

ABSTRACT - STRESS IN FUNGAL PATHOGENESIS

CO₂ SENSING IN ASPERGILLUS FUMIGATUS

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The concentration of carbon dioxide (CO₂) is 0.033% in the environment and can reach up to 5% in the host (about 150-fold higher). Thus, during the infection process, *Aspergillus fumigatus* must adapt to different CO₂ levels. Carbonic anhydrases (CAs) are ubiquitous enzymes, found in all organisms, that catalyse the reversible hydration of CO₂ to bicarbonate (HCO₃⁻), to maintain efficient CO₂/HCO₃⁻ homeostasis. CO₂ sensing and metabolism via CAs play important roles in the proliferation, survival and differentiation of diverse pathogenic fungi infecting human hosts. *A. fumigatus* has four CA-encoding genes, named *cafA-D*. *cafA* and *cafB* are constitutive and strongly expressed, whereas *cafC* and *cafD* are weakly expressed, but CO₂-inducible genes. Only the double mutant $\Delta cafA\Delta cafB$ is unable to grow at 0.033% CO₂, and this growth defect can be restored by high CO₂ concentrations (5%). *A. fumigatus* $\Delta cafA$, $\Delta cafB$, $\Delta cafC$, $\Delta cafD$, and $\Delta cafA\Delta cafB$ mutant strains are fully virulent in a low-dose murine infection, suggesting that the CAs are not required for development and virulence of the *A. fumigatus* in the mammalian host. On the other hand, this fungus modifies the expression of some genes when it is transferred from an atmosphere of 0.033% CO₂ to one of 5% CO₂ (data not published), suggesting the importance of these genes to the virulence of *A. fumigatus*. The *cipC* gene (Afu5g09330) is involved in this adaptation process and is important for the virulence of *A. fumigatus*, making it a target for study of new therapies to treat invasive aspergillosis. Other genes, such as those

encoding tyrosinase (Afu3g01070), HMG-CoA synthase (Afu8g07210), sugar transporter family protein (Afu7g05550), aldo-keto reductase putative (Afu4g11260), flavin-binding monooxygenase (Afu3g15050), oxidoreductase (Afu2g00750), and alpha 1,3-glucanase/mutanase (Afu1g03352), also had their expression altered when *A. fumigatus* was transferred to 5% CO₂; however, the importance of these genes to the virulence has not been established yet.