The nuclear membrane as a lipid ‘sink’—linking cell cycle progression to lipid synthesis

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The nuclear envelope (NE) is a double bilayer structure comprised of the inner and outer nuclear membranes, nuclear lamina and nuclear pore complexes. Not just limited to functioning as a selective barrier between the nucleus and cytoplasm, it regulates a number of cellular processes including gene expression, protein synthesis, DNA damage repair, calcium homeostasis and nuclear shape/volume [2, 6]. Highlighting the importance of nuclear integrity in cellular function, mutations in NE resident proteins lead to a number of disease states, including the ‘laminopathies’, and various cancers [4]. Striking aberrations in NE morphology are associated with several cancers, including small-cell lung cell carcinoma, papillary thyroid carcinoma, urothelial tumours, prostate cancer, invasive ductal carcinoma and high-grade breast cancer [4, 13]. Such aberrations consist of enlarged nuclei, intense staining of nucleoli with haematoxylin and eosin and prominent nuclear invaginations and protrusions [4, 13]. It should be noted that the NE is not a static structure; in eukaryotic cells, it disassembles and reassembles during mitosis. Yeasts, however, undergo a ‘closed’ mitosis, typified by nuclear elongation within

which chromosomes are segregated. This process is accompanied by an increase in NE size, which also changes in shape from spheroid during interphase to an ‘hourglass’ shape during mitosis. Together, these demonstrate that understanding the pathways controlling NE shape and size is of importance.

In a recent paper, Witkin and colleagues have defined a new pathway that regulates nuclear shape in budding yeast [11]. Utilising a high-throughput microscopy approach to computationally analyse nuclear shape, a *Saccharomyces cerevisiae* deletion library was screened, and several mutants displaying a ‘nuclear extension’ phenotype were identified. The extension presents itself as a narrow DNA-containing protrusion into the cytoplasm; however, in some instances, the protrusion was more pronounced, giving the nucleus a bilobed appearance. Since both these phenotypes are observed in the same mutant strains, for example, *rtt107Δ*, it is unclear whether both phenomena represent distinct temporal stages in protrusion formation or whether under certain conditions, such as cell cycle progression, the protrusion takes on a different topology. A time course of protrusion formation would help clarify this issue. Interestingly, unlike yeast *nem1Δ* mutants which display a nuclear ‘flare’ regardless of the cell cycle stage [10]; in this study several mitosis-specific mutants were identified, comprising chiefly of DNA recombination and repair mutants. This led the authors to conclude that activation of the yeast spindle checkpoint and subsequent cell cycle delay in these deletion mutants were responsible for the phenotype observed. This was confirmed when the phenotype could be reproduced by arresting cells with the microtubule-depolymerising agent nocodazole or DNA-damaging agents bleomycin and Zeocin.

An obvious feature of these nuclear extensions is that they will increase the surface area of the nuclear envelope and, as such, will require increased phospholipid synthesis

Commentary on Witkin KL, Chong Y, Shao S, Webster MT, Lahiri S, et al. (2012) The budding yeast nuclear envelope adjacent to the nucleolus serves as a membrane sink during mitotic delay. *Curr Biol* 22: 1128–1133

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to generate the material required. What is interesting is that budding yeast cells appear to continue lipid synthesis, despite undergoing cell cycle arrest, hence the formation of the protrusion. This appears to be a mechanism adopted by the yeast cells so that once the origin of the arrest is resolved, mitosis can proceed as normal utilising the reservoir of membrane in the extension, with no need to upregulate lipid synthesis once more. In this study, phospholipids are quantified by measuring the phosphate content of a cellular lipid extract. While this method is still often used, more quantitative approaches are available. Lipid mass spectrometry is now commonplace, and its utilisation allows the quantification of all the major phospholipid classes and acyl-chain species with relative ease [9]. Thus, the advantage of mass spectrometry over bulk phosphate analysis alone is that a comprehensive lipid profile is generated, and as such, one gains an insight into the potential structure and function of membranes [2].

A striking feature shared by NE ‘flare’ and ‘extension’ phenotypes in yeast is that both these lipid reservoirs originate in the NE adjacent to the crescent-shaped nucleolus. The nucleolus is the centre of ribosome biogenesis and, as such, is not normally associated with lipid synthesis, which takes place in the endoplasmic reticulum. However, the author's previous work indicates that the nucleolus does not dictate protrusion position; rather, it happens to be positioned adjacent to the NE where flare and protrusion formation are favoured [3]. This allows one to speculate that the NE contains sub-domains that regulate its organisation and expansion. This is perhaps not so surprising. In cell-free assays re-capitulating NE formation, heterogeneous vesicle populations are required, one of which is ER derived while another is highly fusogenic by virtue of its proteo-lipid composition [2]. Membrane domains with a novel lipid composition have also been described in the NE of sperm nuclei from various species [5, 7]. This work therefore adds compelling evidence to the existence of the NE sub-domains. While the authors define the spatial origin of protrusions, though not the molecular mechanism on which this observation is based, they do offer us an explanation for their presence. The nucleus is a very complex organelle, with specific roles being played by the numerous nuclear sub-structures [8]. The authors suggest that an increase in the entire NE surface area and the accompanying increase in nuclear volume would incur a disruption to the spatial regulation of the nuclear architecture that would be catastrophic. This explanation seems plausible; there are certainly well-documented precedents for such an assumption. The ‘laminopathies’, a collection of diverse pathologies caused by mutations to the lamin genes [12], are often associated

with an aberrant nuclear morphology at the cellular level [1]. As such, the generation of a temporary membrane reservoir that preserves the integrity of the rest of the nucleus would seem to be a desideratum for a smooth cell cycle progression.

This study successfully uses a screen as a starting point to demonstrate the link between cell cycle progression and lipid synthesis in *S. cerevisiae*. However, the pathways linking DNA repair and chromosome segregation to lipid synthesis and nuclear morphology remain to be elucidated. Understanding these pathways, of which this paper is a first and important step, and defining the composition and function of NE sub-domains will give critical insights into the molecular basis of pathologies where aberrant nuclear morphology is observed.

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