Interkingdom interactions between Candida albicans and Enterococcus faecalis are ruled by secreted peptides

M. Lorenz *[I], L. Vega[I], G. Buda de Cesare[I], S. Guha[I], S. Cristy[I], M. Cruz[I], D. Garsin *[I]

[I]University of Texas McGovern Medical School, Houston, United States of America

Interactions amongst the many species in the microbiome shape these communities and significantly impact human health. Communication between microbes can take the form of excreted primary or secondary metabolites, physical contact, modulation of immune responses, and the secretion of bioactive molecules that directly impact neighboring cells. The Gram-positive bacterium *Enterococcus faecalis* and *Candida albicans* are a model for how host-pathogen interactions can be controlled by products - namely peptides – secreted from competing species. As opportunistic pathogens, they infect patients with similar risk factors and are often co-isolated in polymicrobial infections. But these two species are more often commensals and generally benefit from this benign host interaction. We have demonstrated that *C. albicans* and *E. faecalis* actively inhibit virulence behaviors via secreted peptides. EntV is a bacteriocin produced by *E. faecalis* that inhibits adhesion, hyphal formation, and virulence of *C. albicans*. We have optimized the antifungal activity to a 10-amino acid helix that is orally bioavailable and dramatically reduces fungal virulence in mouse models of oral, systemic, catheter, and vaginal infections. Importantly, this peptide has no fungicidal or fungistatic activity; instead, it promotes a commensal interaction with the host. The mechanism of action involves inhibition of extracellular vesicle release. In *C. albicans* and other fungal pathogens, EVs play important immunomodulatory roles; thus, the presence of *E. faecalis* may regulate how the immune system responds to *C. albicans*. This communication is bi-directional: *C. albicans* induces *E. faecalis* to maintain a non-pathogenic association with the host, and this is also mediated by a peptide that is neither bacteriocidal nor bacteriostatic through a mechanism that is under investigation. Thus, each of these species modulates the pathogenic potential of the other through specific peptide mediators.

* The authors marked with an asterisk equally contributed to the work.