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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Humanized yeast models in Biomedicine: Assembling Signaling Modules in Cancer and Innate Immunity

Victor Jiménez Cid

Signaling pathways are essential for cell-to-cell communication as well as for sensing environmental changes both in higher and lower eukaryotes. They are responsible for reprogramming cell physiology in response to hormonal stimuli or stress, ensuring cell differentiation through development, adaptation to their environment and, ultimately, survival. The model yeast *Saccharomyces cerevisiae* has been thoroughly exploited to unravel the molecular mechanisms conserved through phylogeny that govern eukaryotic cell physiology. Extrapolation to higher cells of the knowledge attained through basic research in yeast has been a pillar for molecular studies on the genetic and molecular determinants of human disease. In addition, regardless of the existence of homologous pathways in this model organism, yeast cells can be engineered to express particular human proteins of biomedical interest, leading to the development of "humanized yeast" models that provide ready tools for genetic and molecular research. Heterologous co-expression of several components of a given human pathway by Synthetic Biology approaches may permit the assembly of complex signaling modules, giving rise to versatile platforms for the study of disease-related pathways. Along the years, we have developed a humanized yeast model to study in *S. cerevisiae* the human phosphatidylinositol 3-kinase (PI3K) pathway, involving the p85, p110 and Akt oncoproteins and the tumor suppressor PTEN. This model has been exploited to exhaustively investigate the functional impact of pathologic mutations in these proteins, especially in human PTEN, which is commonly mutated in autism- and cancer-related syndromes. With this experience at hand, we are currently approaching the reconstitution in yeast of the major human SupraMolecular Organizing Centers (SMOCs) involved in innate immunity signaling upon the recognition of Pathogen-Associated Molecular Patterns (PAMPs). Namely, we have been able to reproduce in yeast some features of Toll-like receptor TLR4-dependent myddosome, the NOD-like receptor NLRP3-dependent canonical inflammasome, and the RIG-I-like receptor (RLR)-triggered riggosome.

All these modules operate by assembling large complexes of intricate hierarchy and stoichiometry. We will discuss the putative applications of such humanized yeast models based on expression of heterologous human SMOCs for the design of viable platforms for pharmacological or genetic screens.