

The pheromone module SteC-MkkB-MpkB-SteD-HamE regulates development, stress responses and secondary metabolism in *Aspergillus fumigatus*.

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Abstract

In order for eukaryotes to efficiently detect and respond to environmental stimuli, a myriad of protein signalling pathways are utilised. An example of highly conserved signalling pathways in eukaryotes are the mitogen-activated protein kinase (MAPK) pathways. In fungi, MAPK pathways have been shown to regulate a diverse array of biological processes, such as asexual and sexual development, stress responses and the production of secondary metabolites (SMs). In the model fungus *Aspergillus nidulans*, a MAPK pathway known as the pheromone module is utilised to regulate both development and SM production. This signalling cascade consists of the three kinases SteC, MkkB and MpkB, as well as the SteD adaptor protein and the HamE scaffold. In this study, homologs of each of these proteins have been identified in the opportunistic human

pathogen *A. fumigatus*. By performing epitope tagging and mass spectrometry experiments, we have shown that these proteins form a pentameric complex, similar to what is observed in *A. nidulans*. This complex has been shown to assemble in the cytoplasm and MpkB enters the nucleus, where it would presumably interact with various transcription factors. Pheromone module mutant strains exhibit drastic reductions in asexual sporulation, vegetative growth rate and production of SMs, such as gliotoxin. Mutants also display increased sensitivity to cell wall and oxidative stress agents. Overall, these data provide evidence of the existence of a conserved MAP kinase signalling pathway in *Aspergillus* species and suggest that this pathway is critical for the regulation of fungal development and secondary metabolism

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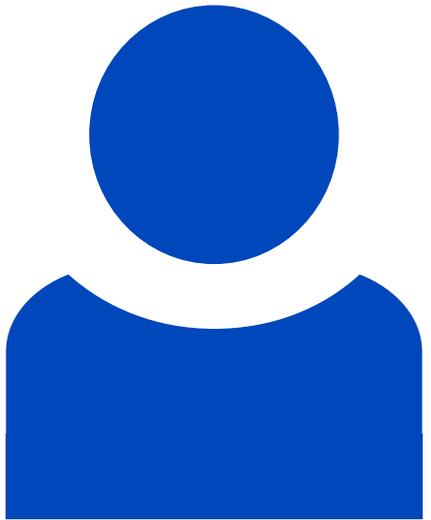
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