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Three Superoxide Dismutases in *Candida albicans*

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Candida albicans is the major fungal pathogen of humans that causes not only the oral and vaginal thrush but also systemic or life-threatening infections in immunocompromised patients. Once *C. albicans* infects a host, it inevitably encounters the ROS produced by host phagocytes as well as by the consequences of its own oxygen metabolism. Therefore, Superoxide dismutase (SOD) has been suspected as antioxidant enzymes and virulence determinants. In *C. albicans*, the *SOD1*, *SOD2*, and *SOD3* genes encoding cytosolic CuZnSOD, mitochondrial MnSOD, and unusual cytosolic MnSOD were identified, respectively. To elucidate the role of SODs, their genes have been disrupted by the URA-blaster technique. The disruption of SODs was verified by Southern blot analysis and the loss of their activity was confirmed by Western blot analysis and/or activity staining.

The resultant *sod1/sod1* mutant was more sensitive to menadione, a redox-cycling agent, than the wild-type cells, but still showed adaptive response to oxidative stress. Moreover, the *sod1/sod1* cells exhibited a slow growth in respect to wild-type cells in minimal synthetic-dextrose medium, where the retarded growth of the *sod1/sod1* mutant was restored by the addition of lysine or under anaerobic condition flushed with nitrogen gas. Interestingly, *C. albicans* cells lacking Cu,ZnSOD was more susceptible to macrophage attack than wild-type cells and showed attenuated virulence in a mouse model for systemic candidiasis. Thus, our results suggest that Cu,ZnSOD is required for the protection against oxidative stress and the full virulence of *C. albicans*.

The null mutant lacking of mitochondrial MnSOD was more sensitive than wild-type cells to various stresses such as redox-cycling agents, heating, ethanol, high concentration of sodium or potassium, and 99.9% O_2. Interestingly, the *sod2/sod2* mutant was rather more resistant against lithium and diamide than the wild type, whereas overexpression of *SOD2* increased susceptibility of *C. albicans* to these compounds. The inverse effect of mitochondrial MnSOD on lithium toxicity was relieved when the *sod2/sod2* and *SOD2*-overexpressing cells were grown on the synthetic dextrose medium containing sulfur compounds such as methionine, cysteine, glutathione, or sulfite indicating that mitochondrial MnSOD may affect lithium toxicity through sulfur metabolism. Moreover, disruption or overexpression of *SOD2* increased or decreased glutathione reductase activity and cyanide-resistant respiration by alternative oxidase, respectively. Taken all together, it is suggested that mitochondrial MnSOD be important for stress responses, lithium toxicity, and cyanide-resistant respiration of *C. albicans*.

The sod3/sod3 mutant showed similar sensitivity with other null mutants against oxidative stress. Even though the expression of SOD3 was stimulated during the stationary phase, concomitantly with the repression of SOD1, sod3/sod3 doesn't show attenuate virulence in a mouse model suggesting a typical role of SOD3 in *C. albicans*. And we are still investigating the different function of three SODs in *C. albicans*.

References

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