at least one order of magnitude higher compared to Sapp2. As with *C. albicans* Saps, both *C. parapsilosis* Sapp proteins are synthesized as preproenzymes and can be activated autocatalytically or by a membrane-bound Kex2-like protein. It has been previously demonstrated that the epidermal and epithelial damage caused by *C. parapsilosis* in reconstituted human tissue was significantly reduced in the presence of the proteinase inhibitor pepstatin A, that suggested that *C. parapsilosis* Sapps are involved in virulence.

In this study, we analyzed the role of Sapp1 in virulence. The *in silico* analysis of *SAPP1* sequence revealed a 2871bp duplicated region (*SAPP1a* and *SAPP1b*) in the genome of *C. parapsilosis*. With the help of the *caSAT1* flipper cassette system we generated homozygous Δ*Δsapp1a*, Δ*Δsapp1b* and Δ*Δsapp1a*-Δ*Δsapp1b* mutants. Sapp1 production in an inducer medium was reduced by approximately 50% in the Δ*Δsapp1a* and Δ*Δsapp1b* mutants but the production of Sapp2 was nat affected. In contrast, Sapp2 production was increased in the Δ*Δsapp1a*-Δ*Δsapp1b* mutant relative to the wild type (WT) strain. The Δ*Δsapp1a*-Δ*Δsapp1b* strain was hypersusceptible to human serum and was attenuated in its capacity to damage host-effector cells. The phagocytosis and killing of Δ*Δsapp1a*-Δ*Δsapp1b* yeasts by human peripherial blood mononuclear cells (PBMCs) and PBMC-derived macrophages (PBMC-DM) was significantly enhanched relative to WT. Phagolysosomal fusion in PBMC-DMs occured more than twice as frequently with ingested Δ*Δsapp1a*-Δ*Δsapp1b* yeast cells compared to WT.

All these data suggests that *C. parapsilosis* Sapp1 is an important virulence factor, since it is associated with the capacity of the fungus to grow in human serum and to survive inside macrophages, and this particular proteinase can be a potential target for the development of new antifungal drugs.

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Oxidative stress/antioxidant defense system

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Oxidative stress involves a shift towards the pro-oxidant in the pro-oxidant/antioxidant balance, which can occur as a result of an increase in oxidative metabolism. It is well known that reactive free radicals lead to a number of damaging effects as they can attack lipids, proteins, carbohydrates and DNA in cells as a consequence of various factors, including exposure to heavy metals, medication, toxins or surgical interventions. To protect against reactive oxygen species and other toxic materials that can generate oxidative stress, aerobic organisms have evolved a complex antioxidant defense systems. During the stress response, molecular processes are activated, which help to restore / remove the damaged molecules, to make the cells temporarily more resistant against the stressor. Some components of the response, including activation of the endogenous antioxidant defense system, are highly preserved throughout the evolution. The major aim of the work in our research group is to study the molecular mechanisms leading to the activation of the antioxidant defense system.

We have identified and studied numerous members of this coordinated system, such as antioxidant enzymes, metal-binding proteins and low molecular weight antioxidants. In two model organisms, three different approaches were used to induce an increased level of free radical formation: we studied heavy metal-induced changes in fish, and followed the changes caused by Streptozotocin induced diabetes and endotoxin induced inflammation in rat models.

In this study, we have focused on two quite different (in structure and operation mechanism) protein families: heme-oxygenases (HOs) and metallothioneins (MTs) with several isoforms. HOs are rate-limiting enzymes in the heme catabolic pathway. HOs play roles in heme degradation, and also produce carbon monoxide, a vasoactive dilator agent with important free radical scavenging properties. Two major isoforms of HO have been characterized: HO-1, which is inducible in response to stressors, such as heavy metals, oxidative stress and cytokines, and the constitutively expressed HO-2. The MTs are a family of low–molecular weight metal-binding proteins. These non-enzymatic intracellular proteins are characterized by their unusual high cysteine contents. The MTs are involved in the detoxification of certain heavy metals, the homeostasis of essential trace elements and the scavenging of free radicals. Consistently with these roles, MT genes in eukaryotes are transcriptionally induced by a variety of stressors, including metals, hormones, oxidative agents, cold exposure and irradiation. Though the regulations of the HO and MT genes differ substantially and their expression is regulated temporarily and spatially (which may suggest distinct physiological roles), there are common inductors of these genes, including metal- and antioxidant-responsive elements in their promoter regions.

To summarize our results, it may be concluded that the HO and MT genes are induced in all the studied systems. Elevated levels of expression of HO and MT isoforms are observed in all models; their expression demonstrates stressor-, isoform- and tissue-specificity. As mentioned above, the members of the two gene family have very different characters and regulations, however in the three tested models, the control of MT and HO genes are finely coordinated and they are induced in a complementary manner.

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