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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Yeast to study the function of the translation factor eIF5A in health and disease

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eIF5A is an essential protein in all eukaryotes involved in cell proliferation and animal development. At molecular level, eIF5A acts as a translation elongation factor which binds to ribosomes to facilitate the translation of certain peptide motifs such as stretches of consecutive prolines, called polyprolines. The binding of eIF5A to ribosomes occurs upon its activation by hypusination, a modification that requires spermidine and two enzymatic steps, the two enzymes involved also being essential in eukaryotes. We showed that eIF5A is required for the translation of the polyproline-containing Bni1, an actin-nucleating formin required for polarized growth during *Saccharomyces cerevisiae* mating (1). Our studies in yeast, fly and mammalian cells show that the role of eIF5A in the regulation of cytoskeleton-dependent processes through translation of formins is evolutionary conserved and, consequently, *Drosophila* and mouse eIF5A functionally replaced yeast eIF5A (2). In search for additional targets of eIF5A, we performed a genome-wide analysis of ribosome stalling in *S. cerevisiae* eIF5A-depleted cells using 5Pseq assay (3). We confirmed that, in the absence of eIF5A, ribosomes stall at proline stretches, but also extended previous studies by identifying eIF5A-dependent ribosome pauses at motifs containing the dipeptide proline-glycine (PG), which is highly repeated in the collagen proteins (4). To investigate the role of eIF5A in the synthesis of collagen we

used yeast cells expressing mammalian collagen fragments fused to reporters and observed that depletion of eIF5A reduces their synthesis. Additionally, using the double luciferase system in yeast cells and *in vitro* translation with yeast extracts we confirmed that translation of PG containing motifs required activated eIF5A. Correspondingly, inhibition of eIF5A hypusination or depletion of eIF5A in mouse fibroblasts reduced the levels of collagen I and yielded a lost in cell mobility and reduction of the ability to close wounds in a wound healing assay. These results open the possibility that human diseases caused by a deficiency (collagenopathies) or an excess (fibrosis) of collagen production correlate with low and high expression levels of eIF5A, respectively, and point to eIF5A as a new therapeutic target. Additionally, our studies stand out the use of yeast as a model to interpret at molecular level physiological processes and human diseases.

References cited:

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