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Lipid signalling in pathogenic fungi

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Summary

In recent years, the study of lipid signalling networks has significantly increased. Although best studied in mammalian cells, lipid signalling is now appreciated also in microbial cells, particularly in yeasts and moulds. For instance, microbial sphingolipids and their metabolizing enzymes play a key role in the regulation of fungal pathogenicity, especially in *Cryptococcus neoformans*, through the modulation of different microbial pathways and virulence factors. Another example is the quorum sensing molecule (QSM) farnesol. In fact, this QSM is involved not only in mycelial growth and biofilm formation of *Candida albicans*, but also in many stress related responses. In moulds, such as *Aspergillus fumigatus*, QSM and sphingolipids are important for maintaining cell wall integrity and virulence. Finally, fungal cells make oxylipins to increase their virulence attributes and to counteract the host immune defences. In this review, we discuss these aspects in details.

Introduction

The involvement of lipids as signalling molecules in physiopathological processes, such as inflammation, vasculogenesis, cancer, cardiovascular diseases, neurological disorders, metabolic syndrome and post-infectious autoimmune diseases, is now well established. In mammalian cells, changes in lipid network signalling may alter cellular homeostasis, thus leading to a disease (reviewed in Bielawski *et al.*, 2010; Gault *et al.*, 2010; Gomez-Munoz *et al.*, 2010; Hinkovska-Galcheva and Shayman, 2010; Holthuis and Luberto, 2010; Kawamori, 2010; Messner and Cabot, 2010; Wymann and Schneider, 2008; Fox and Kester, 2010; Nikolova-Karakashian and Rozenova, 2010; Oskouian and Saba, 2010; Riboni *et al.*, 2010; Sonnino and Prinetti, 2010; Stiban *et al.*, 2010; Strub *et al.*, 2010). Similarly, fungal lipid signalling renders the microorganisms hypervirulent (e.g. more resistant to cell death by environmental and host stresses, more resistant to the killing by the host immune responses). Lipids, such as sphingolipids, farnesol and oxylipins, are signalling molecules in pathogenic fungi. They trigger and mediate specific cellular processes such as cell growth, proliferation,

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apoptosis and senescence. Insights into their unique nature and an in-depth study on the lipid signalling events can lead to significant understanding of the physiopathological events regulated by lipids and open up the possibility to exploit new means for the development of new therapeutic strategies. In the past, we have already reviewed this area of research (Shea and Del Poeta, 2006; Rhome *et al.*, 2007; Rhome and Del Poeta, 2010), and with the present paper we discuss the latest discoveries.

Sphingolipid

Mammalian sphingolipids were first discovered as bioactive molecules in late 1980s with sphingosine to be the first to be identified as having pleiotrophic effects on protein kinases and other targets (Hannun *et al.*, 1986; Merrill *et al.*, 1986; Wilson *et al.*, 1986; Smal and De Meyts, 1989). In late 1990s, sphingosine kinase genes were discovered in the yeast *Saccharomyces cerevisiae* (Nagiec *et al.*, 1998) and sphingosine-1-phosphate was shown to act as a second messenger in this fungus (Spiegel, 1999). Since then, a Medline search of 'Lipid', 'Fungi' and 'Signaling' as keywords revealed 2994 papers of which 255 are related to sphingolipid signalling.

The role of sphingolipids in stress response, cell cycle arrest, apoptosis and cell growth has been established in the non-pathogenic fungus *S. cerevisiae* (Patton *et al.*, 1992; Jenkins *et al.*, 1997; Wells *et al.*, 1998), and only very recently studies on sphingolipid signalling have been engaged in pathogenic fungi, such as *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*. In *C. albicans*, filamentous hyphal growth is essential for fungal virulence and pathogenesis and occurs in a polarized fashion and mediated by actin cytoskeleton (Oberholzer *et al.*, 2006). In this pathogenic fungus, sphingolipids are important for normal hyphal growth (Martin and Konopka, 2004). Additionally, lipid raft domains enriched in sphingolipids and sterols influence the distribution of the raft domains (Martin and Konopka, 2004), and they are involved in virulence by mediating the partitioning of specific proteins into lipid rafts, such as the acylated proteins, pleckstrin homology (PH) domain-containing proteins and GPI-anchored protein (Farhang-Fallah *et al.*, 2002; Klopfenstein and Vale, 2004). These GPI-anchored proteins in turn include members of the adhesion protein family Hwp1p and Als1p, the epithelial adhesion protein-family, such as Eap1p, Dfg5p and Phr1p that mediate adhesion to host cells, and the secreted aspartyl protease family, such as Sap9p and sap10p, all of which are virulence factors (Martin and Konopka, 2004). Thus, in this context, membrane sphingolipids are particularly important for the formation of microdomains containing fungal proteins that function as signalling regulators.

On the other hand, other *C. albicans* sphingolipids such as glucosylceramide (GlcCer) is important in inducing hyphal elongation (Oura and Kajiwara, 2008; 2010), although how this lipid regulates such even is not known. Interestingly, *C. albicans* GlcCer synthase 1 (Gcs1) was found to be required for virulence (Noble *et al.*, 2010).

Exciting work has shown that *Candida* GlcCer can bind to plant defensins, which results in the killing of the pathogen (Thevissen *et al.*, 2004; 2007; Aerts *et al.*, 2009; Zauner *et al.*, 2010), although the mechanism of fungal cell death is not clear. The biochemical structure

of GlcCer differs among pathogenic fungi and, as a consequence, different GlcCers bind to different types of plant defensins (Ramamoorthy *et al.*, 2009). The same defensin can kill different fungi but for it to happen their GlcCer structure must be similar. For instance, the plant defensin RsAFP2 kills *C. albicans* and other *Candida spp.* and it is not toxic to mammalian cells because the structure of mammalian GlcCer is different from the structure of fungal GlcCer. Very intriguingly, administration of RsAFP2 to mice protects against murine candidiasis (Tavares *et al.*, 2008), suggesting that these plant peptides may be potential antifungals in mammalian hosts (Thevissen *et al.*, 2007), differently from human defensins which are structurally different and are thought not to interact with fungal GlcCer (Aerts *et al.*, 2008).

In non-pathogenic moulds, such as *Aspergillus nidulans*, sphingolipids play a major role in cell polarity by regulating the organization of the actin cytoskeleton (Cheng *et al.*, 2001), and they are also required for both the maintenance of hyphal cell polarity and the establishment of hyphae. The inositolphosphoryl ceramide (IPC) synthase enzyme (Ipc1) appears to be responsible for such regulation (Cheng *et al.*, 2001), but whether this mechanism is regulated by IPC or by diacylglycerol (DAG) (byproduct of the Ipc1 reaction) is still not known. In addition, since Ipc1 also regulates the level of phytoceramide (substrate of the Ipc1 reaction and substrate for ceramidases for the production of phyto- and dihydrosphingosine), it is also possible that Ipc1 regulates cellular effects through sphingolipids not directly involved in the biochemical reaction that it catalyses. This hypothesis is supported by the observation that both phyto- and dihydrosphingosine are inducers of apoptosis in *A. nidulans* (Cheng *et al.*, 2003) and by studies suggesting that a novel C18 phytoceramide may be responsible for cell death of a different mould (e.g. *Neorospora crassa*) under certain stress responses (Plesofsky *et al.*, 2008). However, the role of these sphingolipids or/and Ipc1 in *Aspergillus* pathogenesis is unknown. Indeed, since the identification of the *IPC1* gene in *A. fumigatus* in 2000 (Heidler and Radding, 2000), studies on the role of Ipc1 (or other sphingolipid-metabolizing enzymes) in the regulation of virulence and signalling in pathogenic moulds are largely missing. One report showed that inhibition of GlcCer synthase affects growth and differentiation of *A. fumigatus* (Leverly *et al.*, 2002), but the mechanism of such regulation is unknown. Interestingly, production of complex sphingolipids in *A. fumigatus* may differ compared with that observed in pathogenic yeasts, such as *C. albicans* and *C. neoformans* (Ramage *et al.*, 2005), highlighting that more studies are needed in this mould to dissect the role and mechanism by which fungal sphingolipids regulate pathogenicity.

In *C. neoformans*, sphingolipids are being studied in detail. These studies highlight that sphingolipids play a key role in the regulation of cryptococcal pathogenesis (Fig. 1). In this pathogenic fungus, sphingolipids regulate many cellular processes, including cell wall integrity (CWI) and production of melanin through protein kinase C1 (Pkc1) (Luberto *et al.*, 2001; Heung *et al.*, 2004). They modulate the signalling events leading to phagocytosis through the transcriptional activation of the antiphagocytic protein 1 (App1) by the activating transcription factor 2 (Atf2) (Luberto *et al.*, 2003; Mare *et al.*, 2005; Tommasino *et al.*, 2008), the regulation of fungal growth in the intracellular (Luberto *et al.*, 2001; Heung *et al.*, 2004; Shea *et al.*, 2006) and extracellular (Rittershaus *et al.*, 2006; Kechichian *et al.*, 2007) environments by the activities of inositol phosphosphingolipid phospholipase C1

(Isc1) and GlcCer synthase (Gcs1) respectively (Fig. 1). The regulation of these processes significantly affects the interaction of *C. neoformans* with alveolar macrophages (AMs) in the lung environment with an important effect on the outcome of the disease. Intriguingly, intracellular and extracellular growth appears to be regulated by different and specific sphingolipids, suggesting that the microbe has built an efficient network of molecules that might intervene depending on which compartment the fungus finds itself in. This hypothesis is supported by microarray studies (Fan *et al.*, 2005) showing that, when *C. neoformans* cells are localized within the phagolysosome of host macrophages, expression of only certain sphingolipid-metabolizing enzyme(s), such as Ipc1, increases, and by a mathematical model representing the sphingolipid network, showing that when cells are shifted from a neutral/alkaline to acidic pH, two proteins, Ipc1 and Isc1, are needed for cell adaptation (Garcia *et al.*, 2008a). This is important because *C. neoformans* enters the body through inhalation and finds a neutral environment in the alveolar spaces and an acidic niche within the phagolysosome of AMs once phagocytosed. Thus, understanding how the fungus adapts to these environments will lead to a better understanding of how it interacts with the host.

The mathematical model was formulated as a system of non-linear ordinary differential equations in the format of power-law functions, as suggested in the biochemical system theory (Voit, 2000). With this framework, it was straightforward to set up symbolic equations that reflect the known or the assumed connectivity and respective regulatory signals of the pathway. There are many reasons why characterizing solely the parts of the sphingolipid pathway system is insufficient for its full understanding: the most obvious is the absolute high number of the components and a second reason is the non-linear nature of the system. Specifically, a slight increase in a sphingolipid metabolite may lead to a slight change in a signal output or to no response whereas a stronger increase may have a distinct and visible effect. Thus, if several thresholds are in play, it is no longer possible to make reliable predictions on responses. A third layer of complexity is represented when the product of one reaction can be the substrate for the reverse reaction, especially when a metabolite exerts a competing effect on some other part of the system (e.g. In *C. neoformans* DAG, product of the Ipc1 reaction, activates Pkc1, whereas phytoceramide, substrate of the Ipc1 reaction, inhibits Pkc1). These complexities render mathematical modelling a valuable tool with unique facilities that are difficult – if not impossible – to match with wet experimentations. Thus, once the parameter values in the system are specified, one can execute computational analyses and make simulations on what it will happen to metabolite 'x' when metabolite 'y' or when the enzyme activity of 'z' is decreased or increased. Subsequently, the model is tested for stability, sensitivity and robustness analyses, through comparison with experimental data that had not been used in the estimation phase. Finally, the model is validated by performing key experimentation(s) based on the results of the simulations. For instance, our model predicted that plasma membrane ATPase 1 (Pma1) activity was controlled by both Isc1 and Ipc1. Indeed, Pma1 was experimentally impaired in the *C. neoformans* *isc1* and *GAL7::IPC1* mutants compared with the wild-type strain (Garcia *et al.*, 2008b). Additional validation studies allowed the proposition that the function of Pma1 is not only regulated by phytoceramide but also by complex sphingolipids (Fig. 1). Thus, mathematical modelling is a rich tool for analyses of diverse enzymatic activities that lead to an observed phenotype at a steady state. Ultimately, models could help in

determining which enzyme(s) would need to be altered and in what manner to obtain a desired phenotype.

Whereas Ipc1 and Isc1 are important for adaptation of *C. neoformans* at acidic pH, a different enzyme, GlcCer synthase 1 (Gcs1) was found to be essential for neutral/alkaline tolerance of *C. neoformans* (Rittershaus *et al.*, 2006). Gcs1 synthesizes GlcCer, a membrane sphingolipid biochemically different from the one found in mammals and plants (Warnecke and Heinz, 2003; Rhome *et al.*, 2007). The regulation of fungal adaptation and replication by GlcCer in neutral/alkaline environments is particularly intriguing because it does not occur when fungal cells are exposed to atmospheric concentration of CO₂ (0.03–0.05%), but only when cells are exposed to a concentration of CO₂ of 5% (or a PaCO₂ of 40 mmHg), which is characteristically found in alveolar spaces. Hence, when the *C. neoformans* *gcs1* was inoculated intranasally into mice, it could not replicate in the lung and, thus, mice were able to contain the fungus within a lung granuloma (Rittershaus *et al.*, 2006). Interestingly, *C. albicans* *gcs1* has no growth defect at neutral/alkaline growing conditions (Noble *et al.*, 2010), suggesting that GlcCer may have different function(s) in different fungi.

In *C. neoformans*, Gcs1 or/and GlcCer may be involved in signalling through the carbonic anhydrases Can1 or/and Can2 but the deletion of the latter genes causes a fungal growth defect at low and not at high CO₂ concentrations (Bahn *et al.*, 2005; Mitchell, 2005; 2006; Mogensen *et al.*, 2006). *C. neoformans* GlcCer appears to be associated with lipid rafts in which other proteins are found, such as superoxide dismutase 1 (Sod1) and phospholipase B 1 (Plb1) (Siafakas *et al.*, 2006; 2007), but these enzymes do not regulate cryptococcal growth at neutral/alkaline pH. How Gcs1 or/and GlcCer regulate the tolerance of *C. neoformans* at neutral/alkaline pH only in physiological concentration of CO₂ is not known. It is possible, however, that GlcCer itself exerts specifically this function through its characteristic biochemical structure. Fungal GlcCer is peculiarly methylated at position 9 of the sphingosine backbone by a fungal specific enzyme, named C9 methyltransferase, which is absent in plants or in humans (Warnecke and Heinz, 2003; Rhome *et al.*, 2007). In *Pichia pastoris*, sphingolipid C9 methylation of GlcCer occurs in the membrane, suggesting a role in membrane integrity (Ternes *et al.*, 2006), whereas in *C. albicans* methylation of GlcCer is required for hyphal elongation (Oura and Kajiwarra, 2010), suggesting a role for virulence. Importantly, fungal mutants lacking the sterol methyl transferase gene (*erg6*) have been shown to have altered membrane structural features (Kleinhans *et al.*, 1979; Lees *et al.*, 1979). Together, these studies suggest that methylation of membrane lipids, and in particular sphingolipids, is important for membrane integrity and, perhaps for the adaptation of fungal cells to different pH/CO₂ environments.

Farnesol

Microbes regulate their growth, metabolism and virulence by both intra- and inter-communication by a phenomenon known as quorum sensing (QS). Farnesol was identified by gas chromatography-mass spectrometry as 1-hydroxy-3,7,11-trimethyl-2,6,10-dodecatriene (*E,E*-farnesol) and is the major QS molecule (QSM) produced by fungi (Hornby *et al.*, 2001; and reviewed in Nickerson *et al.*, 2006). In *C. albicans*, farnesol prevents hypha development from budding yeasts although it does not block the elongation

of pre-existing hyphae. Farnesol is also involved in the formation of mature *Candida* biofilms (Ramage *et al.*, 2002; Ramage and Lopez-Ribot, 2005), in which it reaches very high level (1 mM). Interestingly, *Candida* can tolerate farnesol concentrations that are fungicidal/fungistatic to other fungi. Perhaps *Candida* can tolerate high level of farnesol because its lipophilic nature allows it to diffuse freely through the membranes and extracellular matrix without being toxic to *Candida* cells (Weber *et al.*, 2010), a characteristic not shared by other fungi or bacteria. This feature could be exploited by *C. albicans* for protection from other human commensals.

Additional studies have also shown that Farnesol protects yeast cells from H₂O₂ and superoxide anion-generating agents establishing its direct linkage to oxidative stress response (Westwater *et al.*, 2005). It mediates the induction of catalase expression and ROS resistance by repressing the Ras1-cAMP pathway (Deveau *et al.*, 2010), perhaps by regulating the phosphorylation of stress-activated protein kinase, such as Hog1 (Smith *et al.*, 2004; Enjalbert *et al.*, 2006). In other yeast systems, schizostatin, which is predicted to be a close relative of farnesol, inhibits growth in *Schizophyllum commune* (Tanimoto *et al.*, 1996), although the mechanism for such regulation is unknown.

The role of farnesol as an activator of transcription is well established (Uhl *et al.*, 2003). It positively regulates the expression of *TUP1* (Braun and Johnson, 1997; Braun *et al.*, 2001; Kadosh and Johnson, 2001; Khalaf and Zitomer, 2001; Kaneko *et al.*, 2006), a global transcriptional co-repressor, and prevents activation of *CPH1* and *HST7*, two genes that activate filamentation. Thus, the downregulation of *CPH1* may be equated as a secondary effect of farnesol on *TUP1* (Enjalbert and Whiteway, 2005). In addition, farnesol influences the expression of genes involved in iron transport, cell wall synthesis, drug resistance and cell cycle progression, DNA replication, chromatin formation and cell adhesion (Kruppa, 2009). The molecular mechanisms by which farnesol regulates such effect are largely unknown.

In addition to regulate cell morphology, farnesol is also a cell density modulator in *C. albicans*, but not in other fungi (Semighini *et al.*, 2006; Fairn *et al.*, 2007). How farnesol regulates cell density in this yeast is not known but it is reasonable that a human commensal microbe such as *C. albicans* has developed a mechanism to block its own growth and replication to prevent tissue damage and, thus, a host immune response. Intriguingly, studies have shown that farnesol triggers apoptosis in mammalian cells (Edwards and Ericsson, 1999) and it has an anticancer activity (Joo and Jetten, 2010), suggesting that, through its production, *C. albicans* may be able to control in its favour the host microenvironment in which the fungus resides.

In *A. fumigatus*, farnesol interferes with CWI pathway by inhibiting Rho GTPases that control the CWI through AfRho1, which regulates the intracellular localization of AfRho3 in the hyphal tip (Dichtl *et al.*, 2010). However, farnesol production by *A. fumigatus* is minimal and, thus, its role in *A. fumigatus* pathogenesis is unclear. *C. neoformans* appears not to have a QS phenotype although regulation of cell density may exist in some strains (Lee *et al.*, 2007; 2009).

Oxylipins

Oxylipins are the collective term used for all oxygenated lipids. Fungal oxylipins are derived from oleic acid (18:1), linoleic (18:2) and linolenic acid (18:3), after the addition of an O₂ molecule to polyunsaturated fatty acids. Eicosanoids like prostaglandins (PG), prostaglandin-like molecules, leucotriens and thromboxanes are oxygenated lipids shown to be produced in *C. albicans* and *C. neoformans* (Noverr *et al.*, 2001) even though these yeasts do not have cyclooxygenases.

Candida albicans produces endogenous eicosanoids from exogenous arachidonic acid, suggesting that host arachidonic acid can be used to synthesize fungal PG (Noverr *et al.*, 2001). One of these fungal oxylipins compete with the host PG, such as PGE₂, thus suggesting that fungal PG could interfere with the modulation of the host immune responses regulated by host PG (Noverr *et al.*, 2001; 2004; Kuroda and Yamashita, 2003). The eicosanoids/oxylipins pathway in *C. albicans* also plays a central role in the control of morphogenesis and biofilm formation and, thus, these lipids are also viewed as regulators of *Candida* virulence. The enzyme(s) responsible for PG synthesis in *C. albicans* is (are) not known. This fungus possesses a family of laccase homologues (the Fet family of multicopper oxidases) and Fet3 may be involved in PGE₂ production. Fungal PGE₂ downregulates the innate effector phase or protective Th1 response to the infection (Kuroda and Yamashita, 2003). As a consequence, the development of drugs that specifically target the fungal prostaglandins pathways may be one strategy to combat fungal colonization and infection (Erb-Downward and Noverr, 2007).

A different metabolite of linoleic acid, 3(R)-hydroxytetradecanoic acid DE, participates in the QS mechanism of *C. albicans* by accelerating cell morphogenesis with alteration of gene expression necessary for hyphal formation at the right cell population density utilizing the aerobic pathway of endogenous lipid metabolism. It increases germ tube formation and also increases biofilm formation. This metabolite upregulates *CAP1* gene, which is an adenylate cyclase-associated protein involved in the formation of Cap protein as well as hyphal wall protein 1 (Hwp1), involved in the regulation of filamentous growth (Nigam *et al.*, 2010).

In *A. fumigatus* three genes (*PPOA*, *PPOB* and *PPOC*) have been implicated in the production of PGs (Tsitsigiannis *et al.*, 2005). Alterations in the *PPO* genes lead to a malfunctioning signalling system in fungal cells, resulting in the inability to regulate a myriad of processes required for pathogenicity (Garscha *et al.*, 2007). Interestingly, an *A. fumigatus* mutant in which the three genes are silenced is actually hypervirulent and showed increased tolerance to hydrogen peroxide (Tsitsigiannis *et al.*, 2005). This suggests that for *A. fumigatus* synthesis of certain PG may actually be detrimental perhaps by activating a robust host immune response. Thus, both *Candida* and *Aspergillus* have their own 'oxylipin signature profile', which functions as a switch in adapting fungal cells to the ever-changing environment and therefore by temporally balancing their development, and dictating the 'fitness' of the organism during the infection (reviewed in Tsitsigiannis and Keller, 2007).

Cryptococcus neoformans has been reported to produce PGE₂ through laccase 1 (Lac1) enzyme and, possibly, through two additional enzymes (Erb-Downward and Huffnagle,

2007; Erb-Downward *et al.*, 2008) yet to be characterized. In addition, *C. neoformans* Lac1 can generate a series of oxylipins, potentially produced in the mitochondria (Sebolai *et al.*, 2008), deposited onto the cell wall, excreted through tubular protuberances and attached to the surrounding capsule material (Sebolai *et al.*, 2007). However, their role on *C. neoformans* virulence is not known.

In conclusion, although a vast number of cellular processes in which bioactive lipids are associated with have been revealed, the studies of the molecular mechanisms by which these lipids exert their biological questions are still largely unknown. The epistasis analysis of such lipid signalling mechanisms will provide new insights not only for the understanding of the fungus-host interaction but, importantly, for the development of new therapeutic strategies.

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References

- Aerts AM, Francois IE, Cammue BP, Thevissen K. The mode of antifungal action of plant, insect and human defensins. *Cell Mol Life Sci.* 2008; 65:2069–2079. [PubMed: 18360739]
- Aerts AM, Carmona-Gutierrez D, Lefevre S, Govaert G, Francois IE, Madeo F, et al. The antifungal plant defensin RsAFP2 from radish induces apoptosis in a meta-caspase independent way in *Candida albicans*. *FEBS Lett.* 2009; 583:2513–2516. [PubMed: 19596007]
- Bahn YS, Cox GM, Perfect JR, Heitman J. Carbonic anhydrase and CO₂ sensing during *Cryptococcus neoformans* growth, differentiation, and virulence. *Curr Biol.* 2005; 15:2013–2020. [PubMed: 16303560]
- Bielawski J, Pierce JS, Snider J, Rembiesa B, Szulc ZM, Bielawska A. Sphingolipid analysis by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). *Adv Exp Med Biol.* 2010; 688:46–59. [PubMed: 20919645]
- Braun BR, Johnson AD. Control of filament formation in *Candida albicans* by the transcriptional repressor TUP1. *Science.* 1997; 277:105–109. [PubMed: 9204892]
- Braun BR, Kadosh D, Johnson AD. NRG1, a repressor of filamentous growth in *C. albicans*, is down-regulated during filament induction. *EMBO J.* 2001; 20:4753–4761. [PubMed: 11532939]
- Cheng J, Park TS, Fischl AS, Ye XS. Cell cycle progression and cell polarity require sphingolipid biosynthesis in *Aspergillus nidulans*. *Mol Cell Biol.* 2001; 21:6198–6209. [PubMed: 11509663]
- Cheng J, Park TS, Chio LC, Fischl AS, Ye XS. Induction of apoptosis by sphingoid long-chain bases in *Aspergillus nidulans*. *Mol Cell Biol.* 2003; 23:163–177. [PubMed: 12482970]
- Deveau A, Piispanen AE, Jackson AA, Hogan DA. Farnesol induces hydrogen peroxide resistance in *Candida albicans* yeast by inhibiting the Ras-cyclic AMP signaling pathway. *Eukaryot Cell.* 2010; 9:569–577. [PubMed: 20118211]
- Dichtl K, Ebel F, Dirr F, Routier FH, Heesemann J, Wagener J. Farnesol misplaces tip-localized Rho proteins and inhibits cell wall integrity signalling in *Aspergillus fumigatus*. *Mol Microbiol.* 2010; 76:1191–1204. [PubMed: 20398212]
- Edwards PA, Ericsson J. Sterols and iso-prenoids: signaling molecules derived from the cholesterol biosynthetic pathway. *Annu Rev Biochem.* 1999; 68:157–185. [PubMed: 10872447]
- Enjalbert B, Whiteway M. Release from quorum-sensing molecules triggers hyphal formation during *Candida albicans* resumption of growth. *Eukaryot Cell.* 2005; 4:1203–1210. [PubMed: 16002646]

- Enjalbert B, Smith DA, Cornell MJ, Alam I, Nicholls S, Brown AJ, Quinn J. Role of the Hog1 stress-activated protein kinase in the global transcriptional response to stress in the fungal pathogen *Candida albicans*. *Mol Biol Cell*. 2006; 17:1018–1032. [PubMed: 16339080]
- Erb-Downward JR, Huffnagle GB. *Cryptococcus neoformans* produces authentic prostaglandin E2 without a cyclooxygenase. *Eukaryot Cell*. 2007; 6:346–350. [PubMed: 17158733]
- Erb-Downward JR, Noverr MC. Characterization of prostaglandin E2 production by *Candida albicans*. *Infect Immun*. 2007; 75:3498–3505. [PubMed: 17470538]
- Erb-Downward JR, Noggle RM, Williamson PR, Huffnagle GB. The role of laccase in prostaglandin production by *Cryptococcus neoformans*. *Mol Microbiol*. 2008; 68:1428–1437. [PubMed: 18410494]
- Fairn GD, Macdonald K, McMaster CR. A chemogenomic screen in *Saccharomyces cerevisiae* uncovers a primary role for the mitochondria in farnesol toxicity and its regulation by the Pkc1 pathway. *J Biol Chem*. 2007; 282:4868–4874. [PubMed: 17164236]
- Fan W, Kraus PR, Boily MJ, Heitman J. *Cryptococcus neoformans* gene expression during murine macrophage infection. *Eukaryot Cell*. 2005; 4:1420–1433. [PubMed: 16087747]
- Farhang-Fallah J, Randhawa VK, Nimnual A, Klip A, Bar-Sagi D, Rozakis-Adcock M. The pleckstrin homology (PH) domain-interacting protein couples the insulin receptor substrate 1 PH domain to insulin signaling pathways leading to mitogenesis and GLUT4 translocation. *Mol Cell Biol*. 2002; 22:7325–7336. [PubMed: 12242307]
- Fox TE, Kester M. Therapeutic strategies for diabetes and complications: a role for sphingolipids? *Adv Exp Med Biol*. 2010; 688:206–216. [PubMed: 20919656]
- Garcia J, Shea J, Alvarez-Vasquez F, Qureshi A, Luberto C, Voit EO, Del Poeta M. Mathematical modeling of pathogenicity of *Cryptococcus neoformans*. *Mol System Biology*. 2008b; 4:183–195.
- Garcia J, Shea J, Alvarez-Vasquez F, Qureshi A, Luberto C, Voit EO, Del Poeta M. Mathematical modeling of pathogenicity of *Cryptococcus neoformans*. *Mol Syst Biol*. 2008a; 4:183. [PubMed: 18414484]
- Garscha U, Jerneren F, Chung D, Keller NP, Hamberg M, Oliw EH. Identification of dioxygenases required for *Aspergillus* development. Studies of products, stereochemistry, and the reaction mechanism. *J Biol Chem*. 2007; 282:34707–34718. [PubMed: 17906293]
- Gault CR, Obeid LM, Hannun YA. An overview of sphingolipid metabolism: from synthesis to breakdown. *Adv Exp Med Biol*. 2010; 688:1–23. [PubMed: 20919643]
- Gomez-Munoz A, Gangoiiti P, Granado MH, Arana L, Ouro A. Ceramide-1-phosphate in cell survival and inflammatory signaling. *Adv Exp Med Biol*. 2010; 688:118–130. [PubMed: 20919650]
- Hannun YA, Loomis CR, Merrill AH Jr, Bell RM. Sphingosine inhibition of protein kinase C activity and of phorbol dibutyrate binding *in vitro* and in human platelets. *J Biol Chem*. 1986; 261:12604–12609. [PubMed: 3462188]
- Heidler SA, Radding JA. Inositol phosphoryl transferases from human pathogenic fungi. *Biochim Biophys Acta*. 2000; 1500:147–152. [PubMed: 10564728]
- Heung LJ, Luberto C, Plowden A, Hannun YA, Del Poeta M. The sphingolipid pathway regulates Pkc1 through the formation of diacylglycerol in *Cryptococcus neoformans*. *J Biol Chem*. 2004; 279:21144–21153. [PubMed: 15014071]
- Hinkovska-Galcheva V, Shayman JA. Ceramide-1-phosphate in phagocytosis and calcium homeostasis. *Adv Exp Med Biol*. 2010; 688:131–140. [PubMed: 20919651]
- Holthuis JC, Luberto C. Tales and mysteries of the enigmatic sphingomyelin synthase family. *Adv Exp Med Biol*. 2010; 688:72–85. [PubMed: 20919647]
- Hornby JM, Jensen EC, Lisec AD, Tasto JJ, Jahnke B, Shoemaker R, et al. Quorum sensing in the dimorphic fungus *Candida albicans* is mediated by farnesol. *Appl Environ Microbiol*. 2001; 67:2982–2992. [PubMed: 11425711]
- Jenkins GM, Richards A, Wahl T, Mao C, Obeid L, Hannun Y. Involvement of yeast sphingolipids in the heat stress response of *Saccharomyces cerevisiae*. *J Biol Chem*. 1997; 272:32566–32572. [PubMed: 9405471]
- Joo JH, Jetten AM. Molecular mechanisms involved in farnesol-induced apoptosis. *Cancer Lett*. 2010; 287:123–135. [PubMed: 19520495]

- Kadosh D, Johnson AD. Rfg1, a protein related to the *Saccharomyces cerevisiae* hypoxic regulator Rox1, controls filamentous growth and virulence in *Candida albicans*. *Mol Cell Biol*. 2001; 21:2496–2505. [PubMed: 11259598]
- Kaneko A, Umeyama T, Utena-Abe Y, Yamagoe S, Niimi M, Uehara Y. Tcc1p, a novel protein containing the tetratricopeptide repeat motif, interacts with Tup1p to regulate morphological transition and virulence in *Candida albicans*. *Eukaryot Cell*. 2006; 5:1894–1905. [PubMed: 16998076]
- Kawamori T. Animal models for studying the pathophysiology of ceramide. *Adv Exp Med Biol*. 2010; 688:109–117. [PubMed: 20919649]
- Kechichian TB, Shea J, Del Poeta M. Depletion of alveolar macrophages decreases the dissemination of a glucosylceramide-deficient mutant of *Cryptococcus neoformans* in immunodeficient mice. *Infect Immun*. 2007; 75:4792–4798. [PubMed: 17664261]
- Khalaf RA, Zitomer RS. The DNA binding protein Rfg1 is a repressor of filamentation in *Candida albicans*. *Genetics*. 2001; 157:1503–1512. [PubMed: 11290707]
- Kleinhans FW, Lees ND, Bard M, Haak RA, Woods RA. ESR determinations of membrane permeability in a yeast sterol mutant. *Chem Phys Lipids*. 1979; 23:143–154. [PubMed: 222496]
- Klopfenstein DR, Vale RD. The lipid binding pleckstrin homology domain in UNC-104 kinesin is necessary for synaptic vesicle transport in *Caenorhabditis elegans*. *Mol Biol Cell*. 2004; 15:3729–3739. [PubMed: 15155810]
- Kruppa M. Quorum sensing and *Candida albicans*. *Mycoses*. 2009; 52:1–10.
- Kuroda E, Yamashita U. Mechanisms of enhanced macrophage-mediated prostaglandin E2 production and its suppressive role in Th1 activation in Th2-dominant BALB/c mice. *J Immunol*. 2003; 170:757–764. [PubMed: 12517938]
- Lee H, Chang YC, Nardone G, Kwon-Chung KJ. TUP1 disruption in *Cryptococcus neoformans* uncovers a peptide-mediated density-dependent growth phenomenon that mimics quorum sensing. *Mol Microbiol*. 2007; 64:591–601. [PubMed: 17462010]
- Lee H, Chang YC, Varma A, Kwon-Chung KJ. Regulatory diversity of TUP1 in *Cryptococcus neoformans*. *Eukaryot Cell*. 2009; 8:1901–1908. [PubMed: 19820119]
- Lees ND, Bard M, Kemple MD, Haak RA, Kleinhans FW. ESR determination of membrane order parameter in yeast sterol mutants. *Biochim Biophys Acta*. 1979; 553:469–475. [PubMed: 222316]
- Leverly SB, Momany M, Lindsey R, Toledo MS, Shayman JA, Fuller M, et al. Disruption of the glucosylceramide biosynthetic pathway in *Aspergillus nidulans* and *Aspergillus fumigatus* by inhibitors of UDP-Glc:ceramide glucosyltransferase strongly affects spore germination, cell cycle, and hyphal growth. *FEBS Lett*. 2002; 525:59–64. [PubMed: 12163162]
- Luberto C, Toffaletti DL, Wills EA, Tucker SC, Casadevall A, Perfect JR, et al. Roles for inositol-phosphoryl ceramide synthase 1 (*IPC1*) in pathogenesis of *C. neoformans*. *Genes Dev*. 2001; 15:201–212. [PubMed: 11157776]
- Luberto C, Martinez-Marino B, Taraskiewicz D, Bolanos B, Chitano P, Toffaletti DL, et al. Identification of App1 as a regulator of phagocytosis and virulence of *Cryptococcus neoformans*. *J Clin Invest*. 2003; 112:1080–1094. [PubMed: 14523045]
- Mare L, Iatta R, Montagna MT, Luberto C, Del Poeta M. APP1 transcription is regulated by inositol-phosphorylceramide synthase 1-diacylglycerol pathway and is controlled by ATF2 transcription factor in *Cryptococcus neoformans*. *J Biol Chem*. 2005; 280:36055–36064. [PubMed: 16129666]
- Martin SW, Konopka JB. Lipid raft polarization contributes to hyphal growth in *Candida albicans*. *Eukaryot Cell*. 2004; 3:675–684. [PubMed: 15189988]
- Merrill AH Jr, Sereni AM, Stevens VL, Hannun YA, Bell RM, Kinkade JM Jr. Inhibition of phorbol ester-dependent differentiation of human promyelocytic leukemic (HL-60) cells by sphinganine and other long-chain bases. *J Biol Chem*. 1986; 261:12610–12615. [PubMed: 3462189]
- Messner MC, Cabot MC. Glucosylceramide in humans. *Adv Exp Med Biol*. 2010; 688:156–164. [PubMed: 20919653]
- Mitchell AP. Fungal CO₂ sensing: a breath of fresh air. *Curr Biol*. 2005; 15:R934–R936. [PubMed: 16303555]
- Mitchell AP. Cryptococcal virulence: beyond the usual suspects. *J Clin Invest*. 2006; 116:1481–1483. [PubMed: 16741574]

- Mogensen EG, Janbon G, Chaloupka J, Steegborn C, Fu MS, Moyrand F, et al. *Cryptococcus neoformans* senses CO₂ through the carbonic anhydrase Can2 and the adenylyl cyclase Cac1. *Eukaryot Cell*. 2006; 5:103–111. [PubMed: 16400172]
- Nagiec MM, Skrzypek M, Nagiec EE, Lester RL, Dickson RC. The LCB4 (YOR171c) and LCB5 (YLR260w) genes of *Saccharomyces* encode sphingoid long chain base kinases. *J Biol Chem*. 1998; 273:19437–19442. [PubMed: 9677363]
- Nickerson KW, Atkin AL, Hornby JM. Quorum sensing in dimorphic fungi: farnesol and beyond. *Appl Environ Microbiol*. 2006; 72:3805–3813. [PubMed: 16751484]
- Nigam S, Ciccoli R, Ivanov I, Szczepanski M, Deva R. On mechanism of quorum sensing in *Candida albicans* by 3(R)-hydroxytetradecaenoic acid. *Curr Microbiol*. 2010; doi: 10.1007/s00284-010-9666-6
- Nikolova-Karakashian MN, Rozenova KA. Ceramide in stress response. *Adv Exp Med Biol*. 2010; 688:86–108. [PubMed: 20919648]
- Noble SM, French S, Kohn LA, Chen V, Johnson AD. Systematic screens of a *Candida albicans* homozygous deletion library decouple morphogenetic switching and pathogenicity. *Nat Genet*. 2010; 42:590–598. [PubMed: 20543849]
- Noverr MC, Phare SM, Toews GB, Coffey MJ, Huffnagle GB. Pathogenic yeasts *Cryptococcus neoformans* and *Candida albicans* produce immunomodulatory prostaglandins. *Infect Immun*. 2001; 69:2957–2963. [PubMed: 11292712]
- Noverr MC, Williamson PR, Fajardo RS, Huffnagle GB. CNLAC1 is required for extrapulmonary dissemination of *Cryptococcus neoformans* but not pulmonary persistence. *Infect Immun*. 2004; 72:1693–1699. [PubMed: 14977977]
- Oberholzer U, Nantel A, Berman J, Whiteway M. Transcript profiles of *Candida albicans* cortical actin patch mutants reflect their cellular defects: contribution of the Hog1p and Mkc1p signaling pathways. *Eukaryot Cell*. 2006; 5:1252–1265. [PubMed: 16896210]
- Oskouian B, Saba JD. Cancer treatment strategies targeting sphingolipid metabolism. *Adv Exp Med Biol*. 2010; 688:185–205. [PubMed: 20919655]
- Oura T, Kajiwar S. Disruption of the sphingolipid Delta8-desaturase gene causes a delay in morphological changes in *Candida albicans*. *Microbiology*. 2008; 154:3795–3803. [PubMed: 19047747]
- Oura T, Kajiwar S. *Candida albicans* sphingolipid C9-methyltransferase is involved in hyphal elongation. *Microbiology*. 2010; 156:1234–1243. [PubMed: 20019081]
- Patton JL, Srinivasan B, Dickson RC, Lester RL. Phenotypes of sphingolipid-dependent strains of *Saccharomyces cerevisiae*. *J Bacteriol*. 1992; 174:7180–7184. [PubMed: 1429441]
- Plesofsky NS, Levery SB, Castle SA, Brambl R. Stress-induced cell death is mediated by ceramide synthesis in *Neurospora crassa*. *Eukaryot Cell*. 2008; 7:2147–2159. [PubMed: 18952903]
- Ramage G, Lopez-Ribot JL. Techniques for antifungal susceptibility testing of *Candida albicans* biofilms. *Methods Mol Med*. 2005; 118:71–79. [PubMed: 15888936]
- Ramage G, Saville SP, Wickes BL, Lopez-Ribot JL. Inhibition of *Candida albicans* biofilm formation by farnesol, a quorum-sensing molecule. *Appl Environ Microbiol*. 2002; 68:5459–5463. [PubMed: 12406738]
- Ramage G, Saville SP, Thomas DP, Lopez-Ribot JL. *Candida* biofilms: an update. *Eukaryot Cell*. 2005; 4:633–638. [PubMed: 15821123]
- Ramamoorthy V, Cahoon EB, Thokala M, Kaur J, Li J, Shah DM. Sphingolipid C-9 methyltransferases are important for growth and virulence but not for sensitivity to antifungal plant defensins in *Fusarium graminearum*. *Eukaryot Cell*. 2009; 8:217–229. [PubMed: 19028992]
- Rhyme R, Del Poeta M. Sphingolipid signaling in fungal pathogens. *Adv Exp Med Biol*. 2010; 688:232–237. [PubMed: 20919658]
- Rhyme R, McQuiston T, Kechichian T, Bielawska A, Hennig M, Drago M, et al. Biosynthesis and immunogenicity of glucosylceramide in *Cryptococcus neoformans* and other human pathogens. *Eukaryot Cell*. 2007; 6:1715–1726. [PubMed: 17693597]
- Riboni L, Giussani P, Viani P. Sphingolipid transport. *Adv Exp Med Biol*. 2010; 688:24–45. [PubMed: 20919644]

- Rittershaus PC, Kechichian TB, Allegood JC, Merrill AH Jr, Hennig M, Luberto C, Del Poeta M. Glucosylceramide synthase is an essential regulator of pathogenicity of *Cryptococcus neoformans*. *J Clin Invest*. 2006; 116:1651–1659. [PubMed: 16741577]
- Sebolai OM, Pohl CH, Botes PJ, Strauss CJ, van Wyk PW, Botha A, Kock JL. 3-hydroxy fatty acids found in capsules of *Cryptococcus neoformans*. *Can J Microbiol*. 2007; 53:809–812. [PubMed: 17668042]
- Sebolai OM, Pohl CH, Botes PJ, van Wyk PW, Kock JL. The influence of acetylsalicylic acid on oxylipin migration in *Cryptococcus neoformans* var. *neoformans* UOFS Y-1378. *Can J Microbiol*. 2008; 54:91–96. [PubMed: 18388977]
- Semighini CP, Hornby JM, Dumitru R, Nickerson KW, Harris SD. Farnesol-induced apoptosis in *Aspergillus nidulans* reveals a possible mechanism for antagonistic interactions between fungi. *Mol Microbiol*. 2006; 59:753–764. [PubMed: 16420349]
- Shea JM, Del Poeta M. Lipid signaling in pathogenic fungi. *Curr Opin Microbiol*. 2006; 9:352–358. [PubMed: 16798065]
- Shea JM, Kechichian TB, Luberto C, Del Poeta M. The cryptococcal enzyme inositol phosphosphingolipid-phospholipase C confers resistance to the antifungal effects of macrophages and promotes fungal dissemination to the central nervous system. *Infect Immun*. 2006; 74:5977–5988. [PubMed: 16988277]
- Siafakas AR, Wright LC, Sorrell TC, Djordjevic JT. Lipid rafts in *Cryptococcus neoformans* concentrate the virulence determinants phospholipase B1 and Cu/Zn superoxide dismutase. *Eukaryot Cell*. 2006; 5:488–498. [PubMed: 16524904]
- Siafakas AR, Sorrell TC, Wright LC, Wilson C, Larsen M, Boadle R, et al. Cell wall-linked cryptococcal phospholipase B1 is a source of secreted enzyme and a determinant of cell wall integrity. *J Biol Chem*. 2007; 282:37508–37514. [PubMed: 17947228]
- Smal J, De Meyts P. Sphingosine, an inhibitor of protein kinase C, suppresses the insulin-like effects of growth hormone in rat adipocytes. *Proc Natl Acad Sci USA*. 1989; 86:4705–4709. [PubMed: 2660145]
- Smith DA, Nicholls S, Morgan BA, Brown AJ, Quinn J. A conserved stress-activated protein kinase regulates a core stress response in the human pathogen *Candida albicans*. *Mol Biol Cell*. 2004; 15:4179–4190. [PubMed: 15229284]
- Sonnino S, Prinetti A. Gangliosides as regulators of cell membrane organization and functions. *Adv Exp Med Biol*. 2010; 688:165–184. [PubMed: 20919654]
- Spiegel S. Sphingosine 1-phosphate: a prototype of a new class of second messengers. *J Leukoc Biol*. 1999; 65:341–344. [PubMed: 10080537]
- Stiban J, Tidhar R, Futerman AH. Ceramide synthases: roles in cell physiology and signaling. *Adv Exp Med Biol*. 2010; 688:60–71. [PubMed: 20919646]
- Strub GM, Maceyka M, Hait NC, Milstien S, Spiegel S. Extracellular and intracellular actions of sphingosine-1-phosphate. *Adv Exp Med Biol*. 2010; 688:141–155. [PubMed: 20919652]
- Tanimoto T, Onodera K, Hosoya T, Takamatsu Y, Kinoshita T, Tago K, et al. Schizostatin, a novel squalene synthase inhibitor produced by the mushroom, *Schizophyllum commune*. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activities. *J Antibiot*. 1996; 49:617–623. [PubMed: 8784419]
- Tavares PM, Thevissen K, Cammue BP, Francois IE, Barreto-Bergter E, Taborda CP, et al. *In vitro* activity of the antifungal plant defensin RsAFP2 against *Candida* isolates and its *in vivo* efficacy in prophylactic murine models of candidiasis. *Antimicrob Agents Chemother*. 2008; 52:4522–4525. [PubMed: 18824606]
- Ternes P, Sperling P, Albrecht S, Franke S, Cregg JM, Warnecke D, Heinz E. Identification of fungal sphingolipid C9-methyltransferases by phylogenetic profiling. *J Biol Chem*. 2006; 281:5582–5592. [PubMed: 16339149]
- Thevissen K, Warnecke DC, Francois IE, Leipelt M, Heinz E, Ott C, et al. Defensins from insects and plants interact with fungal glucosylceramides. *J Biol Chem*. 2004; 279:3900–3905. [PubMed: 14604982]

- Thevissen K, Kristensen HH, Thomma BP, Cammue BP, Francois IE. Therapeutic potential of antifungal plant and insect defensins. *Drug Discov Today*. 2007; 12:966–971. [PubMed: 17993416]
- Tommasino N, Villani M, Qureshi A, Henry J, Luberto C, Del Poeta M. Atf2 transcription factor binds to the APP1 promoter in *Cryptococcus neoformans*: stimulatory effect of diacylglycerol. *Eukaryot Cell*. 2008; 7:294–301. [PubMed: 18083832]
- Tsitsigiannis DI, Keller NP. Oxylipins as developmental and host-fungal communication signals. *Trends Microbiol*. 2007; 15:109–118. [PubMed: 17276068]
- Tsitsigiannis DI, Bok JW, Andes D, Nielsen KF, Frisvad JC, Keller NP. Aspergillus cyclooxygenase-like enzymes are associated with prostaglandin production and virulence. *Infect Immun*. 2005; 73:4548–4559. [PubMed: 16040966]
- Uhl MA, Biery M, Craig N, Johnson AD. Haploinsufficiency-based large-scale forward genetic analysis of filamentous growth in the diploid human fungal pathogen *C. albicans*. *EMBO J*. 2003; 22:2668–2678. [PubMed: 12773383]
- Voit, EO. Computational Analysis of Biochemical System. A Practical Guide for Biochemists and Molecular Biologists. Cambridge: Cambridge University Press; 2000.
- Warnecke D, Heinz E. Recently discovered functions of glucosylceramides in plants and fungi. *Cell Mol Life Sci*. 2003; 60:919–941. [PubMed: 12827281]
- Weber K, Schulz B, Ruhnke M. The quorum-sensing molecule E,E-farnesolits variable secretion and its impact on the growth and metabolism of *Candida* species. *Yeast*. 2010; 27:727–739. [PubMed: 20641010]
- Wells GB, Dickson RC, Lester RL. Heat-induced elevation of ceramide in *Saccharomyces cerevisiae* via de novo synthesis. *J Biol Chem*. 1998; 273:7235–7243. [PubMed: 9516416]
- Westwater C, Balish E, Schofield DA. *Candida albicans*-conditioned medium protects yeast cells from oxidative stress: a possible link between quorum sensing and oxidative stress resistance. *Eukaryot Cell*. 2005; 4:1654–1661. [PubMed: 16215173]
- Wilson E, Olcott MC, Bell RM, Merrill AH Jr, Lambeth JD. Inhibition of the oxidative burst in human neutrophils by sphingoid long-chain bases. Role of protein kinase C in activation of the burst. *J Biol Chem*. 1986; 261:12616–12623. [PubMed: 3017982]
- Wymann MP, Schneider R. Lipid signalling in disease. *Nat Rev Mol Cell Biol*. 2008; 9:162–176. [PubMed: 18216772]
- Zauner S, Ternes P, Warnecke D. Biosynthesis of sphingolipids in plants (and some of their functions). *Adv Exp Med Biol*. 2010; 688:249–263. [PubMed: 20919660]

Fig. 1.

Regulation of cryptococcal pathogenicity by the sphingolipid pathway. PI, phosphatidylinositol; Ipc1, inositol phosphoryl ceramide synthase; IPC, inositol phosphoryl ceramide; DAG, diacylglycerol; Pkc1, protein kinase C1; Lac1, laccase; Atf2, activating transcription factor 2; App1, antiphagocytic protein 1; Isc1, inositol phosphosphingolipid phospholipase C; IP, inositol phosphate; Pma1, plasma membrane ATPase 1; Gcs1, glucosylceramide synthase; UDP, uridine diphosphate; GlcCer, glucosylceramide. (A) Colonies of *C. neoformans* with wild-type (brown) and downregulated Ipc1 (white) grown on dopamine plates. (B) *C. neoformans* wild-type is about to be engulfed by a murine primary alveolar macrophages. White bar: 10 μ m. (C) A J774.16 peritoneal macrophage containing several *C. neoformans* wild-type cells within its phagolysosome. White bar: 10 μ m. (D) Mouse lung stained with mucicarmine shows several *C. neoformans* wild-type H99 cells in bronchioles. White bar: 5 μ m.