ABSTRACT

Candida spp., especially *Candida albicans*, represent the third most frequent cause of infection in Intensive Care Units worldwide, with a mortality rate approaching 40%. The increasing antifungal resistance drastically reduces therapeutical options for treating candidiasis. Moreover, finding new molecules that specifically recognize the microbial cell without damaging the host is further complicated by the similarity between fungi and human cells.

Epigenetic writers and erasers have emerged as promising targets in different contexts, including the treatment of fungal infections. In this context, histone acetylation-deacetylation plays a leading role since it regulates pathogenic processes and influences *C. albicans* virulence, especially the Lys 56 of the H3 histone acetylation, particularly abundant in yeasts. The fungal sirtuin Hst3, responsible for histone H3K56 deacetylation in *C. albicans*, is essential for the fungus viability and virulence, representing a unique and interesting target for the development of new antifungals since Hst family proteins diverge significantly from their human counterparts. In this study, using the non-specific Hst3 inhibitor nicotinamide (NAM), the effects of H3K56ac accumulation in *C. albicans* were evaluated. In particular, by Chromatin immunoprecipitation followed by sequencing (ChIP-seq) analysis the acetylation patterns of H3K56 were identified in yeast promoting conditions. In those conditions, Hst3 inhibition triggers the formation of a peculiar phenotype, namely V-shaped hyphae, associated with increased levels of H3K56ac. Moreover, by RNA-seq were identified some virulence-related genes regulated directly or indirectly by H3K56ac associated to the promoter. Furthermore, the roles of H3K56ac in *C. albicans* infection were evaluated. Specifically, since several studies pointed out the possible implication of *C. albicans* secretome in mitigating innate immune cells response, the supernatants from *Candida* cultures, treated with NAM (CaNAM-CM) or not (Ca-CM), were used to treat J774A.1 macrophages. Interestingly, the exposure to the metabolites produced by NAM-treated *C. albicans* resulted in a rapid activation of macrophages and an improved phagocytic activity. By contrast, the macrophages pre-stimulated with Ca-CM displayed abnormal membrane ruffle and the phagocytosis resulted delayed.

Of note, quantitative MS analysis showed that farnesol, a quorum sensing molecule that also affects innate immune system response, is significantly more abundant in CaNAM-CM. Finally, ChIP-seq experiments in infection conditions revealed a different genomic distribution of H3K56ac. Also, transcriptomic studies revealed a dysregulation of several genes associated to host immune evasion and PAMPs exposure. Overall, this study provides the first map of H3K56 acetylation across the *C. albicans* genome in two different growth conditions, representing a rich resource for future studies.