

Genetic interactions of the *Aspergillus fumigatus* *pkcA* with different components of the cell wall integrity pathway

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Aspergillus fumigatus is an allergen of mammals and an important opportunistic pathogen that causes invasive pulmonary aspergillosis in immunosuppressed individuals. The ability to handle different stress conditions is essential to the survival and virulence of the pathogen at the site of infection. Therefore, environmental changes are sensed by invading microorganisms and transduced through signaling transduction pathways that lead to cell adaptation strategies. The Cell Wall Integrity Pathway (CWIP) is a signaling cascade primarily activated in fungal cells under conditions of synthesis and/or remodeling of the cell wall. In *S. cerevisiae*, CWIP is initiated by the activation of the Protein Kinase C (PKC1), which interplays with a MAP kinase cascade leading to the phosphorylation of the associated RLM1 transcription factor. Here, we analyzed the genetic interactions of the *A. fumigatus* *pkcA*^{PKC1}, *rlmA*^{RLM1} and *mpkA*^{MPK1} during the cell wall stress. Our results indicate that there is an epistatic relationship between these genes. In addition, both the *pkcA*^{G579R} mutation and *rlmA* deletion led to increased TNF- α production by bone marrow derived macrophages. However, unlike the Δ *rlmA* strain, the *pkcA*^{G579R} mutant did not cause virulence attenuation in a mouse model of invasive pulmonary aspergillosis. Both strains also showed higher levels of β -1,3-glucans and lower levels of ergosterol than the wild type and complementing strains suggesting that the mutant strains had altered cell wall and cell membrane organization. Our results demonstrate that the canonical CWIP is conserved in this pathogen and plays important roles in virulence and host's recognition. However, other unidentified signaling circuit(s) may coordinately operate alongside the canonical *A. fumigatus* CWIP pathway to promote cell wall homeostasis

Keywords: *Aspergillus fumigatus*, protein kinase C, cell wall integrity pathway

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