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MINIREVIEWS

Mitogen-Activated Protein Kinase Pathways and Fungal Pathogenesis[▽]

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In eukaryotic cells, a family of serine/threonine protein kinases known as mitogen-activated protein (MAP) kinases (MAPKs) is involved in the transduction of a variety of extracellular signals and the regulation of different developmental processes. The MAPK is activated by dual phosphorylation of the TXY motif by MAPK kinase (MEK or MAPKK), which is activated in turn by MEK kinase (MEKK or MAPKKK). The sequential activation of the MAPK cascade eventually results in the activation of transcription factors and the expression of specific sets of genes in response to environmental stimuli. In the budding yeast *Saccharomyces cerevisiae*, five MAPK pathways are known to regulate mating, invasive growth, cell wall integrity, hyperosmoregulation, and ascospore formation (50). In the past decade, MAPKs in various plant and human pathogenic fungi have been characterized. In this review, we will compare their functions in different fungal pathogens with a focus on infection-related morphogenesis and virulence.

MAPK PATHWAYS IN *S. CEREVISIAE*

Because of advanced studies with *S. cerevisiae*, we will first present a brief overview of yeast MAPKs (Fig. 1). The pheromone response pathway (for reviews, see the work of Bardwell [9] and of Schwartz and Madhani [132]) is initiated by the binding of pheromone with a G-protein-coupled receptor (GPCR), Ste2 or Ste3, and the dissociation of an inhibitory Gα subunit, Gpa1, from stimulatory Gβγ subunits. The liberated Gβ directly associates with a scaffold protein Ste5 and a p21-activated protein (PAK) kinase, Ste20, and is essential for the activation of the Ste11-Ste7–Fus3/Kss1 cascade. The cyclin-dependent kinase inhibitor Far1 and the Ste12 transcription factor are activated by Fus3 and Kss1 MAPKs for regulating the mating processes. Several elements of the pheromone response pathway are also involved in filamentous growth, which represents invasive growth in haploid and pseudohyphal development in diploid cells. The specificity of Fus3 and Kss1 cascades is regulated by Ste5, the Ste12/Tec1 transcription factor complex, and controlled degradation of Tec1 or Ste12 (12, 28, 132). For filamentous growth, the Kss1 pathway is activated by Ras2, Cdc42, 14-3-3 proteins Bmh1 and Bmh2, and Ste50 (9). The Ras2/cyclic AMP (cAMP) signaling also regulates filamentous growth via the GPCR Gpr1 and Gα Gpa2 subunit (114).

The Pkc1-Slt2 (Mpk1) cell integrity pathway monitors cell wall integrity and promotes cell wall biosynthesis (for a review, see the work of Heinisch [52]). It is also involved in responses to certain environmental signals, including low osmolarity, high temperature, alkaline pH, and nutrient limitations. Extracellular signals are transmitted from surface sensors to Rom2, a guanine exchange factor of the GTP-binding protein Rho1. Rho1 then activates Pkc1 and the Bck1-Mkk1/Mkk2-Slt2 cascade (Fig. 1). Downstream transcription factors, such as Rlm1, Sbf, and Swi6, are activated by Slt2 to regulate cell wall synthesis and cell cycle (52, 60). The high-osmolarity glycerol (HOG) response pathway is required for growth under hyperosmotic conditions (54, 129). The Pbs2 MEK-Hog1 MAPK module can be activated by two upstream branches. One involves MEKKs Ssk2p and Ssk22p and a two-component histidine kinase phospho-relay system comprised of Sln1, Ypd1, and Ssk1. The other involves the activation of Pbs2 by Ste11 (Fig. 1), which functions downstream from Sho1 and Msb2 (112). In addition to its role in osmoregulation, the HOG pathway has recently been implicated in the response to nonosmotic stresses, such as arsenite, lower temperatures, and acid pH (89, 100, 115, 138). The other yeast MAPK is Smk1, a sporulation-specific MAPK activated by intracellular signals (50). It lacks upstream MEK or MEKK and has no homolog in other fungi except for some ascomycetous yeasts, such as *Ashbya gossypii* and *Kluyveromyces lactis*.

HOMOLOGS OF THE YEAST *FUS3*/*KSS1* MAPKs

While fungi in the saccharomycetales, such as *A. gossypii*, *K. lactis*, and *Candida albicans*, have both Fus3 and Kss1 homologs, most filamentous fungi, like the archiascomycete *Schizosaccharomyces pombe*, have only one MAPK, which is homologous either to yeast Fus3 or to Kss1.

***Ustilago maydis*.** The corn smut fungus *U. maydis* has been extensively studied for signal transduction pathways regulating mating and pathogenesis (for a review, see the work of Kahmann and Kamper [63]). It is a facultative biotrophic pathogen with a haploid, saprophytic yeast phase. Fusion of compatible yeast cells leads to the development of dikaryotic hyphae that can infect corn plants and cause tumors. The cAMP signaling pathway plays a critical role in regulating hyphal growth and pathogenic development. Strains blocked in the cAMP signaling pathway, such as the *gpa3* (Gα subunit), *uac1* (adenylate cyclase), and *adr* (catalytic subunit of PKA) deletion mutants, are nonpathogenic and grow filamentously (10, 63). Mating

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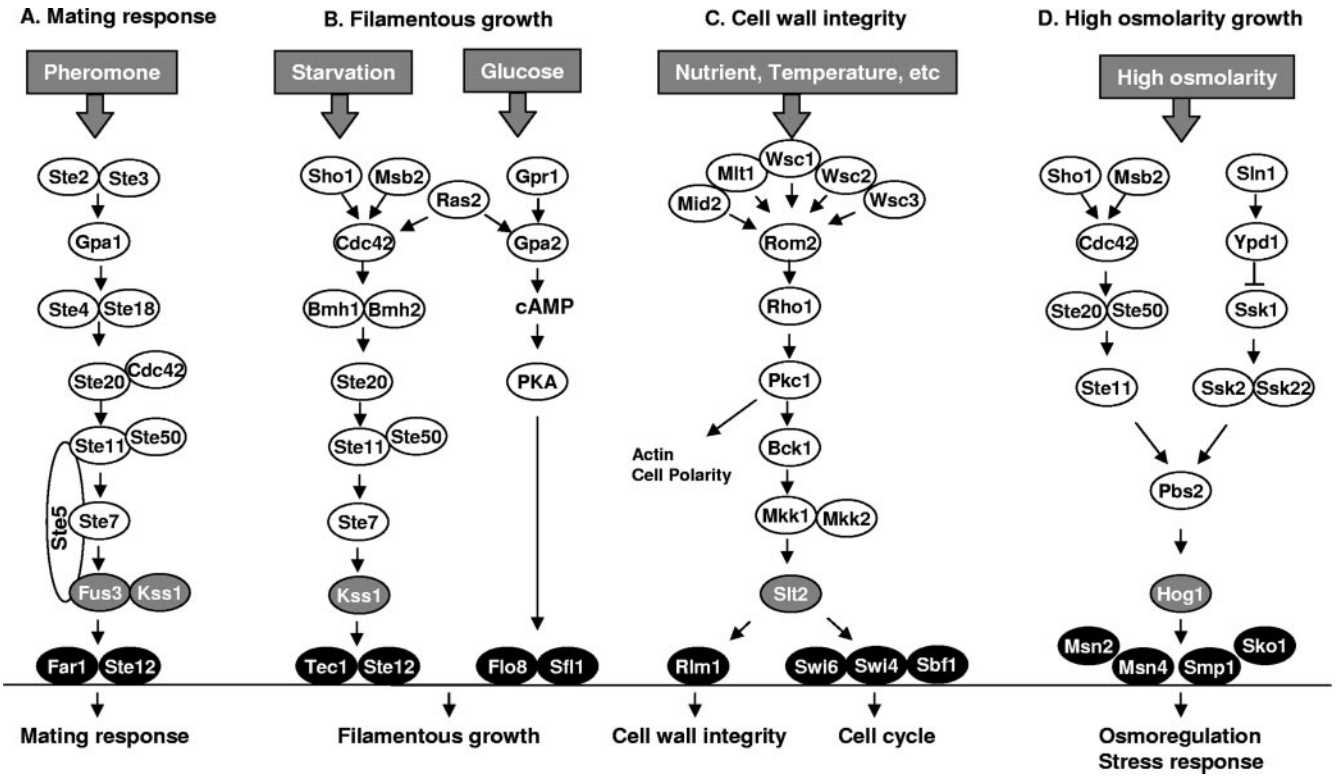

FIG. 1. MAPK pathways in *Saccharomyces cerevisiae*.

recognition occurs between pheromones and receptors and results in the activation of a downstream MAPK cascade consisting of the MEKK Kpp4 (Ubc4), MEK Fuz7 (Ubc5), and MAPKs Kpp2 (Ubc3) and Kpp6. Fuz7, a homolog of yeast Ste7, is the first element of this cascade to be characterized. It is important for conjugation tube production, filamentous growth, tumor induction, and teliospore formation and germination.

Kpp2 (Ubc3) and Kpp6 are two MAPKs with overlapping functions in mating and plant infection (10, 63). The *kpp2* (*ubc3*) mutant is defective in pheromone responses and the formation of filamentous dikaryons and reduced in virulence. Kpp6 contains an unusual N-terminal domain and plays a more critical role in appressorial penetration than Kpp2. The *kpp6* mutant is reduced in virulence and defective in the penetration of plant cuticle (15). The *kpp2 kpp6* double mutants are abolished in mating and nonpathogenic on maize plants. Because transformants expressing the kinase dead *kpp6* allele and the unphosphorylatable *kpp2* allele are more severely compromised in pathogenesis than the *kpp6* and *kpp2* mutants, respectively (106), the inactive *kpp6* and *kpp2* alleles may have additional inhibitory effects or downstream targets. Crk1 was first identified as a homolog of yeast Ime2 but later described as a novel MAPK in *U. maydis* that regulates morphogenesis, cell cycle, and plant infection (48). The *crk1* mutant is defective in *prf1* expression, mating, and plant infection.

The MEKK acting upstream from Fuz7 is Kpp4/Ubc4. Similar to *fuz7* mutants, *kpp4* deletion mutants are nonpathogenic and defective in the induction of pheromone-responsive genes (63). Deletion of Ubc2 (Ste50 homolog) also impairs pheromone responses and virulence (91). Different from other Ste50 homologs, Ubc2 has two C-terminal Src homology 3 domains that may be involved in protein-protein interactions. Ubc2 may function as an adaptor protein for the Kpp4-Fuz7-Kpp2/Kpp6 cascades. In *U. maydis*, the Smu1 PAK kinase is not directly involved in the activation of Kpp4 and downstream MAPKs, and it is dispensable for mating, plant infection, or tumor formation (134).

Ras2, one of the Ras proteins in *U. maydis*, has been placed upstream from Kpp4 and Ubc2. Mutation in the *ras2* gene suppresses a constitutively filamentous phenotype of the *adr1* mutant (80). Expression of a dominant active *ras2* allele promotes pseudohyphal growth in a manner dependent on the Ubc4-Fuz7-Ubc3 cascade. In contrast, constitutive activation of Ras1 increases the expression of *mfa1* but has no effect on cell morphology and yeast growth (104). Therefore, Ras2 and Ras1 in *U. maydis* may affect the MAPK and the cAMP-protein kinase A (PKA) pathway, respectively. A potential activator of Ras2 is the Cdc25-like guanine exchange factor protein Sql2 (104). However, unlike the *ras2* mutant, the *sql2* deletion mutant is defective in plant infection but not in mating. Sql2 may be an in planta-specific activator of Ras2 in response to lipid signals for promoting and maintaining filamentous growth (68). Although Gpa3 is essential for pheromone signaling and pathogenic development, the pheromone receptors Pra1 and Pra2 have not been functionally linked with any of the four Gα submits in *U. maydis*. The Gβ subunit Bpp1 is involved in the cAMP-PKA pathway, but it is not an effector for the MAPK cascade (105).

The HMG-domain transcription factor Prf1 is required for

mating and plant infection. It has consensus MAPK and PKA phosphorylation sites and interacts with Adr1 as well as MAPK Kpp2 in vivo (62). While the PKA phosphorylation sites of Prf1 are essential for the induced expression of both *a* and *b* mating type genes, the MAPK phosphorylation sites are required only for *b* gene expression. Another HMG-domain protein, Rop1, is involved in mating, filamentous growth, and regulation of *prf1* expression in axenic cultures. However, Rop1 is dispensable for conjugation, *prf1* expression, and virulence on maize plants (17). In addition, Prf1 is not required for Kpp4 to control conjugation tube formation (106). Acidic pH still induces the yeast-to-hypha transition in haploid cells of the *prf1* mutant but not the *ubc4* or *fuz7* mutant (90). Therefore, an additional transcription factor(s) may function downstream from this MAPK pathway for regulating responses to different signals and filamentous growth.

***Magnaporthe grisea*.** Rice blast caused by *M. grisea* is one of the most severe fungal diseases of rice throughout the world. The fungus develops specialized infection structures called appressoria and uses the enormous turgor pressure generated in appressoria for plant penetration. While surface recognition and the initiation of appressorium formation are mediated by the cAMP signaling, late stages of appressorium formation and penetration are regulated by the *PMK1* pathway. The *pmk1* deletion mutant fails to form appressoria but still recognizes hydrophobic surfaces and responds to cAMP (151). *PMK1* also is essential for infectious hyphal growth after penetration. In transformants expressing a *PMK*-green fluorescent protein construct, enhanced green fluorescent protein signals and nuclear localization are observed in appressoria and developing conidia (18).

Several upstream components of the *PMK1* pathway, including the MEKK Mst11 and the MEK Mst7 and an Ste50 homolog, Mst50, have been characterized (118, 158). The *mst7*, *mst11*, and *mst50* mutants fail to form appressoria and are nonpathogenic. Mst50 directly interacts with both Mst7 and Mst11 and may function as an adaptor protein for the Mst11-Mst7-Pmk1 cascade. The direct interaction of Mst7 with Pmk1 is mediated by the docking site and occurs specifically during appressorium formation (159). *MST20*, a homolog of yeast *STE20*, is dispensable for *PMK1* activation in *M. grisea* (85). Consistent with this observation, the *CDC42* homolog in *M. grisea* is dispensable for appressorium formation and plant infection (S. Wu and Z. Wang, personal communication). Therefore, unlike the yeast pheromone response pathway, PAK kinase and MgCdc42 are not essential for activating the Pmk1 MAPK cascade in *M. grisea.*

Mst50 and Mst11 both interact with Ras1 and Ras2, two Ras proteins in *M. grisea* (118). The *ras1* deletion mutant has no defect in plant infection and appressorium formation, but *RAS2* appears to be an essential gene. Expression of a dominant active *RAS2* allele in the wild-type strain but not in the *pmk1* mutant stimulates appressorium formation on nonconducive surfaces (118), indicating that *RAS2* functions upstream from the Mst11-Mst7-Pmk1 cascade. In addition, the Gα subunit MagB, Gβ subunit Mgb1, and a negative regulator of G-protein signaling (Rgs1) have been implicated in regulating appressorium formation (86, 87, 110). Exogenous cAMP induces appressorium formation in *mgb1* mutants, but these appressoria are morphologically abnormal and nonfunctional. *MGB1* may control surface recognition via the cAMP signaling but function through the *PMK1* pathway to regulate appressorial penetration and invasive growth.

The *M. grisea* genome has no recognizable receptor protein kinase genes but contains a large number of GPCR-like genes (75), including putative homologs of Ste2, Ste3, GprD, and Pre-1. Twelve of them form a subfamily containing the CFEM domain, which is unique to fungi (32). In *M. grisea*, deletion of the yeast Ste2 and Ste3 homologs has no obvious effects on appressorium formation or plant infection (J.-R. Xu, unpublished data), but one putative CFEM-GPCR gene, *PTH11*, has been implicated in surface recognition via cAMP signaling (35). However, exogenous cAMP restores appressorium formation and pathogenicity in the *pth11* mutant, suggesting that *PTH11* may be involved in the regulation of cAMP signaling. Also, predicting GPCRs is not reliable, and there is no direct evidence to support the sensory role of Pth11 in *M. grisea*.

One putative downstream transcription factor regulated by Pmk1 is Mst12 (Ste12 homolog), which is essential for pathogenesis. Appressoria formed by the *mst12* mutant have normal appressorium turgor but fail to develop penetration pegs, probably due to cytoskeleton defects in mature appressoria (117). *MST12* may regulate genes involved in penetration and infectious growth, but another transcription factor(s) must function downstream of *PMK1* for regulating appressorium formation. One of the REMI mutants defective in appressorium formation is disrupted in a homeobox gene, *PTH12*. However, the *pth12* deletion mutant still occasionally forms melanized appressoria and responds to exogenous cAMP for appressorium formation (Y. Peng, personal communication). Several genes regulated by *PMK1* have been identified by subtractive hybridization, including *GAS1* and *GAS2*, two homologous genes that are unique to filamentous fungi and specifically expressed during appressorium formation (153).

Other plant pathogenic fungi. (i) Appressorium-forming pathogens. Homologs of *FUS3/KSS1* in several other plant pathogenic fungi that form well-developed appressoria, including *Cochliobolus heterostrophus*, *Colletotrichum lagenarium*, *C. gloeosporioides*, and *Pyrenophora teres*, have been characterized. In all these fungi, *PMK1* homologs are essential for appressorium formation (128, 151). Similar to the *pmk1* mutant, the *P. teres ptk1* and *C. lagenarium cmk1* mutants are nonpathogenic and fail to colonize healthy or wounded host tissues. Conidia of the *cmk1* mutant fail to germinate on plant and glass surfaces. In contrast, the *STE12* homolog is essential for penetration and infectious growth but dispensable for appressorium formation in *C. lagenarium* (139). In the rice leaf spot pathogen *Bipolaris oryzae*, *BMK1* is required for plant infection and conidiation, but its role in appressorium formation and penetration has not been examined (101).

In *C. heterostrophus*, *CHK1* is important for invasive growth and efficient colonization of leaf tissue after penetration, but the *chk1* mutant still forms a few small, restricted lesions on corn leaves. Other phenotypes of the *chk1* mutant include reduced aerial hyphae, autolysis, lack of conidiation, and loss of female fertility (83). Genes for cellobiohydrolase Cbh1, for endoglucanase Eg6, for transcription factor Cmr1, and for three enzymes for melanin synthesis are among those known to be regulated by Chk1 (43, 82). Similar to *CHK1*, the *CGB1* (Gβ) gene is essential for appressorium formation, female

fertility, hyphal pigmentation, and full virulence (47). However, the *cgb1* mutant still produces conidia and is more severely reduced in virulence than the *chk1* mutant. Deletion of *CGA1* (Gα) reduces appressorium formation but has no effect on pathogenesis, suggesting that *CGB1* and other upstream components, but not *CGA1*, may function upstream from the Chk1 cascade.

(ii) Non-appressorium-forming foliar pathogens. The *PMK1* homologs also are essential for infection in two foliar pathogens of wheat, *Mycosphaerella graminicola* and *Stagonospora nodorum*. In *M. graminicola*, the *MgFus3* deletion mutant is nonpathogenic and fails to colonize the mesophyll tissue through stomata (30). *MgFUS3* is important for aerial hyphal growth, melanization, and pycnidium formation. Similar to what is seen for the *mst20* mutant in *M. grisea*, deletion of a putative *STE20* homolog has no obvious effect on the vegetative growth or virulence of *M. graminicola* (30). In *S. nodorum*, *mak2* disruption mutants have reduced growth rates and are defective in conidiation, but they have no significant changes in the level of secreted protease activity, osmotic stress response, or melanin synthesis (135). Although *mak2* mutants fail to form penetration structures and are essentially nonpathogenic, they are able to enter the leaf via natural openings. However, the infection progress and the ability to cause disease once inside the leaf are compromised in the *mak2* mutant, which causes only limited necrosis on leaves (135).

(iii) Root or vascular pathogens. In *Fusarium oxysporum* f. sp. *lycopersici*, the *fmk1* mutant displays normal growth and conidiation but is nonpathogenic on tomato plants and significantly reduced in the expression of the pectate lyase gene *PL1* (37). *FMK1* is dispensable for conidium germination but is required for the differentiation of penetration hyphae and root attachment. In the vascular wilt pathogen *Verticillium dahliae*, *vmk1* mutants are nonpathogenic on a variety of host plants tested and defective in microsclerotium production (123). Interestingly, *PMK1* is also required for root infection in *M. grisea*, and it can functionally complement the *fmk1* mutant (37), suggesting a conserved role for this MAPK pathway in soilborne and foliar pathogens. A *FMK1* homolog from *Tuber borchii* is phosphorylated during plant colonization and partially restores invasive growth of the *fmk1* mutant. Therefore, the same MAPK pathway may regulate the establishment of symbiosis and ectomycorrhizae (95).

The *fgb1* (Gβ) deletion mutant of *F. oxysporum* also is reduced virulence, but it has an unaltered Fmk1 phosphorylation level and is defective in hyphal growth (33). Exogenous cAMP reverses part but not all of the *fgb1* growth phenotypes. Therefore, Fgb1 may act upstream from the cAMP signaling but not the Fmk1 pathway. In infection assays with an immunodepressed mouse model, the *fmk1 fgb1* double mutant but not the *fmk1* mutant or the *fgb1* mutant is significantly reduced in virulence (121). Fmk1 and Fgb1 appear to be components of distinct signaling pathways with overlapping functions.

(iv) Necrotrophic pathogens. *PMK1* homologs are also important for pathogenesis in several other necrotrophic ascomycetes (Table 1). In *Botrytis cinerea*, the *bmp1* mutant has a reduced growth rate and is nonpathogenic. Germ tubes of the *bmp1* mutant fail to penetrate the host tissue (160). Recently, an independent *bmp1* mutant was reported to be defective in conidium germination on hydrophobic surfaces and in responding to carbon sources (39). Differences in conidium germination between two *bmp1* mutants may be related to different spore concentrations used or mutant backgrounds. In *Alternaria brassicicola*, *amk1* mutants are nonpathogenic on intact plants but still colonize wounded leaves in the presence of nutrient supplements. Amk1 is essential for the production of mature conidia and up-regulation of several hydrolytic enzyme genes (26). In *Cryphonectria parasitica*, the *cpmk2* deletion mutant is defective in conidiation and pheromone production and has reduced growth rate and canker size (27). Although the activation of *CpMK2* is not affected, *CpSTE12* is down-regulated by hypovirus infection (34). Many genes affected by the hypovirus are down-regulated in the *cpste12* mutant, which is reduced in virulence and female sterile (34). In *Sclerotinia sclerotiorum*, Smk1 regulates sclerotium development, but its role in plant infection has not been determined (24).

TABLE 1. *FUS3/KSS1* homologs in pathogenic fungi

Fungal pathogen	MAPK	Major function(s)
M. grisea	Pmk1	Appressorium formation, pathogenicity, infectious growth
C. lagenarium	Cmk1	Appressorium formation, pathogenicity, spore germination
P. teres	Ptk1	Appressorium formation, pathogenicity, conidiation
C. heterostrophus	Chk1	Appressorium formation, virulence, conidiation
F. oxysporum	Fmk1	Pathogenicity, infectious growth, root attachment
B. cinerea	Bmp1	Pathogenicity, normal growth rate
U. maydis	Kpp2	Virulence, mating
U. maydis	Kpp6	Virulence, mating, penetration
C. purpurea	Cpmk1	Pathogenicity, penetration, infectious growth
F. graminearum	Gpmk1	Pathogenicity, infectious growth, conidiation
V. dahliae	Vmk1	Pathogenicity, conidiation, microsclerotium formation
B. oryzae	Bmk1	Pathogenicity, conidiation
M. graminicola	MgFus3	Pathogenicity, pycnidium formation, stoma penetration
S. nodorum	Mak2	Virulence, conidiation, normal growth rate
C. parasitica	Cpmk2	Virulence, conidiation, normal growth rate
S. sclerotiorum	Smk1	Sclerotium development
C. albicans	Cek1	Virulence, mating, yeast-hypha transition
C. albicans	Cek2	Mating
C. neoformans	Cpk1	Mating, haploid fruiting

In the wheat scab fungus *F. graminearum*, the *gpmk1* (*map1*) deletion mutants are reduced in conidiation, female sterile, and nonpathogenic (57, 140). The *gpmk1* mutants are impaired in colonizing wheat heads and spreading from inoculated florets to neighboring spikelets. They also fail to infect roots, wounded wheat floral tissues, and tomato fruits but still produce phytotoxic deoxynivalenol. Gpmk1 regulates the early induction of extracellular endoglucanase, xylanolytic, and proteolytic activities and is responsible for the overall induction of secreted lipolytic activities (58). One of the genes regulated by Gpmk1 is *FGL1*, which encodes a secreted lipase and is an important virulence factor in *F. graminearum* (144).

(v) Biotrophic pathogens. The *cpmk1* mutant of *Claviceps purpurea* has no defect in vegetative growth or conidiation but is incapable of penetration and nonpathogenic on rye plants (97). Mutants deleted of the *CDC42* homolog in *C. purpurea* also are nonpathogenic, but they still penetrate the stylar tissue. The invasive growth of the *CpCdc42* mutant is arrested at an early infection stage, presumably due to induced plant defense responses (131). Expression of *CPMK1* in the *pmk1* mu-

tant fully complements its defects, indicating that this MAPK pathway is functionally conserved between hemibiotrophic and biotrophic pathogens. In the barley powdery mildew fungus *Blumeria graminis*, both a MAPK and the cAMP signaling are involved in regulating appressorium development (67). In another obligate biotroph, *Puccinia triticina*, the *PtMAPK1* gene has increased expression levels during urediospore germination and plant infection. When expressed in *U. maydis*, it complements the defect of *kpp2* mutants in mating and plant infection (56).

Model saprophytic filamentous fungi. In the model filamentous fungus *Neurospora crassa*, mutants deleted of the MEKK *NRC-1* and MAPK *MAK-2* genes have the same pleiotropic phenotype, including derepressed conidiation, shortened aerial hyphae, lack of hyphal fusion and conidial anastomosis tube, female sterility, and flattened ascospores (72, 116). The *pp-1* (Ste12 homolog) deletion mutant has similar defects (84). However, none of the individual GPCR, Gα, Gβ, or Gγ deletion mutants are phenotypically similar to the *mak-2* mutant.

Unlike other filamentous fungi, several *Aspergillus* species, including *A. niger*, *A. nidulans*, and *A. fumigatus*, have four MAPK genes (124). The two MAPKs with the TEY dual phosphorylation site, MpkA and MpkB, are homologous to yeast Slt2 and Kss1, respectively. Although MpkB has not been functionally characterized, *SteA* (Ste12 homolog) is required for the development of ascogenous hyphae and cleistothecia. The *steA* deletion mutant is blocked in sexual reproduction but has normal vegetative growth and conidiation (141). However, the *steC* (Ste11 homolog) deletion mutant has a pleiotropic phenotype, including a reduced growth rate, altered conidiophore morphology, and defects in heterokaryon formation and cleistothecium development (148).

***Candida albicans*.** *C. albicans* causes various forms of candidiasis, particularly in immunocompromised patients. The reversible dimorphic transition between the yeast form and the hyphal form is important for its virulence and can be triggered by various signals in vitro, including high temperature, neutral pH, and serum. *C. albicans* also occasionally undergoes switching between white-phase cells that form dome-shaped, white colonies and opaque-phase cells that are more elongated and form flatter, darker colonies on solid agar. Signal transduction pathways regulating filamentous growth and the white-opaque switching have been well studied for *C. albicans* (for reviews, see the work of Alonso-Monge et al. [2], of Bennett and Johnson [11], and of Chen et al. [25]).

The Cek1 (Kss1 homolog) MAPK cascade has been well characterized for its role in the yeast-hypha transition and virulence (2, 11). Homozygous *cek1* mutants are defective in transition from unicellular budding growth to invasive hyphal growth on Spider or synthetic low-ammonium-dextrose (SLAD) medium and are significantly attenuated in virulence with murine models for systemic or superficial candidiasis. All the major components of the yeast pheromone response pathway except Ste5 have been identified in *C. albicans* (11). The PAK kinase Cst20, MEK Hst7, Cph1 (Ste12 homolog), CaTec1, CaRas1, Cdc42, and its exchange factor Cdc24 are also required for hyphal morphogenesis, invasive hyphal growth, and virulence. The defect of the *CaRas1* deletion mutant in morphological transition is suppressed by exogenous cAMP or overexpression of *CEK1* (78), indicating that CaRas1 functions in both signaling pathways.

All the mutants blocked in the *CEK1* pathway, however, are still capable of filamentous growth in response to serum. Multiple signaling pathways, including the cAMP-dependent protein kinase pathway via Efg1, a pH-responsive pathway through Rim101, and Tup1-mediated repression through Rfg1 and Nrg1, are known to regulate hyphal development and infection processes in *C. albicans* (2, 61). Cph1 and Efg1 have overlapping functions for induced expression of genes responsive to serum, and the homozygous *cph1 efg1* double mutant fails to develop hyphae or pseudohyphae in response to many stimuli (16, 88). Unlike Tec1 in yeast, CaTec1 is regulated by Efg1 and the basic helix-loop-helix transcription factor Cph2 but not by Cph1 in *C. albicans* (77). Recently, the Mep2 ammonium permease has been shown to mediate the induction of filamentous growth in response to nitrogen starvation by its interaction with CaRas1 (13).

Although *C. albicans* is a diploid fungus traditionally classified as asexual, mating between genetically modified strains and a parasexual cycle have been observed. *CEK2* (25) and several components of the *CEK1* pathway, including *STE2*, *GPA2*, *CST20*, *HST7*, *CEK1*, and *CPH1* (2), are involved in mating responses. *CEK2* encodes a MAPK highly similar to that encoded by *FUS3.* It is dispensable for filamentous growth on artificial media but has overlapping functions with *CEK1* in mating. While the *cek1* and *cek2* deletion mutants are reduced in mating efficiency, *cek1 cek2* double mutants, like the *hst7* and *cph1* mutants, are completely blocked in mating (25). For upstream components, the GPCR gene *STE2* is essential for mating responses to the alpha pheromone, and the Gpa2 Gα subunit is involved in relaying nutrient signals to mating. In *S. cerevisiae*, Mcm1 is involved in cell type-specific transcription and pheromone response. Overexpression of *CaMCM1* induces the expression of a hypha-specific gene *HWP1* and hyphal development, but its function in mating is not clear in the case of *C. albicans* (126). The Cph1-mediated MAPK pathway is involved in the regulation of white-opaque switching, which is controlled by the mating type locus (2, 98). Unlike the yeast pheromone response pathway, Cek1appears to be activated by quorum sensing and other environmental signals (125, 130). Farnesol, a quorum-sensing molecule, reduces the transcription levels of *HST7* and *CPH1* in *C. albicans*. Diluting stationary-phase cells in fresh rich medium also stimulates the phosphorylation of Cek1. In *C. albicans*, Sho1 is essential for Cek1 activation under different conditions that require active cell growth and cell wall remodeling (125). The *sho1* mutant is sensitive to oxidative stress and cell wall-interfering compounds (Congo red and calcofluor white) and is defective in morphogenesis on SLAD and Spider media, which stimulate hyphal growth (125). These results reveal a role for Sho1 in linking oxidative stress, cell wall biogenesis, and morphogenesis in *C. albicans*.

Cryptococcus neoformans*.** *C. neoformans* is the causal agent of cryptococcal meningoencephalitis. Mating between *MAT*α and *MATa** cells on a nutrient starvation medium leads to the formation of dikaryotic filaments. The mating type locus contains mating type-specific Ste11 and Ste12 homologs, but the Cpk1 MAPK and Ste7 homolog are not linked to the mating type locus (31). The *cpk1* and *ste7* deletion mutants of both

mating types are severely impaired in mating but not completely sterile. The *cpk1*α, *ste7*α, and *ste11*α mutants are also blocked in haploid fruiting (29, 31). However, the *ste11*α, *ste7*, and *cpk1* mutants are as virulent as the wild-type strains in a disseminated mouse model, indicating that the *CPK1* MAPK pathway is important for mating and haploid fruiting but dispensable for virulence.

While the Gpa1 Gα subunit plays a critical role in the cAMP signaling, the Gpb1 Gβ subunit functions upstream from the *CPK1* cascade. The mating defect of the *gpb1* mutant is suppressed by overexpression of *CPK1* but not exogenous cAMP (146). The *gpb1* mutant also is defective in haploid fruiting, which can be suppressed by the overexpression of Ste12α. Therefore, mating and haploid fruiting in *C. neoformans* are mediated by *GPB1* via the *CPK1* MAPK cascade (146). A Ras homolog has also been identified as an upstream component of this pathway. The *ras1* mutant is viable but unable to grow at 37°C, defective in mating, and avirulent in a rabbit model of cryptococcal meningitis. It has no defects in melanin and capsule production, which are two events regulated by Gpa1-cAMP signaling (4, 147). Expression of a dominant active *RAS1* (*RAS1*^{Q67L}) allele enhances haploid fruiting in serotype A strain H99 but not in the *ste12*α mutant (3, 156). Although the mating defect of the *gpb1* mutant is not recovered by the *RAS1*^{Q67L} allele, expression of a dominant *GPB1* allele rescues the mating defect of the *ras1* mutant, indicating that *RAS1* functions upstream of *GPB1* in the mating process (4, 81). Several GPCR genes in *C. neoformans*, including Ste3a, Ste3α, and Gpr4, have also been characterized. The Ste3 homologs are important for mating and have a mating type-specific role in virulence (20). Gpr4 is dispensable for infection, but it may function as an amino acid sensor and interact with Gpa1 for regulating the cAMP-PKA pathway (154).

Ste12α may function downstream of Cpk1 because overexpression of Ste12α suppresses the defects of the *cpk1* mutant in mating and haploid fruiting. However, overexpression of Ste11α or Cpk1 can restore haploid fruiting in the *ste12*α mutant, suggesting that Ste12α does not function downstream from Cpk1 in a strictly linear pathway (31). Interestingly, Ste12α and Ste12a are important for virulence in a serotype-specific manner. Unlike the *ste11a*, *ste7*, and *cpk1* mutants, the *ste12* mutants in serotype D are significantly reduced in virulence (22, 156). In contrast, the PAK kinase Ste20α contributes to virulence in serotype A but not in serotype D strains (145).

Other human pathogenic fungi. The *FUS3*/*KSS1* homologs have been identified in several other human pathogens, including *A. fumigatus*, *Penicillium marneffei*, and *Pneumocystis carinii* (44). However, their function in pathogenesis has not been characterized. In *P. carinii*, phosphorylation assays and expression analyses of a few candidate components of the *PCM* MAPK pathway, including PcSte11, PcSte20, and PcSte3, have suggested that this MAPK pathway may play regulatory roles in the life cycle and infection processes of this opportunistic pathogen (143). In *P. marneffei*, StlA (Ste12 homolog) is dispensable for asexual development and dimorphic switching but can complement the sexual reproduction defect of the *A. nidulans steA* mutant (14).

TABLE 2. *SLT2* homologs in pathogenic fungi

Fungal pathogen	MAPK	Major functions
M. grisea	Mps1	Pathogenicity, penetration, conidiation, cell wall integrity
C. lagenarium	Maf1	Pathogenicity, appressorium formation, conidiation
C. purpurea	Cpmk2	Pathogenicity, penetration, conidiation, cell wall integrity
F. graminearum	Mgv1	Pathogenicity, hyphal fusion, cell wall integrity
M. graminicola	MgSlt2	Pathogenicity, infectious growth
B. cinerea	Bmp3	Pathogenicity, penetration, macro- and microconidiation
C. albicans	Mkc1	Virulence, cell wall biogenesis, stress response
C. neoformans	Mpk1	Virulence, cell wall biogenesis, stress response

CELL WALL INTEGRITY PATHWAY

Several orthologs of yeast *SLT2* in plant and human pathogens have been characterized. In general, this MAPK pathway is important for pathogenesis and cell wall integrity.

Plant pathogenic fungi. The *MPS1* MAPK is essential for conidiation, appressorial penetration, and plant infection in *M. grisea* (152). The *mps1* deletion mutant is significantly reduced in aerial hyphal growth and conidiation, but it displays no obvious changes in the growth rate. Unlike Pmk1, Mps1 is dispensable for appressorium formation. Appressoria formed by the *mps1* mutant fail to penetrate and develop infectious hyphae but still elicit plant defense responses. Vegetative hyphae of the mutant have a weakened cell wall, undergo autolysis in aging colonies, and are hypersensitive to cell wall-lytic enzymes (152). The *M. grisea* genome contains distinct homologs of many components of the yeast Pkc1-Slt2 pathway (32), including Pkc, Bck1, Mmk2, Rom2, Rlm1, and Swi6. However, it lacks significant homologs of the receptor genes of the yeast Pkc1-Slt2 pathway except for one gene with limited homology to Wsc1 (e-value, 1e-4). Receptors may not be well conserved, and *M. grisea* may have novel receptors for recognizing plant or environmental signals.

Functional characterization of the *SLT2* homolog in several other plant pathogenic fungi (Table 2) has indicated that this MAPK is well conserved among fungal pathogens and plays important roles during plant infection. In *C. lagenarium*, *MAF1* is required for the early stages of appressorium formation (70). Elongated germ tubes of the *maf1* mutant fail to form appressoria. In *C. purpurea*, *CPMK2* also is necessary for penetration, and the *cpmk2* mutant retains only a limited ability to colonize host tissues (96). In *M. graminicola*, *mgslt2* mutants are normal in penetration of stomata but fail to colonize and grow invasively in plants (92). The *bmp3* mutant of *B. cinerea* is defective in penetrating dead onion epidermal cells and developing necrotic lesions (127). In *F. graminearum*, the *mgv1* mutant is reduced in deoxynivalenol accumulation (55) and hypersensitive to plant defensin MsDef1 (122). Mgv1 also is essential for hyphal fusion and heterokaryon formation (55).

In contrast to its conserved role in pathogenesis, the function of this MAPK in cell wall integrity, conidiation, and stress responses varies among fungal pathogens. Similar to the *mps1* mutant, the *cpmk2* and *mgv1* mutants in *C. purpurea* and *F. graminearum* have weakened cell walls and increased susceptibility to cell wall-lytic enzymes and certain compounds that interfere with the cell wall, such as nikkomycin Z (a chitin

synthase inhibitor) and calcofluor white (55, 96). In contrast, deletion of the *SLT2* ortholog has no obvious effect on sensitivities to cell wall-lytic enzymes and inhibitors in *M. graminicola* and *B. cinerea* (127). Interestingly, the *Mgslt2* mutant is hypersensitive to several azole fungicides, including miconazole and cyproconazole. The *bmp3* mutant has increased sensitivity to paraquat and the phenylpyrrole fungicide fludioxonil, but it is not hypersensitive to the azoles, elevated temperatures, or H_2O_2 (127).

The *SLT2* orthologs are also required for conidiation in *C. lagenarium* and *C. purpurea*. However, conidiation is normal in the *mgv1* mutant of *F. graminearum* and the *mgslt2* mutant of *M. graminicola* (Table 2). The *bmp3* mutant of *B. cinerea* produces fewer macroconidia but more microconidia than the wild type (127). It also is defective in sclerotium formation and germ tube responses to surfaces. Unlike the *pmk1*, *maf1*, and *mgslt2* mutants, the *mgv1* and *bmp3* mutants exhibit reduced growth rates on solid media. However, vegetative growth in liquid cultures is normal in the *mgv1* mutant. The pleiotropic phenotypes observed for these mutants indicate that this MAPK pathway may regulate various growth or differentiation processes in different plant pathogenic fungi.

Model saprophytic filamentous fungi. In *A. nidulans*, MpkA plays an important role in conidium germination and hyphal tip growth. The *mpkA* mutant has a reduced growth rate, and its hyphal tips tend to swell (19). Conidia often grow isotropically and fail to produce germ tubes under normal culture conditions. In *Podospora anserina*, crippled growth is an epigenetic cell degeneration phenomenon caused by *C*, a cytoplasmic and infectious hereditary unit that resembles a prion. *PaASK1*, a *BCK1* homolog, is required for *C* production. The *paask1* mutant is defective in hyphal pigmentation, differentiation of aerial hyphae, and fruiting body development. Mutants deleted of the downstream MEK PaMkk1 or MAPK PaMpk1 have the same phenotype as the *paask1* mutant (65). Overexpression of *PaASK1* or *PaMPK1* facilitates *C* propagation and enhances crippled growth in wild-type strains. The activation and nuclear localization of PaMpk1 appear to be correlated with the presence of the *C* element in vegetative hyphae (65). The autolysis and pigmentation defects of the *mps1* mutants of *M. grisea* and *C. heterostrophus* may be related to cell degeneration.

Human pathogens. In *C. albicans*, Mkc1 (Slt2 homolog) is involved in regulating cell wall integrity and required for growth at elevated temperatures (109). Homozygous *mkc1* deletion mutants exhibit increased susceptibility to caffeine, glusulase, and some inhibitors of cell wall synthesis. Growth rates and cell viabilities of *mkc1* mutants are reduced in cultures grown at 42°C. In addition, Mkc1 has been implicated in morphological transitions and pathogenesis (36, 107). The *mkc1* mutants are also reduced in invasive growth on Spider medium and produce shorter hyphal cells (for a review, see the work of Alonso-Monge et al. [2]). In infection assays with a murine model, *mkc1* mutants are attenuated in virulence. The *mkc1* mutants have increased sensitivities to nitric oxide (NO) in in vitro assays and reduced abilities to inhibit NO production by macrophages (99).

The Mkc1 pathway is also involved in responses to other stresses. The activation of Mkc1 is triggered by various oxidants, certain osmotic stresses, antifungal drugs targeted at cell wall and membrane syntheses, calcium ion, and low-temperature shock (108). The phosphorylation of Mkc1 in response to oxidative stress is partially dependent on the *CaHOG1* pathway (5), suggesting cross talk between these two pathways. The activation of Mkc1 by oxidative stress is blocked in the *capkc1* mutant (108), indicating that *C. albicans* has a similar PKC-Slt2 cell wall integrity pathway. The *capkc1* deletion mutants are normal in the yeast-to-hypha transition but have an osmotically remediable cell lysis defect. Cercosporamide, a selective inhibitor of Pkc1, has synergistic fungicidal effects with caspofungin (a β-1,3-glucan synthase inhibitor) in *C. albicans* (136). In *S. cerevisiae*, Wsc1 acts as the dedicated sensor for caspofungin-induced cell wall damage to activate the Pkc1-Slt2 pathway. Short exposure to caspofungin results in the up-regulation of *MKC1*, and the *mkc1* mutant has increased sensitivity to caspofungin (149). Mkc1 is also activated by physical contact in *C. albicans*. The *mkc1* mutants are defective in invasive hyphal growth on YPS agar and normal biofilm formation, two contact-dependent responses (76).

In *C. neoformans*, the *MPK1* MAPK gene is required for growth at elevated temperatures and the maintenance of cell wall integrity (73). The growth defect of the *mpk1* deletion mutant at 37°C can be remedied by an osmotic stabilizer such as 1 M sorbitol. Phosphorylation of Mpk1 is induced by antifungal compounds nikkomycin Z and caspofungin. The *mpk1* mutant is significantly attenuated in virulence and hypersensitive to fludioxonil or cell wall synthesis inhibitors, but it is normal in the production of melanin and capsule (69, 73). The growth defect at 37°C and weakened cell wall of the *mpk1* mutant may be responsible for its reduced virulence.

Several other components of the putative Pkc1-Mpk1 pathway in *C. neoformans*, including homologs of yeast Rho1, Bck1, Mkk2, Lrg1, Rom2, Rom20, and Rom21, have been characterized, but their functions in virulence remain to be examined (21, 49). Although both Bck1 and Mkk2 homologs are critical for maintaining cell wall integrity and growth at elevated temperatures, the *mkk2* but not the *bck1* deletion mutant is reduced in melanin production. Inhibition of Pkc1 abolishes melanin synthesis in *C. neoformans* (53). Deletion of the phosphatase Ppg1 also reduces melanin production, but *ppg1* mutants have additional defects, such as reduced capsule size. While *ROM2* is dispensable, Lrg1 and two other genes (*SSD1* and *PUF4*) are important for cell wall integrity in *C. neoformans*, which lacks homologs of several yeast membrane-associated stress sensors (49). Therefore, the regulatory mechanisms for maintaining cell wall integrity in *S. cerevisiae* and *C. neoformans* appear to be different. The *C. neoformans* genome also lacks significant homologs of several yeast membrane-associated stress sensors, including Slg1, Wsc2, and Mid2 (49).

The Slt2 homolog has been identified but not functionally characterized for several other human pathogens, including *A. fumigatus*, *P. carinii*, *P. marneffei*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides posadasii.* In *P. carinii*, expression of the *MKP1* MAPK gene and *PcBCK1* can partially complement the yeast *slt2* and *bck1* mutants, respectively (45, 137), but their functions in *P. carinii* are not clear. Mkp1 contains a unique phosphorylation motif repeat (TEY MTEY). Dual phosphorylation of Mkp1 at T186 and Y188 is required for its kinase activity but not for its ability to partially

TABLE 3. *HOG1* homologs in pathogenic fungi

Fungal pathogen	MAPK	Major function(s)
M. grisea	Osm1	Osmoregulation and stress response
C. lagenarium	Osc1	Hyperosmotic stress response, sensitivity to fludioxonil
B. oryzae	Srm1	Osmoregulation and stress response
C. parasitica	Cpmk1	Virulence, pigmentation, conidiation, laccase production
M. graminicola	MgHog1	Pathogenicity, osmoregulation, stress response, transition from yeast-like growth to filamentous growth
B. cinerea	BcSak1	Pathogenicity, osmoregulation, stress response, macroconidiation, appressorium formation
C. albicans	CaHog1	Virulence, stress response, cell wall biosynthesis, morphogenesis
C. neoformans	Hog1	Virulence, stress response
A. fumigatus	SakA	Stress response

complement the *slt2* mutant and interact with the transcription factor Rlm1 (45).

OSMOREGULATION/STRESS RESPONSE PATHWAY

Hog1 and its homologs in filamentous fungi have the TGY dual phosphorylation site, a hallmark of stress-activated MAPKs. While Hog1 has limited functions besides osmoregulation in *S. cerevisiae*, its homolog in pathogens is involved in pathogenesis and response to various stresses.

Plant pathogenic fungi. Unlike what is seen for the other two MAPKs, the role of *HOG1* homologs in pathogenesis differs drastically among plant pathogens, probably due to differences in host defensive responses or infection mechanisms. In *M. grisea*, *OSM1* is dispensable for plant infection (38). Although the *osm1* mutant is hypersensitive to desiccation and hyperosmotic stress, it has no defect in conidiation and appressorium function. In the presence of 0.4 M NaCl, conidia of the *osm1* mutant form multiple appressoria, suggesting that *OSM1* suppresses inappropriate activation of the *PMK1* pathway under hyperosmotic conditions. Deletion of histidine kinase gene *HIK1*, homologous to *OS-1*, also has no effect on appressorium function and virulence (103). Unlike the *N. crassa os-1* mutant, the *hik1* mutant is more sensitive to high concentrations of sugars but not salts, suggesting that *M. grisea* can distinguish between hyperosmotic stresses caused by these compounds.

Mutants deleted of the *HOG1* homolog in *C. parasitica*, *Bipolaris oryzae*, *C. lagenarium*, and *M. graminicola* also are sensitive to hyperosmotic stresses (71, 93, 102, 119). While the *osc1* and *srm1* deletion mutants of *C. lagenarium* and *B. oryzae* are fully pathogenic, the *M. graminicola mghog1* mutant and the *B. cinerea bcsak1* mutant are nonpathogenic (Table 3). The *mghog1* mutant fails to switch to filamentous growth on water agar plates and is defective in melanization and formation of infectious germ tubes (93). In *B. cinerea*, macroconidiation but not microconidiation is regulated by BcSak1. The *bcsak1* mutant is derepressed in sclerotium formation but blocked in appressorium formation and plant penetration (133). In *C. parasitica*, *cpmk1* mutants are reduced in virulence and form cankers smaller than those formed by the wild-type strain (119). In several plant pathogenic fungi, this MAPK pathway also regulates responses to oxidative stress and UV irradiation (71, 102). In general, deletion of the Hog1 homolog increases the sensitivity to various oxidants.

In several filamentous fungi, including *N. crassa*, *C. lagenarium*, and *M. grisea*, mutants blocked in the HOG pathway are resistant to phenylpyrrole, dicarboximide, and aromatic hydrocarbon fungicides (71, 103, 157). Treatments with these fungicides stimulate the activation of the Hog1 homolog, glycerol accumulation, and cell swelling or bursting, indicating that fungicidal effects may result from the overstimulation of the osmoregulation pathway. In *B. cinerea*, the *bcsak1* mutant is resistant to dicarboximide but still sensitive to phenylpyrrole or aromatic hydrocarbon fungicides. In contrast, the deletion of *BOS1* (*OS-1* homolog) confers resistance to all these fungicides. The *bos1* mutant also differs from the *sak1* mutant in virulence and appressorium formation (133, 142). Phenotypic differences between the *bos1* and *bcsak1* mutants may be related to the isolates used in these studies, but it is also possible that the HOG pathway in *B. cinerea* is more complex than that of other fungi.

Model saprophytic filamentous fungi. In *N. crassa*, the Os-2 MAPK cascade plays an important role in osmoregulation, fungicide resistance, and response to oxidative stress (111, 157). Unlike Os-4 (MEK) and Os-5 (MEKK), Os-1 is required only for Os-2 activation by fludioxonil or low osmotic stress. Phosphorylation of Os-2 is still detectable in the *os-1* mutant by hyperosmolarity or heat shock (111), suggesting the involvement of other osmosensors. For the two putative response regulators, only Rrg-1 functions upstream from the Os-2 cascade for osmoregulation (59). Rrg-2 is dispensable for osmoregulation but is involved in response to oxidative stress (8).

In *A. nidulans*, SakA (HogA) is involved in the repression of sexual development, survival of conidia, and response to hyperosmotic and oxidative stresses (51, 64). Under hyperosmotic conditions, reduced growth rate, hyperbranching, abnormal nuclear distribution, and lack of septation near hyphal tips are observed in the *sakA* mutant incubated at 30°C. However, the same growth and branching defects are not detectable when the mutant is cultured at 37°C. *A. nidulans* must have an additional gene(s) involved in regulating response to osmotic stress. One candidate is MpkC, which is also activated by Pbs2. Although the deletion of MpkC has no obvious effect on stress response, the *sakA mpkC* double mutant may be nonviable (46).

Human pathogens. The *HOG1* homologs have been implicated in responses to oxidative and hyperosmotic stresses in a few human pathogens. In *C. albicans*, CaHog1 is activated by various stress conditions, including high osmolarity, salts, oxidants, heavy metals, farnesol, and UV irradiation (for a review, see the work of Alonso-Monge et al. [2]). Several upstream components of the CaHog1 pathway have also been characterized, including *PBS2*, *SSK1*, and *SHO1* (5, 23, 125). Activation of Hog1 by oxidative stress is Pbs2 dependent and is mediated by the Ssk1 branch. Because *ssk1 sho1* double mutants still respond to hyperosmotic stress and grow on high-osmolarity media, additional upstream input may exist in *C. albicans* for CaHog1 activation. Among three putative *C. albicans* histidine kinase genes, *NIK1*, *CHK1*, and *SLN1*, that have been characterized, none has a clearly defined role in CaHog1 activation (2, 74). Although the deletion of *SLN1* results in the constitutive activation of CaHog1 and a lower growth rate, the *sln1*

mutant, similar to the *nik1* mutant, is viable when grown under hyperosmotic conditions. Chk1 regulates responses to oxidative stress and but is dispensable for Hog1 activation.

The *CaHOG1* pathway also plays a role in cell wall biosynthesis and integrity. The *cahog1* and *capbs2* deletion mutants have increased susceptibility to β-1,3-glucanases and are defective in chlamydospore formation (1, 42). Approximately 25% of genes with altered expression levels in the *ssk1* mutant are related to cell wall and stress adaptation functions, including *CHK1*, *HSP12*, *AHP1*, and *FLO1* (23). In addition, the *CaHOG1* pathway has a repressive effect on filamentous growth, and it is important for pathogenesis (2). The *cahog1* and *capbs2* mutants are derepressed in hyphal formation, resistant to iprodione and fludioxonil, and reduced in virulence, probably due to the increased sensitivity to oxidative stress generated by the host immune cells. The *ssk1* deletion mutant is hypersensitive to oxidative stress and human neutrophils and avirulent in an invasive murine model (94). Although their molecular mechanisms remain to be determined, the *NIK1*, *CHK1*, and *SLN1* histidine kinase genes all are required for virulence and cell wall integrity in *C. albicans* (for a review, see the work of Kruppa and Calderone [74]).

In *C. neoformans*, Pbs2 and Hog1 are functionally conserved for regulating responses to UV radiation and hyperosmotic stress in both a highly virulent serotype A stain, H99, and a less virulent serotype D strain, JEC21. However, their functions in responses to elevated temperature (40°C) and oxidative stress appear to be different (6). While the *hog1* mutant of H99 is hypersensitive to H_2O_2, the JEC21 *hog1* mutant is resistant. In H99 but not in JEC21, the Hog1 MAPK cascade negatively regulates the mating processes and production of melanin and capsule. The mating ability and production of mating pheromone, capsule, and melanin are increased in the *hog1* and *pbs2* mutants of H99. In H99, fludioxonil treatment activates the Hog1 pathway and causes growth arrest, glycerol accumulation, and cell swelling. The *hog1* and *pbs2* mutants are resistant to fludioxonil (69). Hog1 is constitutively phosphorylated in H99 under normal conditions and rapidly dephosphorylated after exposure to 1 M NaCl. In JEC21 and a few other serotype D strains tested, like Hog1 in yeast, Hog1 in *C. neoformans* is rapidly phosphorylated in response to hyperosmotic stress. Nuclear localization of Hog1 is associated with its activation in H99 but less dependent on its phosphorylation in JEC21. The unique activation pattern of Hog1 is widespread in serotype A strains and in some clinical serotype D isolates, suggesting that *C. neoformans* may have adapted this pathway to control differentiation and virulence at the subspecies level, probably specific to environmental niches.

The *hog1* and *pbs2* mutants have attenuated virulence in infection assays with a murine cryptococcosis model. The *pbs2* mutant is less virulent than the *hog1* mutant, suggesting that Pbs2 has additional downstream targets that contribute to virulence. Similar to the *hog1* and *pbs2* mutants, deletion of a response regulator homologous to Ssk1 results in resistance to fludioxonil, enhanced mating efficiency, and increased sensitivity to various stresses (7). The *ssk1* mutant also produces more melanin and capsule. However, the *ssk1* mutant is less sensitive to hyperosmotic stress than the *pbs2* and *hog1* mutants. Although Ssk1 is required for Hog1 phosphorylation under normal conditions and in response to fludioxonil, Hog1 is still activated by high osmolarity in the *ssk1* mutant. Therefore, Ssk1 is a major but not the only response regulator of the Pbs2-Hog1 pathway and is important but not essential for osmoregulation. A second response regulator is an Skn7 homolog, which governs resistance to oxidants and Na^+ ions but may be not functionally related to the Hog1 pathway (150).

C. neoformans has seven putative histidine kinase genes (*TCO1* to *TCO7*). One of them (*TCO6*) appears to be essential, but deletion of any other *TCO* genes individually does not cause hypersensitivity to high osmolarity or UV irradiation (7). Tco1 likely is a key sensor for negative regulation of melanin synthesis via the Hog1 pathway but has no effect on capsule production. Tco2 may play a role in Hog1 activation in response to oxidative stress. The *tco2* mutant has increased sensitivity to oxidative stress but is less sensitive than the *hog1* or *pbs2* mutant. Tco2 also has overlapping functions with Tco1 in mediating fludioxonil sensitivity and Hog1 dephosphorylation in response to methylglyoxal (7). The *tco1 tco2* double mutant but not the *tco1* mutant or the *tco2* mutant is as sensitive to hyperosmolarity as the *hog1* mutant or the *pbs2* mutant. Therefore, the Hog1 MAPK pathway may have multiple upstream sensors with shared and distinct functions.

In *A. fumigatus*, SakA and MpkC MAPKs both have the TGY phosphorylation motif, but they differ in functions. SakA is required for responses to heat shock, hyperosmotic, and oxidative stresses. It is also involved in the negative regulation of conidium germination under nitrogen- or carbon-deficient conditions (41, 155). In contrast, MpkC is dispensable for stress responses and conidium germination, but it may be involved in nutrient sensing, because the *mpkC* deletion mutant is defective in hyphal growth and conidium germination with sorbitol or mannitol as the sole carbon source. The expression pattern of *mpkC* also differs from that of *sakA* under various growth conditions, and only the *sakA* mutant is resistant to fludioxonil (66, 124). For putative upstream sensors, an Sln1 homolog, *tcsB*, and the *OS-1* homolog *fos-1* are dispensable for the response to hyperosmotic or oxidative stress (41, 120), but *fos1* may play a role in cell wall assembly and conidiophore development.

CONCLUDING REMARKS

The Fus3/Kss1 homolog is more extensively studied than the other two MAPKs in fungal pathogens. In general, this well-conserved MAPK pathway is essential for regulating plant infection processes in phytopathogenic fungi, but it plays a lesser or no role in the virulence of human pathogens (Fig. 2). In the multihost pathogen *F. oxysporum*, the *fmk1* mutant is nonpathogenic on plants but fully pathogenic in the murine model (113). In plant pathogens, this MAPK pathway may regulate the penetration of host physical barriers, such as cuticle and cell wall, which are not encountered by human pathogens. The Slt2 homologs also are essential for plant infection, but the functions of the *HOG1* pathway vary among phytopathogenic fungi. In human pathogens, both the *HOG1* and cell wall integrity pathways play important roles in virulence, probably for adaptation to physiological conditions and immune responses in the host. Interestingly, three classes of ex-

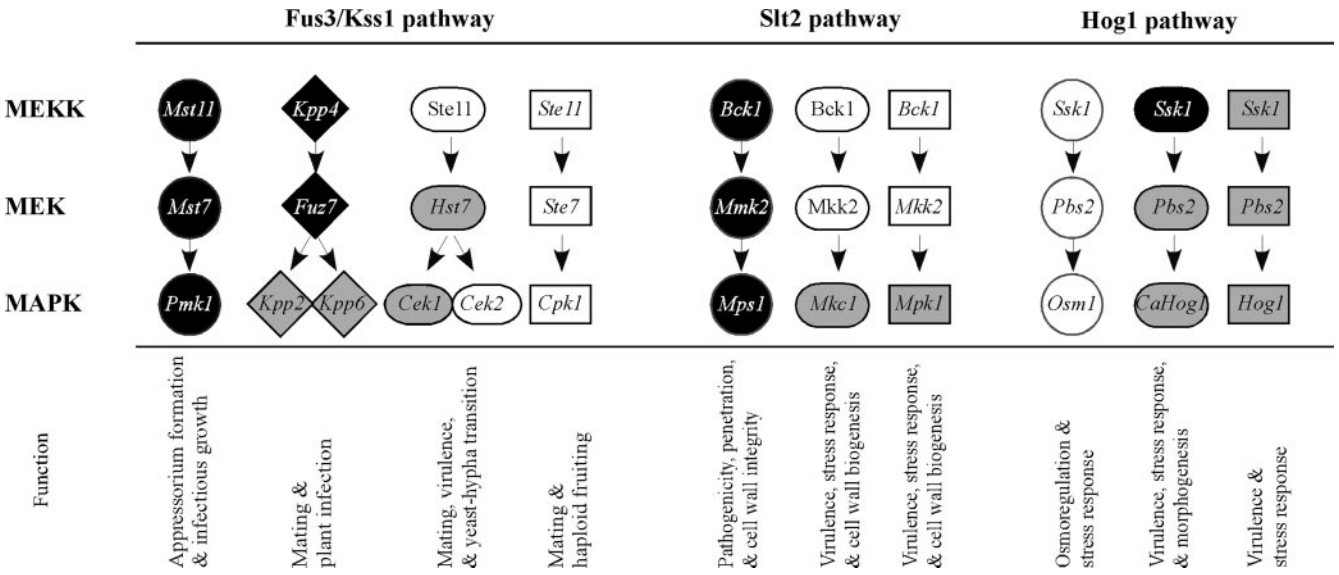

FIG. 2. MAPK pathways in fungal pathogens. The core components of three MAPK signal pathways in four selected fungal pathogens are in circles for *Magnaporthe grisea*, squares for *Ustilago maydis*, ovals for *Candida albicans*, and rectangles for *Cryptococcus neoformans*. Components that have been functionally characterized are in italic. The roles of these genes in fungal pathogenesis are shaded in black for essential, gray for important but not essential, and white for dispensable.

isting fungicides interfere with the HOG pathway in several fungi. Components of this pathway may be suitable as targets for developing new fungicides.

Although the MEKK-MEK-MAPK cascades are conserved, the upstream signal inputs and downstream transcription factors in pathogens are different from those of *S. cerevisiae*. Fungal pathogens may have novel receptors for sensing host and environmental signals to regulate penetration and infectious growth. Although Ras proteins have been shown to activate downstream MAPKs in several fungi, sequenced fungal genomes lack significant homologs of receptor kinase genes that function upstream from Ras in mammalian cells. Related to this subject, pathway specificity in fungal pathogens is not well studied. To date, no Ste5 homolog or Ste5-like scaffold protein in pathogenic fungi has been identified. With genomic resources becoming available for more and more fungi, comparative and functional genomic analyses will be useful to identify the missing regulatory and structural components of these MAPK pathways and their downstream targets or network of transcription factors.

Another interesting area is the interaction between the MAPK cascades and other signaling pathways. Several studies have indicated that cross talk occurs among MAPK pathways in fungal pathogens (42, 43, 69). However, the exact molecular mechanisms regulating their interaction are not clear, and the relationship between these pathways during infection may be more complex than what has been observed in in vitro cultures. MAPKs are also known to interact with the cAMP signaling in pathogenesis, differentiation, and stress response in *U. maydis*, *C. neoformans*, and other fungi (40, 79). Further characterization of these signal transduction pathways and their interaction in various fungal pathogens is necessary for a better understanding of fungal development and pathogenesis.

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