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Candida albicans adaption to host microenvironments drives immune evasion

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Akademisk avhandling

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Abstract
Immunosuppressed patients are frequently afflicted with severe mycoses caused by opportunistic fungal pathogens. Besides being a commensal colonizing predominantly skin and mucosal surfaces, *Candida albicans* is the most common human fungal pathogen. Mast cells are present in tissues prone to fungal colonization being expectedly among the first immune cells to get into contact with *C. albicans*. Here we describe how mast cells acted as tissue sentinels and modulated initial antifungal immune responses. Mast cells response was able to reduce fungal viability and signaled for neutrophil infiltration to the tissue. Upon chemokine sensing circulating neutrophils are rapid infiltrating to the mucosal to help fight infection. A high number of infiltrating cells coupled with the formation of multicellular structures such as biofilm comes with induction of hypoxic and anoxic micro niches. We found that a persistence anoxia hampered neutrophil responses by affecting fungi sensing and consequent antifungal due to cell wall masking. Adaption to low oxygen seems is important for a successful host infection. Hypoxic and anoxic environments do not allow neutrophils to efficiently produce ROS. Neutrophil oxidative burst is essential for antifungal activity and many fungal pathogens evolved antioxidative factors to mediate survival during infection. We reasoned that targeting of fungal redox balances could be a new therapy approach. We have tested tempol, a redox-cycling nitroxide Tempol as a new antifungal drug. Tempol proved an efficient compound in our testing. We found that Tempol affected fundamental pathways for fungal homeostases such as glycolysis and steroid biosynthesis. Additionally, Tempol helped curve fungal infectivity in a mouse model and leads for an enhanced immune system cytokine profile in human blood. The results obtained proposed tempol as a valid new antifungal compound and open new opportunities for the future development of therapies. Efficient antifungal therapies are still urgent since only 6 classes of antimycotics exist and all with few restricted fungal targets. Since primarily fungal infections affect patients with other immunosuppressive conditions, which are undergoing treatment, we reasoned that repurposing drugs could offer clinical benefits. We performed a screening of two US Food and Drug Administration (FDA)–approved compound libraries for compounds with anti-*Candida* activity. From 844 drugs, 26 agents showed activity against *C. albicans*. We identified 7 new off-target drugs all with potent anti- *C. albicans* activity. The use of these new drugs could be prophylactic or to treat both conditions simultaneously offering, therefore the intended benefit.

Overall, in this thesis work, we have focused on the sensing clearing and management of fungal pathogens. These findings open new doors for understanding better fungal pathogenicity and purpose valid new antifungal compounds that pave the way for future development of therapies.

Keywords
Candida albicans, mycoses, antifungals, mast cells, neutrophils, anoxia, immunology

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