Las levaduras: en la intersección entre la Biología de sistemas y la Biomedicina
En memoria del Profesor Julio Rodríguez Villanueva

Yeasts: at the cross-roads of Systems biology and Biomedicine
In memory of Professor Julio Rodríguez Villanueva

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Candidalysin discovery and function

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Invasive fungal infections kill over 1 million individuals per year. One of the most important human fungal pathogens is *Candida albicans*, which causes mucosal and life-threatening systemic infections that contribute to high morbidity and mortality worldwide. *C. albicans* infections are initiated by increased fungal burdens with associated hypha formation. *C. albicans* hyphae damage host tissue and activate innate immune responses during infection but the mechanisms by which the fungus induced these processes were unclear.

In 2016, we discovered that *C. albicans* hyphae secrete candidalysin, a cytolytic peptide toxin. Candidalysin is secreted within an invasion pocket and intercalates into the host cell membrane to form pore-like structures that results in membrane damage and calcium influx. These events lead to the activation of matrix metalloproteinases and the activation of the epidermal growth factor receptor (EGFR). EGFR activation leads to induction of mitogen-activated protein kinase signalling and the activation of the c-Fos transcription factor and MAPK phosphatase 1 (MKP1), which regulate the epithelial immune response to candidalysin.

The release of chemokines and cytokines results in the recruitment of innate immune cells, including neutrophils and innate Type 17 cells. Neutrophils phagocytose and kill the fungus and innate type 17 cells release IL-17 and IL-22. Together, these innate cells promote fungal clearance, activate epithelial tissues and improve barrier function, resulting in reduction in fungal burdens and/or clearance of the fungal infection.

Candidalysin is critically important for both mucosal and systemic infections. Candidalysin orthologues have been identified in other pathogenic *Candida* species, but their mechanism of action appears to differ. In summary, candidalysin is the first cytolytic peptide toxin to be identified in any human fungal pathogen and its discovery paves the way to identifying new mechanisms of infection driven by fungal pathogens in general.