

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

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Regulation of gene expression in yeast through the CWI pathway

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Cell wall damage conditions elicit rescue mechanisms in yeast to provide maintenance of cellular integrity and fungal survival. This is mainly achieved through cellular transcriptional reprogramming by which yeast modulates the expression of genes important for cell wall biogenesis, metabolism, morphogenesis, signal transduction and stress.

The transcriptional program triggered under these conditions is mainly mediated by the cell wall integrity (CWI) pathway through the Mitogen-activated protein kinase (MAPK) Slt2 and the transcription factor Rlm1. Binding of Rlm1 to the promoters of the CWI-responsive genes requires phosphorylation by Slt2. Slt2 MAPK association with chromatin is required for transcriptional activation of Rlm1 dependent genes upon cell wall stress. The interdependence of the binding of Slt2 and Rlm1 supports a preferential recruitment model of the activated Slt2-Rlm1 complex to these promoters. Assembly of the transcription initiation machinery under cell wall stress conditions requires complete nucleosome remodeling at these promoters that is achieved through the cooperation between the ATP-dependent chromatin remodeling complex SWI/SNF and SAGA complex. SWI/SNF complex is recruited through direct interaction with Rlm1 to alter nucleosomes locally, a process which is facilitated through simultaneous recruitment of the SAGA complex that mediates histone acetylation. Moreover, Slt2 interacts with RNA Pol II in a Rlm1-dependent manner to provide further support for a role of this MAPK as an integral component of the transcriptional machinery. Among the CWI-dependent genes both *SLT2*, and *RLM1* are overexpressed upon cell wall stress. Abrogation of this feedback mechanism on *RLM1* severely impairs the transcriptional response elicited by activation of the CWI pathway. Thus, Rlm1 mediates a positive autoregulatory transcriptional feedback that is essential for Slt2-dependent gene expression.

H2B ubiquitination mediated by Rad6 and Ubp8 is necessary for H2B displacement at the coding region of CWI-responsive genes upon cell wall stress suggesting a functional role for this machinery in transcriptional elongation of genes regulated through CWI pathway. Moreover, Sus1, a protein which couples and coordinates transcription and mRNA export processes, is also recruited to the promoter and coding regions of the cell CWI-responsive genes in a SAGA (Ubp8), TREX-2 (Sac3) and Slt2 dependent manner, providing an additional regulatory level in the adaptive CWI-transcriptional response.