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Systemic *Staphylococcus aureus* infection mediated by *Candida albicans* hyphal invasion in a murine model of oral co-infection

Promotionsfach: Immunologie
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The bacterial species *Staphylococcus aureus* and the fungal pathogen *Candida albicans* are currently among the leading bloodstream pathogens in hospitalized patients causing high morbidity and mortality. These species are often co-isolated from an array of nosocomial infections mainly due to their ability to adhere and form biofilms on host and abiotic surfaces. Co-infection by these species often leads to severe clinical courses particularly in terms of therapeutic measures the result of their ability to develop rapid antimicrobial resistance. Previous studies on the characterization of the interaction between *C. albicans* and *S. aureus* demonstrated a high affinity for *S. aureus* to *C. albicans* hyphae *in vitro* as these species co-existed in a biofilm mode of growth indicating a strong physical attraction. More recently, our laboratory characterized the mechanism behind this interaction by identifying the *C. albicans* hyphal-specific protein Als3p as the receptor for *S. aureus*. Further in depth studies revealed significant differential protein expression profiles in both species as they co-adhere. Combined, these novel findings describe a complex dynamic interactive process between these pathogens with potential clinical implications particularly to a critically ill host. To that end and building on our previous findings, a murine model of oral co-infection was developed in order to explore the impact of this interaction *in vivo*. Groups of animals were orally infected with either *S. aureus* or *C. albicans* whereas one group was co-infected with both species. Three days post-infection, animals were sacrificed and tongues and kidneys harvested and assessed for microbial burden by CFU counts and tissue histopathological analyses. The findings demonstrated that although both species were recovered from the tongues of animals in all 3 groups, *S. aureus* was only recovered from the kidneys of the dually infected animals. These animals exhibited severe clinical signs of systemic disease and some succumbed to their infection. In order to investigate the observed *in vitro* involvement of Als3p in this phenomenon, a mutant strain lacking the *ALS3* gene and its complemented strain were also tested in the infection model. The findings from these studies demonstrated that while the *ALS3* complemented strain was similar to the parent strain where co-infection led to a systemic staphylococcal infection, co-infection was limited to the oral cavities of the mice infected with the candida *ALS3* mutant strain with no bacteria recovered from the kidneys. Collectively, these *in vivo* findings not only identified a defined mechanism behind this inter-species interaction but also identified a novel phenomenon of infection with grave clinical consequences. Importantly, the infection model developed and the findings generated from this study will pave the way for further in depth investigations into the study of polymicrobial infections, a critical area of research that is still in its infancy.