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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The NPC basket, a stress-sensing "hub" for nuclear functions

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The Nuclear Pore Complex, a gigantic machine of the nuclear envelope recently emerged as a "hub" coordinating nuclear transport, gene expression, chromatin organization and genome integrity. However the limited number of NPC per cell imposes a certain hierarchy of these functions in time and space. In particular, it is now believed that NPC can organize and control microenvironments at the nuclear internal periphery to favor certain nuclear processes as a function of cell requirements. Our studies led us to the hypothesis that dynamic post-translational modifications (PTMs), and in particular ubiquitin and ubiquitin-like modifications, control the plasticity of the NPC structural organization and its role as a coordinating hub.

Our systematic analysis of the ubiquitylation of *S. cerevisiae* nuclear pore complex proteins (Nups) revealed that more than 50% of them are ubiquitylated, mostly by mono-ubiquitylation suggesting a non-degradative role of this post-translational modification. In addition we found that Nups ubiquitylation involves different components of the ubiquitin conjugation machinery. A detailed analysis of Nup159 mono-ubiquitylation, a Nup exclusively localized on the cytoplasmic face of the NPC, revealed a unexpected function in nuclear segregation at the onset of mitosis. More recently, we focused our attention on PTMs of the components of nuclear basket substructure of the NPC, under normal growth conditions as well as upon cellular stresses, and found that these Nups are extensively modified by ubiquitylation, sumoylation and phosphorylation. Using a precise analysis of on nuclear basket protein Nup60 (and its Nup2 partner), we were able to demonstrate, that genotoxic stress influences the dynamics of the nuclear basket by a control of its ubiquitylation with consequences on the DNA damage response and on telomere repair. In addition, we found that the balance between the dynamics of SUMOylation and deSUMOylation of Nup60 and Nup2 at the NPC deeply differs, particularly in G1 and S phase.

While Nup60 is the unique target of genotoxic stress within the nuclear basket that likely belongs to the SUMO-mediated DNA damage response pathway, both Nup2 and Nup60 show a dramatic increase in SUMOylation upon osmotic stress, with Nup2 SUMOylation being enhanced in Nup60 SUMO-deficient mutant.

Together, our findings support the hypothesis that regulation of NPCs plasticity via PTMs serves to modulate its function as a platform for various nuclear functions, and that the NPC acts as a stress sensor serving to transmit extracellular stress signals into the nucleus.