The protective role of type I interferon pathway activation in an *in vitro* model of vulvovaginal candidiasis

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INTRODUCTION

Previous studies showed that a commensal *Candida albicans* strain (Ca4314) from a healthy colonized woman, in contrast to the isolated vulvovaginal candidiasis-associated strain Ca1887, up-regulates the type I interferon pathway in an *in vitro* model of a human epidermoid carcinoma A-431 cell line. The impact of type I interferon regulation leads to a decrease in fungal shedding, which involves *Candida* cells stuck to exfoliated or loosely adherent A-431 cells. In addition, Ca1887 induces more epithelial damage in the A-431 monolayer than the colonizing strain Ca4314. Here, our goal is to explore the potential protective role of the type I interferon pathway in controlling fungal shedding and production of pro-inflammatory cytokines.

MATERIALS AND METHODS

After co-culturing the A-431 monolayer with Ca4314 and Ca1887 strains for 1.5 h, the Interferon Regulatory Factor 3 (IRF3) expression was analyzed by Flow Cytometry. In addition, after 24h of infection, the potency of Ca1887 and Ca4314 in inducing fungal shedding by colony-forming units (CFU) and cytotoxicity measured from lactate dehydrogenase (LDH) were investigated. To analyze the involvement of the type I interferon pathway, epithelial cells were treated with the neutralizing anti-human IFNAR2 antibody, the JAK1 and JAK2 inhibitor Ruxolitinib, and the STING ligand 2'3'-cGAMP. Moreover, the release of IL-8, IL-1α, and IL-1β in supernatants was assessed by ELISA.

RESULTS

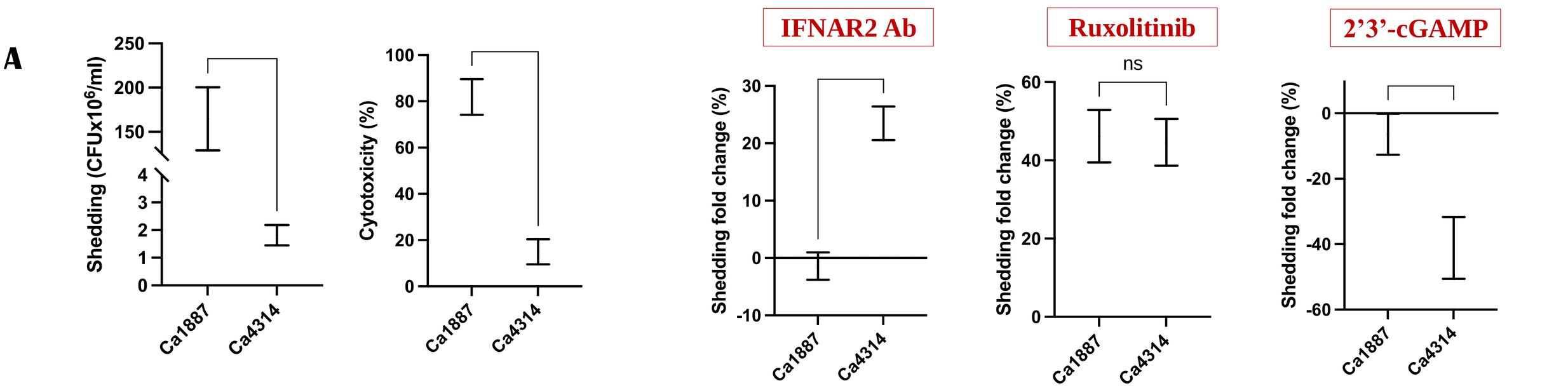


Figure A: The analysis of fungal shedding showed a significant increase of CFU in Ca1887 compared to Ca4314. Moreover, the anti-IFNAR2 neutralizing Ab enhanced the shedding of Ca4314, whereas such effect could not be detected in Ca1887. The treatment with JAK1 and JAK2 inhibitor Ruxolitinib showed an equal increase of CFU in Ca1887 and Ca4314, whereas STING ligand, 2'3'-cGAMP, reduced significantly fungal shedding in Ca4314 compared to Ca1887. Finally, the LDH analysis showed higher cell damage in A-431 co-incubated with Ca1887 cells compared to A-431 incubated with Ca4314.

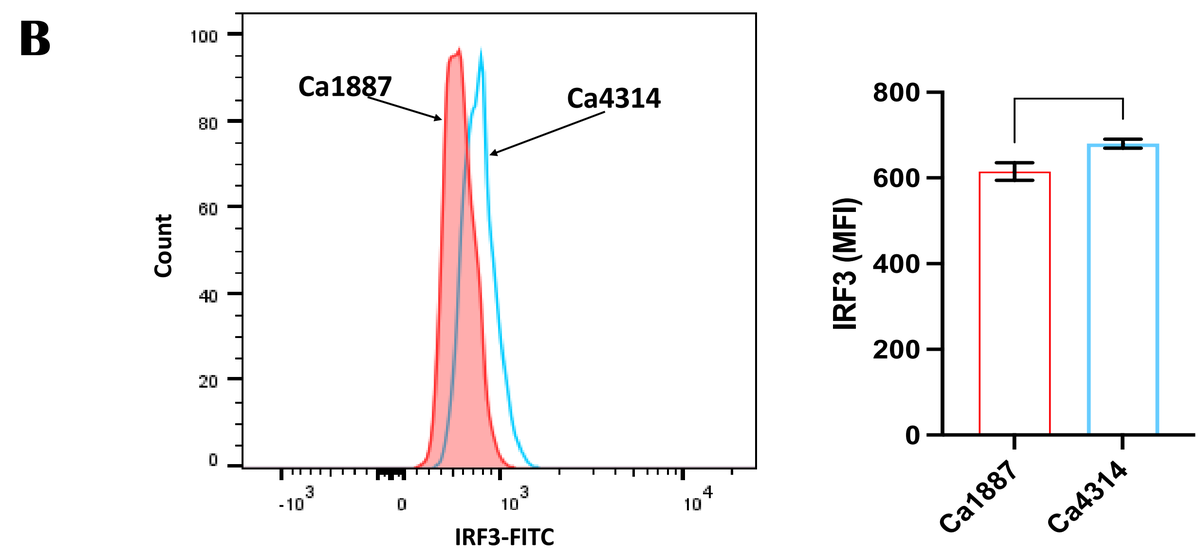


Figure B: The FACS analysis showed higher expression of IRF3 in A-431 cells co-incubated with Ca4314 compared to A-431 incubated with Ca1887.

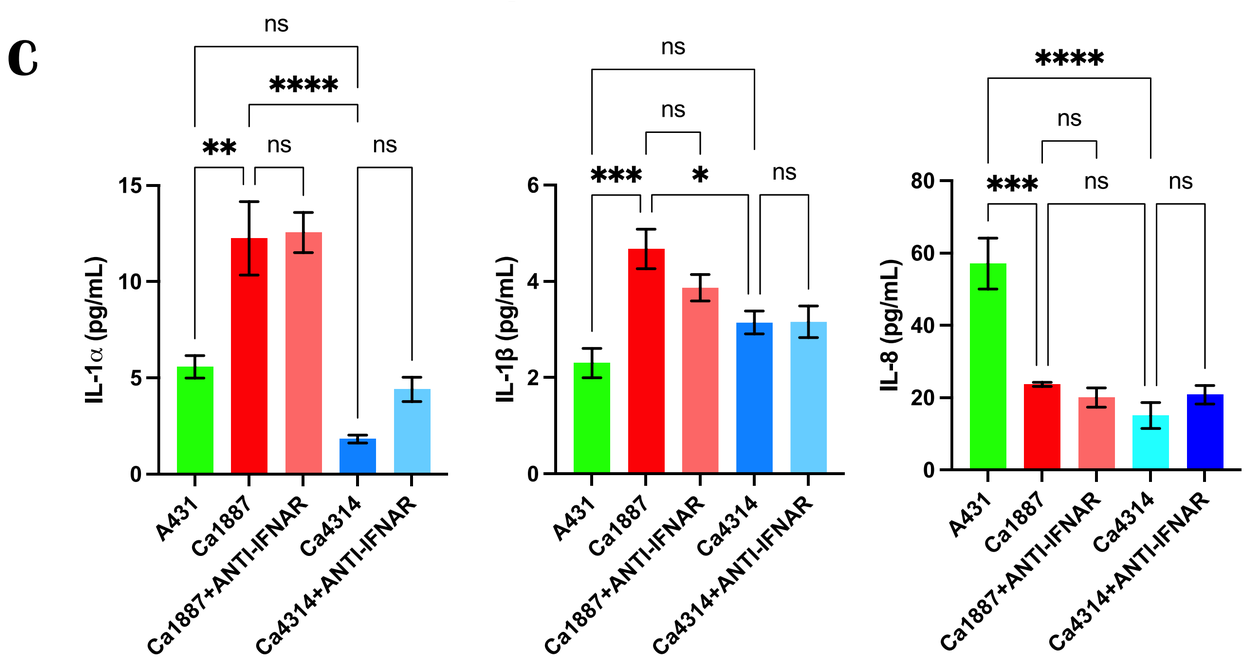
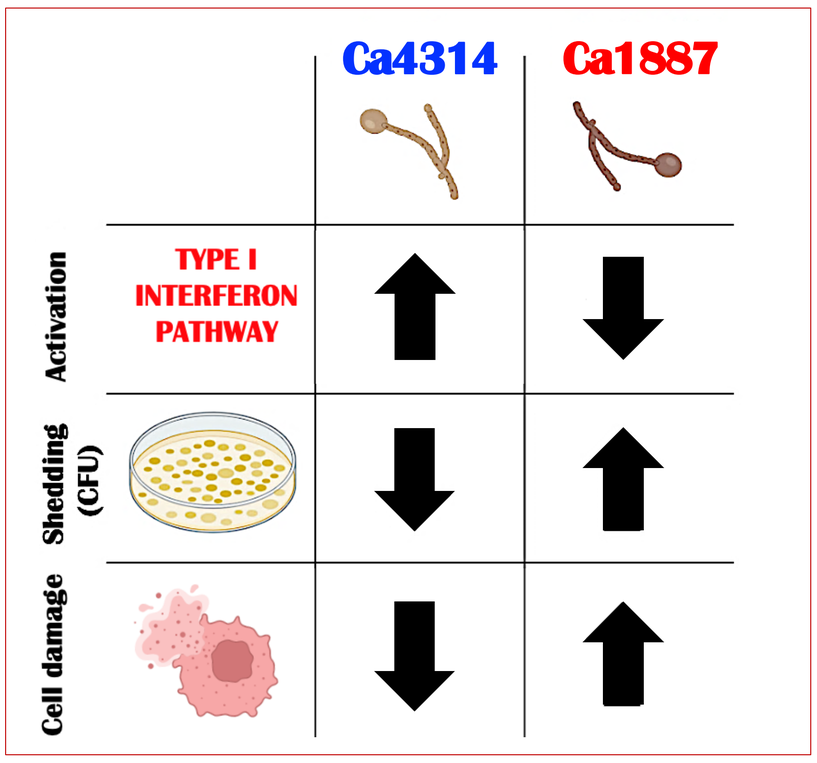


Figure C: The ELISA showed increased levels of pro-inflammatory cytokines IL-1α and IL-1β in supernatants obtained from A-431 co-coltured with Ca1887, whereas no difference in IL-8 release was observed.

DISCUSSION AND CONCLUSIONS



Our results demonstrate the ability of Ca4314 to activate the type I interferon axis, in turn inducing lower levels of fungal shedding and cell damage in A-431 cells. Since the exact mechanisms of *C. albicans* inducing VVC is yet to be elucidated, our results suggest that the stimulation/modulation of the type I interferon pathway may reduce the pathogenic effect of the fungus. Taken together, our data point to type I interferon pathway axis activation as a potential target to reduce the inflammation caused by *C. albicans* during VVC.

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