(ELISA) we found no difference in the PGE2 production of the mutant strains compared to the wild type strain. Although the C. albicans *OLE2* gene proved to be participating in the PGE2 production, these results are intending that the *CpOLE2* gene do not play a role in the *C. parapsilosis* PGE2 biosynthesis. In order to identify genes that play role in the *C. parapsilosis* PGE2 biosynthesis we carried out qRT-PCR on several genes, chosen from literature and by *in silico* work, after treatment of arachidonic acid. The analysis revealed the significant up regulation of the potential multicopper ferro-O2-oxidoreductase (*CpFET3*) gene after the induction of arachidonic acid. Henceforth while we are creating the *CpFET3* homozygous deletion mutant, we are intending to identify further genes that participate in the PGE2 biosynthetic pathway by carrying out a micro-array analysis.

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Role of the HLTF in the tumorigenesis

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The helicase-like transcription factor (HLTF) belongs to the SWI/SNF family of chromatin-remodeling factors. Several SWI/SNF genes are disrupted in cancer, suggesting their possible role as tumor suppressors. Similarly, the HLTF gene was found to be inactivated by hypermethylation in a significant number of colon, gastric and uterine tumors, indicating that HLTF silencing may confer a growth advantage and that HLTF could be considered as a tumor suppressor gene.

Oncogenic activation of signaling pathways downstream of the EGFR, such as mutation of K-RAS and BRAF is central to the progression of colorectal cancer. According to published data the K-RAS mutation may be present in 35%-45% of patients with colorectal cancer.

The HLTF gene was silenced by hypermethylation in 45% of colon cancers. Recent studies did not examine the connection between HLTF and other tumor suppressor genes and oncogenes.

The K-RAS mutation and HLTF promoter hypermethylation can be detected equal frequency in colon cancers, but the correlation between them is not examined yet.

We examined about 100 colorectal cancer samples. We analyzed the K-RAS status, the microsatellite status and HLTF promoter hypermethylation. Our results indicate that there are some correlation between the K-RAS mutation and the HLTF promoter hypermethylation. Additionally there is correlation between HLTF hypermethylation and microsatellite instability.

The DNA Mismatch Repair (MMR) system plays an essential role in maintaining the fidelity of DNA replication by correcting single nucleotide mismatches and insertion/deletion (ID)-loops. Many components of eukaryotic MMR have been identified, the molecular mechanism of MMR has been largely demonstrated. Defects in the mismatch repair system result in a mutator phenotype, manifesting as microsatellite instability (MSI) in DNA of affected cells

Recently it has been published that many DNA repair genes (e.g. RecQ helicases, polymarese κ and HLTF) are possible new players of the MMR. We are developing a new useful research tool to verify the contribution of these potential candidates in the MMR process.

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The Role of *Candida parapsilosis* Secreted Aspartyl Proteinase 1 in Host-Pathogen Interactions

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Yeast of the genus *Candida* remain the most prevalent cause of human mycotic diseases worldwide and range in severity from superficial infections to life-threatening systemic diseases. *Candida parapsilosis* is currently the second most common cause of invasive candidiasis. Adhesion to host surface, cell morphology switching between yeast and filamentous growth, biofilm formation and secretion of hydrolytic enzymes such as lipases, phospholipases and aspartyl proteinases are considered to be the most important features for development of candidial disease. *C. albicans* possesses 10 genes encoding secreted aspartyl proteinases (Saps) where expression of a particular Sap isoenzyme depends on the type, site and stage of infection. In contrast little is known about the exact role of *C. parapsilosis* secreted aspartyl proteinases (Sapps) in the development of virulence in host-pathogen interactions. In *C. parapsilosis SAPP1* and *SAPP2* are the 2 annotated secreted aspartyl proteinase genes. Sapp1 and Sapp2 have been studied at the enzymological level. The production of Sapp1 in inducer medium is

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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