Mitochondrial Function is Involved in Hyphal Invasion and Virulence in *Candida albicans*

RES-177

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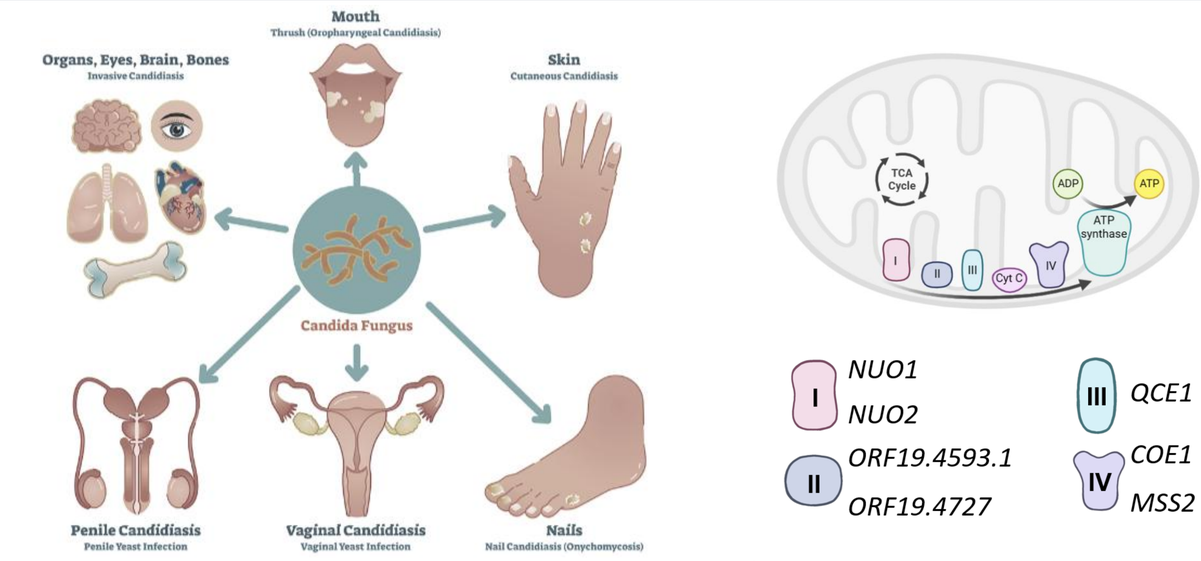
Abstract



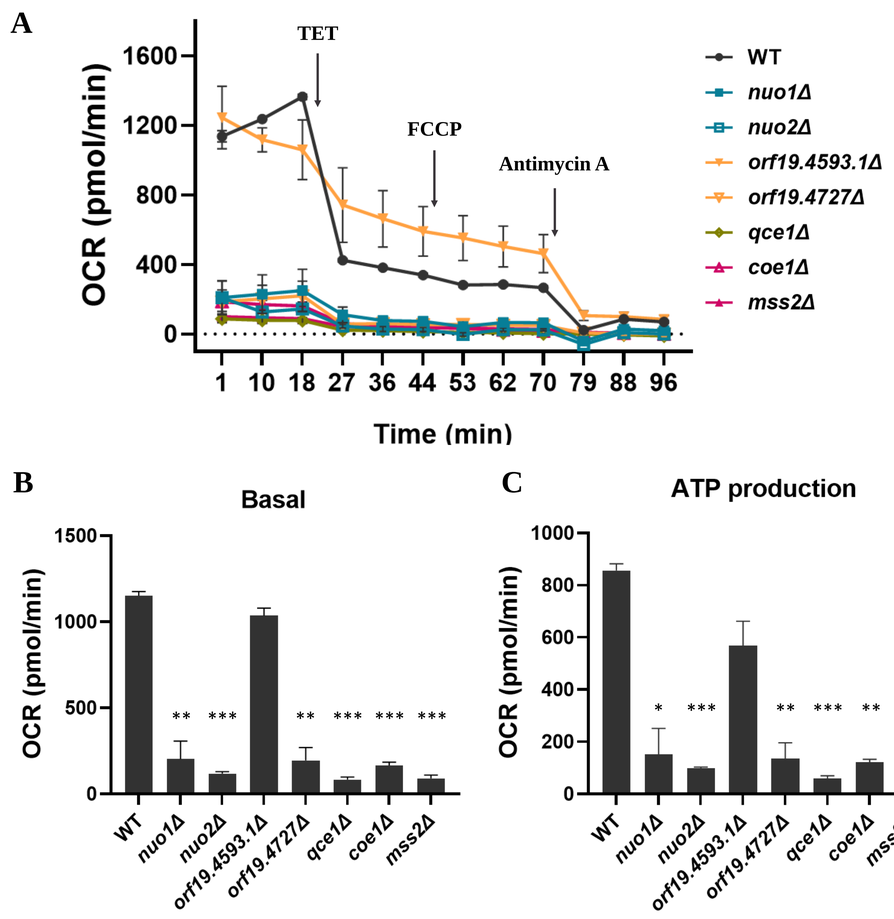
Background: *Candida albicans* is an opportunistic human fungal pathogen that preferentially infects immunocompromised individuals, causing various adverse conditions such as candidemia. It possesses numerous virulence factors, including morphological polymorphism, adhesion, and biofilm formation. Our previous studies have shown that a gene in the mitochondrial electron transport chain (ETC), essential for normal mitochondrial function in *C. albicans*, is involved in hyphal invasion and virulence.
Therefore, the aim of this study is to evaluate the role of each ETC complex in invasive hyphal growth and virulence.

Method: Mutants of mitochondrial ETC-related genes were evaluated for invasive hyphal growth and virulence using both *ex vivo* and *in vivo* models.

Results: We found that mutants of specific genes associated with ETC complexes exhibited impaired invasive hyphal formation and reduced virulence in mice. Further analysis revealed that mitochondrial dysfunction does not impair glycerol accumulation, yet still leads to defective invasive hyphal growth.

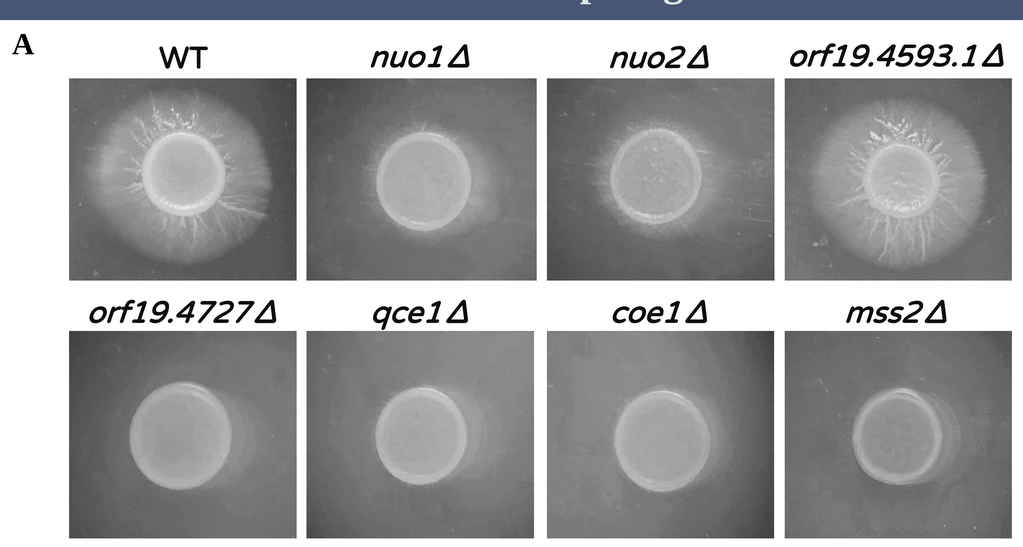
Conclusion: Our results suggest that mitochondrial function regulates invasive hyphal development by modulating intracellular reactive oxygen species (ROS) levels or other mechanisms in *C. albicans*.

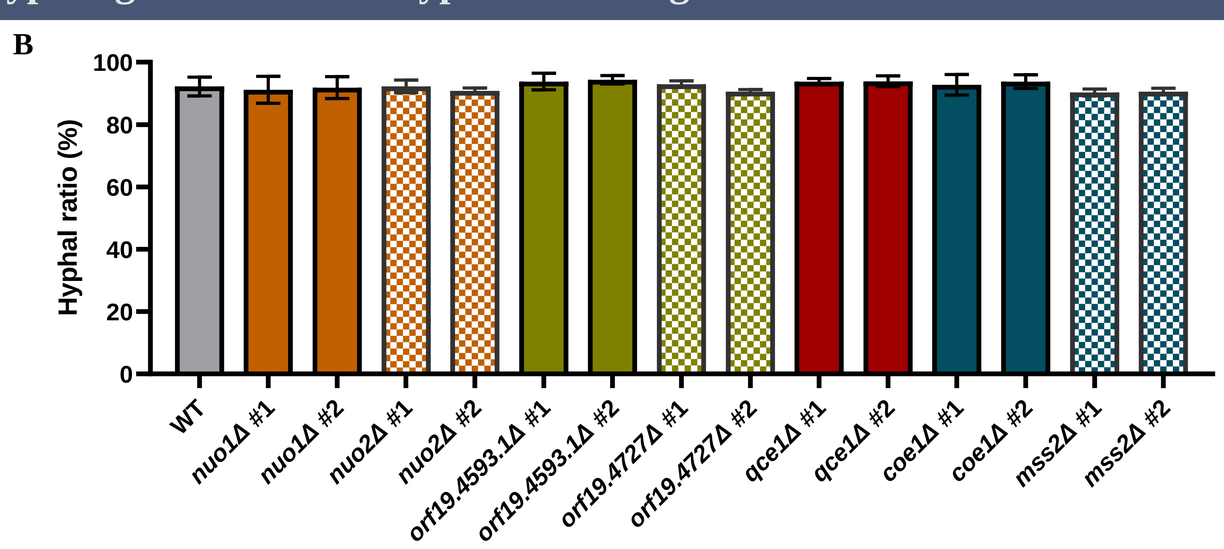
Fig. 1. Deletion of ETC complex genes lead to significantly impaired respiratory activity.



(A) Mitochondria respiration in *C. albicans* is evaluated by measuring the OCR after sequential addition of TET, FCCP, and antimycin A. (B) basal and (C) ATP production were quantified by data obtained in A.

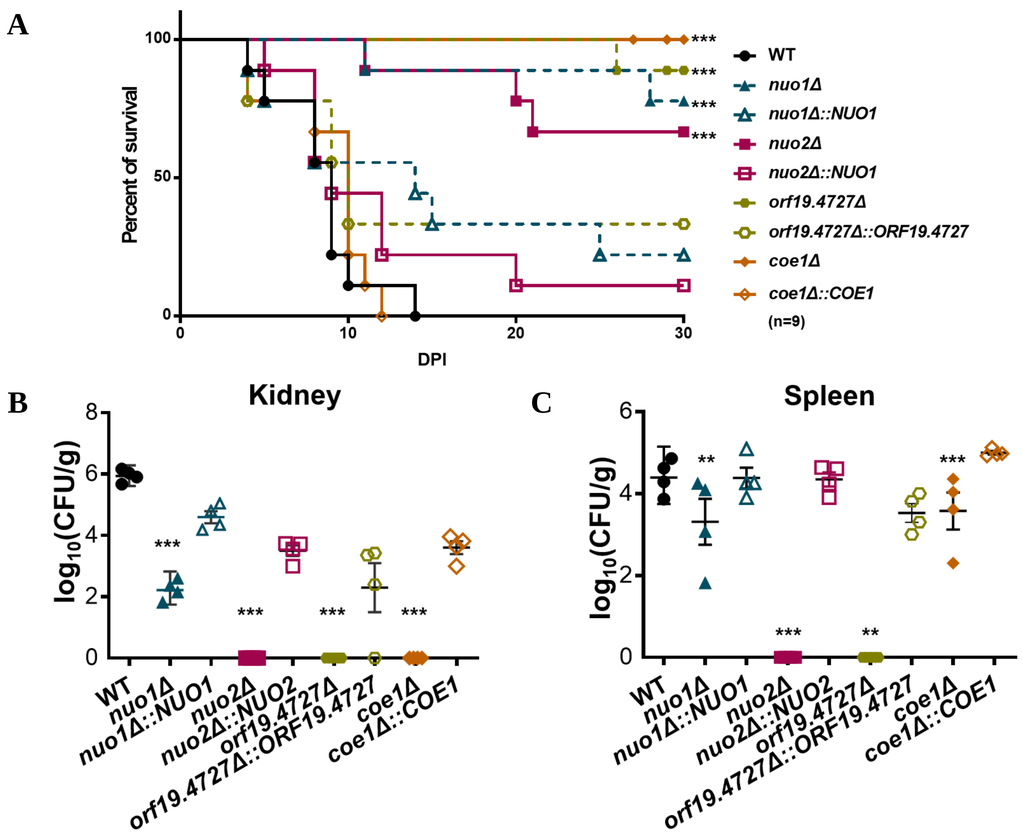
Fig. 2. Deletion mutants of ETC complex genes exhibited defective hyphal growth on solid hyphae-inducing medium.





(A) *NUO1*, *NUO2*, *ORF19.4727*, *QCE1*, *COE1*, and *MSS2* deletion strains show strict defects in invasive hyphal growth on RPMI 1640 media. (B) *NUO1*, *NUO2*, *ORF19.4727*, *QCE1*, *COE1*, and *MSS2* is not related to hyphal formation in RPMI 1640 liquid media.

Fig. 3. Deletion mutants of ETC complex genes show reduced virulence and lower fungal burdens in mice.



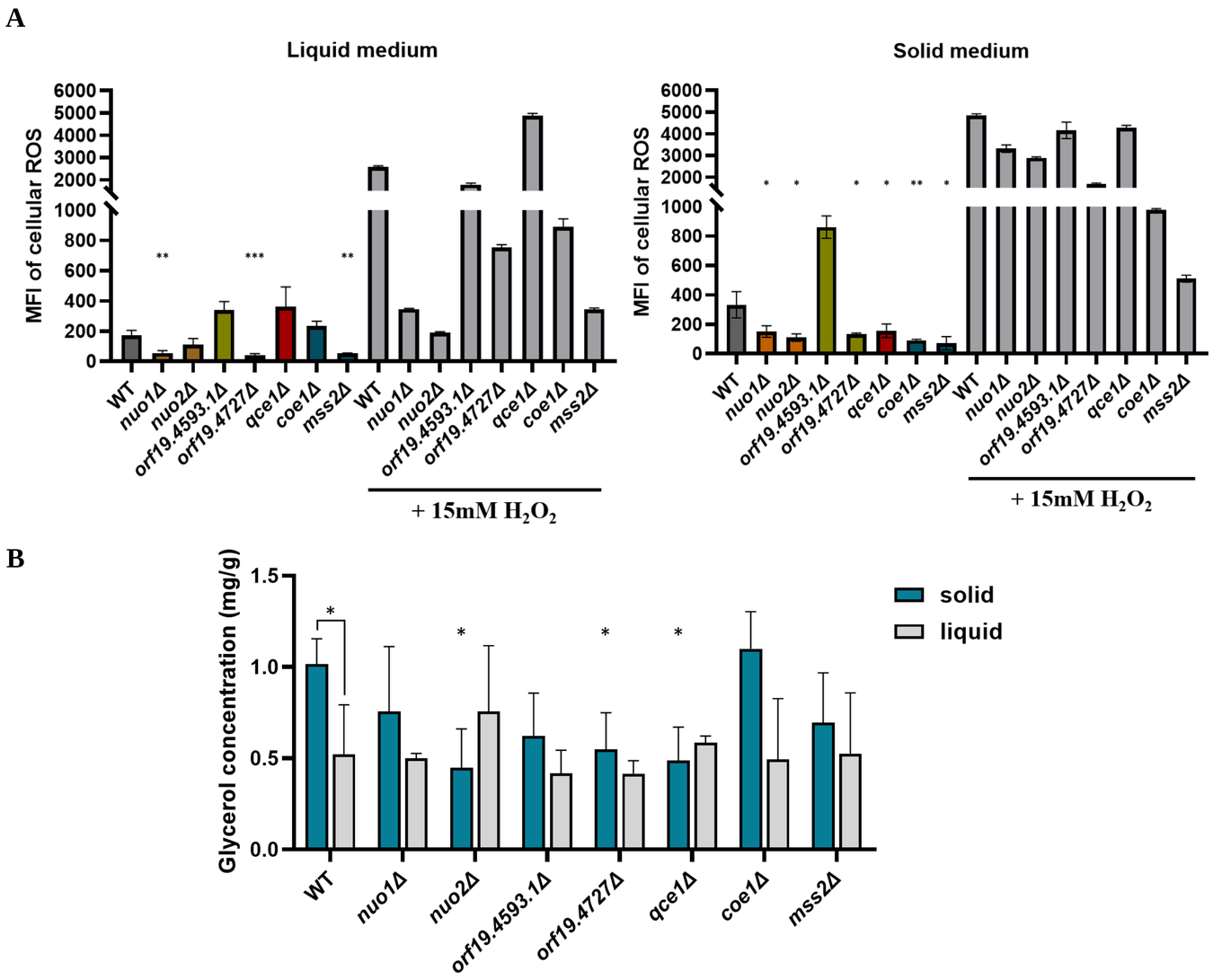
(A) Mice survival was monitored for 30 days following tail vein injection (n = 9), and survival curves were analyzed by the log-rank test (***, P < 0.001). DPI: Day Pass Infection. Fungal burdens in the kidney (B) and spleen (C) were measured on day 3 post infection for each strain (n = 5). Statistical comparisons were performed with an unpaired, two-tailed Student's t-test (**, P < 0.01; ***, P < 0.001).

Reference

Sun, Nuo et al. "Unique, Diverged, and Conserved Mitochondrial Functions Influencing Candida albicans Respiration. " *mBio* vol. 10,3 e00300-19. 25 Jun. 2019, doi:10.1128/mBio.00300-19

Lopes, José Pedro, and Michail S Lionakis. "Pathogenesis and virulence of Candida albicans." Virulence vol. 13,1 (2022): 89-121. doi:10.1080/21505594.2021.2019950

Fig. 4. Mitochondrial dysfunction leads to reduced ROS on solid media and consequently impairs invasive hyphal formation.



(A) Cellular ROS levels under solid and liquid growth conditions were determined by H_2DCFDA staining and FACSCanto™ II Flow Cytometer. MFI: Mean Fluorescence Intensity. (B) Cellular glycerol concentrations under solid and liquid growth conditions were quantified using glycerol assay kit, and were normalized to the dry weight of the cell pellet.