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

Madrid, 23 y 24 de enero de 2020 / January, 23 and 24, 2020

What determines nuclear size? Findings in yeast with cancer implications

Orna Cohen-Fix

Caitlin Moffat[1], Madhuri Arya[1], Latika Matai[1], Alison Walters[1], Sylvain Tollis[2], Mike Tyers[2] and Orna Cohen-Fix[1]

[1]The Laboratory of Biochemistry and Genetics, NIDDK, NIH, Bethesda MD, USA
[2]University of Montreal, Quebec, Canada

In most cell types, nuclei are round or oval, and nuclear size scales with cell size. The mechanism(s) that affect nuclear size are largely unknown. For decades, pathologists have used nuclear morphology as a diagnostic marker for various types of cancer and cancer stages. Specifically, certain cancer cells exhibit abnormally shaped and sized nuclei. And yet, the underlying cause(s) of abnormal nuclear morphology and the consequences, if any, of this phenotype are unknown. We are using budding yeast to understand what determine nuclear size and shape; here I will mainly focus on our recent studies regarding the regulation of nuclear size.

A priori, the size of any organelle could be determined by the availability of its surface area (the "container") or its content (as in a balloon). To examine what determines nuclear size in yeast, we first examined nuclear size scaling under conditions where cell growth, but not cell cycle progression, is inhibited. We found that under these conditions the nuclear envelope continued to expand, as it would during normal cell cycle progression, but the nucleus deformed. Remarkably, the nuclear:cell volume ratio was the same as in unperturbed cells. In other words, in the growth inhibited cells, although the nuclear envelope expanded, the nuclear volume did not, suggesting the nuclear envelope availability is not what determines nuclear size. This led us to conclude the content of the nucleus is likely what determines nuclear volume. Nuclear content is, to a large extend, governed by the nuclear import/export pathways. We therefore inhibited nuclear export, thereby increasing nuclear content, and examined what happens to nuclear size. Consistent with our

hypothesis that nuclear content determines nuclear size, inhibiting nuclear export led to a dramatic increase in nuclear volume relative to cell size. This raises the question of what in nuclear content is important for nuclear size: is it a specific protein or set of proteins, or is it simply the bulk amount of protein in the nucleus? It's been previously shown that nuclear import of lamins is important to the regulation of nuclear size, but budding yeast lack lamins. Moreover, how does nuclear content scale with cell size? To this end, we carried out a high throughput microscopy screen for mutants with an abnormal nuclear:cell volume ratio. Several such mutants were obtained, further supporting the idea that nuclear size is determined by its content. These mutants also suggest that there may not be a "scaling factor" per se that monitors cell size and adjusts nuclear size accordingly. Rather, nuclear size and cell size may be a product of the total amount of nuclear and cellular/cytoplasmic macromolecules, and that the ratio between them is relatively constant, although it may vary between cell types.

How might this relate to cancer cells? First, the abnormal nuclear shape often seen in cancer cells could be a result of elevated synthesis of nuclear envelope components, or, conversely, it could be due to continued nuclear envelope expansion under conditions of sub-optimal cell growth, as observed in certain types of aneuploidy. Second, abnormal nuclear size could point to a perturbed balance in the synthesis of nuclear vs. cytoplasmic macromolecules. Thus, our findings in yeast point to new avenues that could be explored in cancer cells.