Hydrogen Peroxide Sensing and Signaling in *Candida albicans*: A Genome-Wide Transcriptome Analysis

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Hydrogen peroxide (H_2O_2) induces hyphal differentiation in *Candida albicans*.

Candida albicans is a common, dimorphic human pathogen and its hyphal form causes candidiasis, predominantly in immunocompromised patients. Hyphal transition is a potent virulence factor and is triggered by various nutritional and environmental factors such as specific carbohydrates or amino acids, serum, temperature, pH, N-acetyl glucosamine, and starvation (1-4). Previously we reported that hyphal differentiation is induced by sub-toxic concentration (1-4 mM) of exogenous H_2O_2 (5). Since the sub-toxic level of H_2O_2 is known to directly affects various redox systems to regulate cell differentiation, proliferation, signal transduction, ion-transport in other species (6, 7), we suspect the role of H_2O_2 to be an intracellular messenger.

H_2O_2 sensing and signaling in *C. albicans*.

Next, we intended to compare through microarray analysis the transcription profile of cells treated with sub-toxic 1mM H_2O_2 or oxidative stress-inducing 10 mM H_2O_2.with those of yeast cells and hyphal cells grown in YPD with 10 % serum. Genes of a variety of transcription factors, transport proteins, cell wall proteins, and some weak antioxidants such as *SOD5*, *SOD3* and *PRX1* were up-regulated at 1mM H_2O_2. In addition, regulatory and metabolic genes such as *TDH3*, *CTR1* and *GPH1* and hyphal inducing-genes such as *DDR48*, *ALS4* and *ALS2*, and genes for cell wall, iron metabolism and lipid metabolism were also induced. Meanwhile, transcripts of genes involved in DNA repair, stress genes, and heat shock genes were increased at 10 mM H_2O_2. Genes of the methionine pathway were highly expressed in all hyphal cells (H_2O_2-treated cells and serum-induced hyphal cells), associating with higher level of adenosyl methionine in pseudohyphae and hyphae cell than in yeast cells (8). Here we propose that 1 mM H_2O_2 induces hyphal growth in *C. albicans* as an intracellular messenger.

H_2O_2 may induce hyphal differentiation through the MAP kinase pathway.

Two well-characterized hyphal inducing pathways are the mitogen-activated protein kinase (MAPK) pathway and cAMP-protein kinase A (PKA) pathway regulated by transcription factor *CPH1* and *EFG1* respectively (9). When hyphal formation at 1mM H_2O_2 in null mutants of Δ*efg1*, Δ*cph1*, and Δ*efg1*/Δ*cph1* were examined, hyphae were efficiently induced in Δ*efg1*, but not in Δ*cph1* and Δ*efg1*/Δ*cph1*, indicating that H_2O_2

works through the MAP kinase pathway for hyphal differentiation. This was further supported by the finding that the transcriptional level of *CPH1* is highly elevated in contrast to that of *EFG1*.

Together, H_2O_2 works as a novel signal molecule to induce hyphal differentiation through the MAP kinase pathway in *C. albicans*.

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