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Article / Book Information

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論 文 要 旨

THESIS SUMMARY

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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

Candida auris is an emerging pathogenic yeast that has been designated as a global public health threat. Despite this, very few studies dealt with how *C. auris* regulates recognition by host immune cells to modulate the host immune response. This study showed that the often multidrug-resistant fungal pathogen, *C. auris,* undergoes a clade-specific cell wall remodeling when exposed to certain environmental stimuli. Among all conditions tested, lactate (0.25-2.0%), low oxygen (<0.1%), and sublethal concentrations of antifungals such as fluconazole (16 µg/mL) and micafungin (0.63 - 40 µg/mL) all trigger a significant reduction in exposure levels of ß-glucan in *C. auris* UI001. On the contrary, low pH triggers a six-fold increase in ß-glucan levels. Staining of ß-glucan and mannan show that there is no inverse relationship between cell wall ß-glucan and mannan exposure levels.

The effect of the observed masking of ß-glucan on the innate immune response was experimented using human THP-1-derived macrophages and murine RAW 264.7 macrophages. A series of phagocytosis assays reveal that for both types of macrophages, the efficiency of phagocytosis is reduced by more than 50% when yeast cells are pre-cultivated in a lactate-containing medium. The amount of cytokines (MIP-1α, TNF-α, IL-10, and IL-6) released after a 24-hr co-incubation was quantified and results show that macrophages incubated with cells exhibiting lactate-induced ß-glucan masking release 84% less of MIP-1α only. The levels of other cytokines were unaffected. ROS production of macrophages in the first two hours of interaction is not influenced by ß-glucan masking. Mechanisms other than macrophage ROS production may be involved in the observed increased rate of killing of glucose-only grown *C. auris*.

To determine the effect of the observed lactate-induced ß-glucan masking *in vivo*,

yeast cells were injected into domestic silkworms (*Bombyx mori*). Survival analysis shows that cells undergoing ß-glucan masking are more virulent to the host, probably due to evasion of immune recognition and proliferation inside the host. Indeed, cell wall modifications like masking of ß-glucan play key roles in the virulence of *C. auris* as it triggers a reduction in the visibility of the fungus to the immune system thereby decreasing the inflammatory response.

The molecular mechanism behind the observed ß-glucan masking was also elucidated. The use of enzyme inhibitors reveals that cAMP-PKA and calcineurin signaling systems are not involved in ß-glucan masking in *C. auris*. The expression of selected genes was measured in glucose-only (Glu) and glucose-lactate (GluLac) grown cells. Although gene expression is increased by only less than 1.5-fold, the following genes were significantly upregulated in lactate-grown cells, *CDR1, ENG1, MNN14*, and *MNN26.* RNA sequencing was also performed wherein 213 differentially expressed genes were discovered. However, only five genes are considered differentially expressed considering an FDR value of less than 0.5. Of these five genes, two were upregulated. One gene code for a glucose transporter and the other one codes for a GPI-anchored protein which is common in fungal cell walls.

To date, no vaccines for human use have been approved to block the spread of fungal diseases, therefore the ability to study fungal diseases and create novel antifungal therapies is critical. Environmental condition-induced exposure of ß-glucan may increase the chances that fungal cells will be recognized by recently developed anti-ß-glucan antibodies.

Going forward, systems biology techniques that open new avenues for uncovering key pathways in the pathophysiology of fungal infections are important. To get a better knowledge of the host immune response to *C. auris* infections and to build novel antifungal therapies, future research must integrate cutting-edge molecular and cell biological techniques with translational approaches.