Phenotypic Analysis of Genes Whose Expression is Dependent on Calcineurin and their Influence in *Aspergillus fumigatus* Virulence and Pathogenesis

Iran Malavazi

Departamento de Genética e Evolução, Centro de Ciências Biológicas e da Saúde, Universidade Federal de São Carlos, São Carlos, Brazil

Calcineurin plays an important role in the control of cell morphology and virulence in fungi. Calcineurin is a serine/threonine-specific phosphatase heterodimer consisting of a catalytic subunit A and a regulatory Ca\(^2+\)/Calmodulin binding subunit B. The association of the two subunits is essential for activity. A mutant of *A. fumigatus* lacking the calcineurin A (*calA*) catalytic subunit exhibited defective hyphal morphology related to apical extension and branching growth, which resulted in drastically decreased filamentation. Here, we investigated which pathways are influenced by *A. fumigatus* calcineurin during proliferation by comparatively determining the transcriptional profile of *A. fumigatus* wild type and \(\Delta\)calA mutant strains during growth in complete medium in a time-course experiment. Our results showed that although the mitochondrial function is reduced in the \(\Delta\)calA mutant strain, its respiratory chain is functional. The mutant has increased both alternative oxidase (*aoxA*) mRNA accumulation and protein activity. Also, the mitochondrial copy number is reduced in the \(\Delta\)calA mutant strain. Furthermore, we identified several genes that encode transcription factors that have increased mRNA expression in the \(\Delta\)calA mutant and that could be potentially involved in the CalA-CrzA pathway. Deletion mutants for these transcription factors had also reduced susceptibility to itraconazole, caspofungin, and sodium dodecyl sulfate. Our study provides evidences for several pathways that are dependent on calcineurin–CrzA and that could be responsible for the observed decreased virulence in the \(\Delta\)calA strain. These findings open exciting new possibilities for research into environmental sensing and nutrient acquisition in *A. fumigatus*.

Financial support: FAPESP and CNPQ, Brazil