinase, PI3K) that are selectively activated upon recognition of fungal antigens to cell surface receptors. In only a few cases is the identity of the cell receptor known: macrophage dectin-1 receptor recognition of *C. albicans* and NK-Fc R recognition of *C. neoformans*). Intriguingly, in some cases, cells can differentiate between a relatively harmless dormant spore or yeast form and the pathogenic and invasive hyphal (filamentous) form. In *A. fumigatus*-infected lung alveolar cells MAP kinases are only weakly activated by conidia and strongly activated by culture filtrate secreted by growing hyphae. Similarly in *C. albicans*-infected oral epithelial cells only the hyphal form strongly activates sustained MAP-kinase activity, leading to the production of cytokines. In general, MAP-kinase signaling of fungal-infected host cells most often involves ERK1/2 and results, together with NFκB activation, in the transcription of genes encoding proinflammatory cytokines such as TNF-α, that activate a strong immune response. There have been relatively few attempts to manipulate the MAP-kinase based cellular response during fungal infection to reduce damage. Addition of ERK1/2 or JNK inhibitors significantly reduced cell peeling and death of A549 cells incubated in the presence of *A. fumigatus* culture filtrate.[15] However, in most cases of fungal infection, host MAP kinase inhibition as a potential therapy is not advised as it may favor the pathogen by reducing fungal killing or cytokine release. In fact, treatment of *C. albicans*-infected mice with a MEK-inhibitor reduced their survival rates, arguing against this type of therapeutic approach.[25] In such cases, therapy that augments and amplifies MAP-kinase signaling, resulting in a stronger host immune response, may be beneficial.

The study of fungal-induced host cell responses involving MAP-kinase signaling is at a very early stage. Only a few publications (<20) have directly addressed this topic. More *in vitro* work needs to be carried out to independently repeat and verify in primary cells the results described from immortalized cell lines. It is important to identify the responsible cell surface receptors and the fungal PAMPs they bind and to delineate the entire signaling pathways and networks involved in the cellular response. Consideration needs to be taken in reaching conclusions based only on the use of so-called selective kinase inhibitors. Such results need to be repeated with additional independent methods such as siRNA and knockout cell lines. In addition, *in vitro* results need to be verified in more sophisticated *in vivo* models of fungal infection, using to full advantage modern techniques of selective tissue manipulation and imaging.

Numerous unanswered questions remain: Can MAP-kinase inhibitors be used to weaken an over-active and therefore damaging immune response during fungal infection? Do fungi and in particular *C. neoformans*, manipulate MAP-kinase signaling in infected cells to undergo endocytosis and escape immune surveillance? If so, can infection be controlled by using MEK or MAP-kinase inhibitors? Do fungi such as the commensal dermatophytes and *C. albicans* secrete effectors that modulate host MAP-kinase signaling and dampen the immune response against them? Clearly, answering these questions and many others will contribute significantly towards our ability to better understand and treat invasive fungal infections.

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