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The dynamic nuclear periphery as a facilitator of gamete health and rejuvenation

Grant A. King[1], **Elçin Ünal**[1,§]

[1]Department of Molecular and Cell Biology, University of California Berkeley, United States, 94720

Abstract

The nuclear periphery is a hotspot for the accumulation of age-induced damage in eukaryotic cells. The types of damage that occur at the periphery and their phenotypic consequences have begun to be characterized; however, the mechanisms by which cells repair or eliminate nuclear damage remain poorly understood. Using budding yeast meiosis as a natural system to study cellular rejuvenation, we recently discovered a novel nuclear quality control event, in which age-induced damage is sequestered away from dividing chromosomes to a discarded nuclear compartment that we term the GUNC (for "**G**ametogenesis **U**ninherited **N**uclear **C**ompartment"). Interestingly, extensive nuclear remodeling occurs even in young cells, including a surprising modularity of the nuclear pore complex, suggesting a general contribution to gamete fitness. In this review, we discuss these findings in the context of recent evidence that the nuclear periphery is a highly dynamic region critical for cellular health.

Introduction

The nuclear periphery, which consists of two lipid bilayers – inner and outer nuclear envelope as well as the associated proteins, acts as a guardian to the genome and mediates nucleocytoplasmic transport in all eukaryotic cells. Notably, this region undergoes a number of changes during natural and pathological aging in metazoans. In natural aging, long-lived nuclear pore complexes (NPCs) accumulate damage and display reduced functionality in both *Caenorhabditis elegans* and mammals (D'Angelo et al., 2009; Savas et al., 2012; Toyama et al., 2013). In pathological aging, the nuclear permeability barrier is disrupted during the course of progressive neurodegenerative diseases, such as amyotrophic lateral sclerosis and Huntington's disease (Chou et al., 2018; Gasset-Rosa et al., 2017; Grima et al., 2017; Zhang et al., 2015). Changes in nuclear organization may be causal to aging phenotypes, since the premature aging disease Hutchison-Gilford progeria syndrome results from mutations in the nuclear gene lamin A and is associated with enlarged nucleoli (Buchwalter and Hetzer, 2017; Eriksson et al., 2003). Consistent with this, small nucleolar size correlates with increased lifespan in *C. elegans*, files, mice, and humans (Tiku et al., 2017). The model organism in which aging has been most extensively studied, the budding yeast *Saccharomyces cerevisiae*, likewise exhibits changes at the nuclear periphery with age

§Correspondence: elcin@berkeley.edu.

including: the appearance of protein aggregates (Cabrera et al., 2017; Saarikangas et al., 2017), the deformation and enlargement of the nucleolus (Morlot et al., 2019; Sinclair et al., 1997; Unal et al., 2011), the clustering and altered stoichiometry of NPCs (Lord et al., 2015; Rempel et al., 2019), and the accumulation of non-chromosomal rDNA circles (Denoth-Lippuner et al., 2014; Sinclair and Guarente, 1997). Given the connection between aging and changes at the nuclear periphery, improved characterization of nuclear envelope organization and dynamics is required.

Cell divisions involve dramatic nuclear envelope remodeling and, therefore, represent an important opportunity for periphery-associated damage to be eliminated. In most metazoan cells, the nuclear envelope undergoes coordinated disassembly and reassembly during cell divisions (reviewed in Ungricht and Kutay, 2017). In addition to facilitating the division of genetic material, these “open” cell divisions allow rejuvenation of the periphery; as a consequence, damage to NPCs and disruption of the nuclear permeability barrier are confined to post-mitotic cells (D’Angelo et al., 2009; Toyama et al., 2019; Toyama et al., 2013). In budding yeast, the nuclear envelope instead remains intact during both mitosis and meiosis (reviewed in Boettcher and Barral, 2013). The nuclear periphery undergoes dramatic morphological changes in these “closed” divisions to accommodate the division of genetic material; however, the elimination of nuclear age-induced damage in offspring requires specialized mechanisms. In mitosis, compartmentalization of the nuclear periphery by the bud neck ensures that age-induced damage is asymmetrically retained in the mother cell (Caudron and Barral, 2009; Clay et al., 2014; Gehlen et al., 2011). In meiosis, age-induced nuclear damage is eliminated as part of gamete rejuvenation (Ünal et al., 2011), but the mechanisms mediating this elimination were unknown until recently.

Principles discovered by studying fungal nuclear divisions are often conserved in metazoan cells (e.g., NIMA-regulated NPC disassembly Laurell et al., 2011 and septin-mediated diffusion barriers Saarikangas and Barral, 2011); as such, we sought to determine how budding yeast meiotic nuclear rejuvenation occurs. We performed in-depth characterization of the nuclear periphery during the meiotic divisions using time-lapse fluorescence microscopy, which allowed us to define a novel remodeling event that facilitates cellular rejuvenation (King and Goodman et al., 2019). In this review, we discuss: (1) the unconventional nuclear reorganization that occurs during budding yeast meiosis; (2) the contribution of nuclear compartmentalization to cellular rejuvenation in budding yeast; and (3) the dynamic structure of NPCs during cell divisions. Further characterization of nuclear behavior during budding yeast meiosis provides a unique opportunity to improve our understanding of nuclear organization and its contributions to cellular health.

Remodeling of the nuclear periphery during budding yeast meiosis

A fundamental property of eukaryotic life is that age-induced damage is not inherited by subsequent generations. Recent work has begun to characterize the specialized mechanisms that facilitate this rejuvenation during sexual reproduction. In metazoans, for example, protein aggregates in the germline are eliminated by activation of the lysosome (Bohnert and Kenyon, 2017; Goudeau and Aguilaniu, 2010). We turned our focus to budding yeast, where meiosis resets lifespan symmetrically such that all resultant gametes are born young (Unal

and Amon, 2011; Unal et al., 2011). Coincident with this rejuvenation, various types of age-induced damage associated with the nuclear periphery, including protein aggregates, non-chromosomal rDNA circles, and abnormal nucleolar material, are eliminated (Unal et al., 2011). Given that the nuclear envelope remains continuous during the meiotic divisions (Moens, 1971; Moens and Rapport, 1971), it was unclear how age-associated damage could be separated away from inherited genomic material.

To answer this question, we performed live-cell fluorescence microscopy to observe the behavior of age-induced damage and various other nuclear components during the meiotic divisions (King and Goodman et al., 2019). We found that protein aggregates and abnormal nucleolar material are physically separated away from dividing chromosomes during meiosis II (Figure 1B). Notably, rDNA circles are similarly sequestered, indicating that cells can distinguish them from chromosomal DNA perhaps due to the lack of centromeres in rDNA circles (Figure 1B). The sequestration is coupled to a nuclear envelope remodeling event that takes place in both young and old cells, culminating in the formation of a fifth nuclear envelope-bound compartment outside of the developing gametes (Figure 1A–B). This compartment, which we term the "GUNC" (for "**G**ametogenesis **U**n-inherited **N**uclear **C**ompartment"), contains select nuclear components – such as the core of the NPC and some nucleolar material – even in young cells (Figure 1A). During gamete maturation, the material in the GUNC is destroyed when the vacuole, the yeast equivalent of the lysosome, undergoes programmed permeabilization and releases its hydrolases (Eastwood et al., 2012; Eastwood and Meneghini, 2015). Notably, the sequestration of nuclear material to this compartment requires nuclear compartmentalization mediated by the formation of *de novo* gamete plasma membranes. When gamete plasma membrane formation is prevented, NPCs and age-induced protein aggregates become randomly distributed along the nuclear periphery (King and Goodman et al., 2019). The sequestration and elimination of nuclear age-induced damage is likely to be a fundamental aspect of meiotic cellular rejuvenation.

Nuclear envelope compartmentalization and its contributions to cellular rejuvenation

Our work provides evidence that compartmentalization of the nucleus is vital to sequestration of age-induced damage away from gametes during budding yeast meiosis (Figure 1A–B). In a similar manner, delineation of mother and daughter nuclear space at the bud neck during mitosis is required for the asymmetric retention of nuclear damage in mother cells (Figure 1C–D; Denoth-Lippuner et al., 2014; Gehlen et al., 2011). In this context, asymmetric partitioning is achieved by compartmentalization of both the nucleoplasm and nuclear envelope during anaphase. Nucleoplasmic partitioning of mother and daughter nuclei results from the nuclear envelope's geometry, as its narrow constriction at the bud neck and the brief duration of mitotic anaphase limit diffusion of nuclear components like rDNA circles (Boettcher et al., 2012; Gehlen et al., 2011). Nuclear envelope partitioning is the consequence of a sphingolipid diffusion barrier in the outer nuclear membrane, established by a septin-mediated signaling cascade at the bud-neck (Chao et al., 2014; Clay et al., 2014; Singh and Li, 2018). This barrier restricts the movement of large nuclear envelope protein complexes, such as NPCs, and associated molecules, such as rDNA circles tethered to NPCs, into daughter cells (Denoth-Lippuner et al., 2014). However, the barrier between daughter and mother nuclei is not absolute: a

cytoplasmic pool of the channel nucleoporin Nsp1 facilitates regulated inheritance of NPCs through the diffusion barrier (Colombi et al., 2013; Makio et al., 2013). Collectively, this work suggests that a dynamic barrier established by at least two parallel mechanisms, namely nucleoplasmic and nuclear envelope partitioning, is responsible for nuclear compartmentalization at the mitotic bud neck.

It is currently unclear what mechanisms achieve nuclear compartmentalization during meiosis. As in mitosis, meiotic compartmentalization relies on a plasma membrane-coupled mechanism, since blocking gamete plasma membrane development prevents sequestration of NPCs and age-induced damage (King and Goodman et al., 2019). The lips of gamete plasma membranes localize to the boundaries of the GUNC, making them attractive candidates to organize a structure that divides the nucleus into distinct domains. However, meiotic septins, known lip-localizing proteins (e.g., the leading edge complex members Don1, Ady3, Irc10), and other constituents of the mitotic diffusion barrier (e.g., Sur2, Epo1, Bud6, Scs2) are not required for sequestration of age-induced protein aggregates or NPCs (unpublished data; King and Goodman et al., 2019), suggesting the existence of a novel mechanism that establishes meiotic nuclear compartmentalization. Intriguingly, the nuclear envelope also exhibits bud neck-independent compartmentalization during mitotic growth, with the nuclear envelope region proximate to the nucleolus preferentially undergoing Cdc5-dependent expansion upon mitotic delay (Walters et al., 2014; Witkin et al., 2012). Together with our study, this implies that multiple mechanisms exist to establish distinct nuclear envelope regions in budding yeast. Given that the nucleoplasm is already known to be organized non-randomly into chromatin domains in both yeast and metazoans (reviewed by Bonev and Cavalli, 2016; Van de Vosse et al., 2011), nuclear envelope compartmentalization seems likely to be an underappreciated layer of nuclear organization that merits future study.

Nuclear pore complex dynamics during cell divisions and differentiation

Given the dynamic behavior of the nuclear periphery during meiosis in young cells, nuclear remodeling is likely to play a role in gamete health beyond facilitating rejuvenation. Dramatic changes to the nuclear periphery occur during “closed” meiosis in other fungal species, including a transient loss of the nuclear permeability barrier in fission yeast (Arai et al., 2010; Asakawa et al., 2010). In this context, virtual nuclear envelope breakdown is required for proper spindle disassembly during meiosis II (Flor-Parra et al., 2018), providing an example of meiosis-specific nuclear behavior that is vital to gamete health. One of the most striking nuclear changes we observe in young cells is the sequestration of NPC cores away from genomic material (King and Goodman et al., 2019). A similar sequestration event occurs during metazoan spermatogenesis coincident with the development of the acrosome, a structure external to the nucleus that may be acting in a manner akin to the yeast gamete plasma membrane (Fawcett and Chemes, 1979; Ho, 2010; Troyer and Schwager, 1982). Moreover, the NPC displays modular behavior during meiosis II, suggesting its dynamics are tightly regulated: the core subcomplexes of the NPC are sequestered and eliminated, while the nuclear basket separates and returns to developing nuclei (Figure 2). Nuclear basket separation in meiosis is a new example of nuclear pore complex plasticity, which is becoming increasingly appreciated as a feature of many types of cell divisions and differentiation (reviewed in Raices and D’Angelo, 2012). As such, determining the

mechanism and function underlying this NPC remodeling will improve our understanding of how NPC modularity contributes to cellular health.

In terms of how this modularity is achieved, we hypothesize that the interaction between the basket and the core is weakened by a post-translational modification such as phosphorylation, similar to regulatory events observed during the cell divisions of other fungal species and metazoans (Figure 2). In *Aspergillus nidulans* mitosis, the conserved NIMA kinase facilitates partial NPC disassembly, disrupting the nuclear permeability barrier in an otherwise closed cell division (De Souza et al., 2004). In metazoan mitosis and meiosis, nuclear envelope breakdown is initiated by phosphorylation and disassembly of NPCs by a NIMA homolog and other kinases (Laurell et al., 2011; Ungricht and Kutay, 2017). The nuclear basket is also ubiquitinated and sumoylated in budding yeast (Folz et al., 2019; Nino et al., 2016), raising the possibility that these post-translational modifications could instead be involved in nuclear basket separation. Intriguingly, the nuclear basket displays a transient association with the NPC core even during mitotic growth (Denning et al., 2001; Dilworth et al., 2001; Niepel et al., 2013), with a subpopulation of NPCs near the nucleolus lacking nuclear baskets (Galy et al., 2004). Characterization of the proteins required for basket separation during meiosis is thus likely to reveal NPC regulators important in other contexts.

In terms of what this modularity achieves, we hypothesize that nuclear basket separation plays a role in both sequestration of core nucleoporins and insertion of new gamete NPCs (Figure 2). Given that nuclear basket nucleoporins associate with chromatin during cell divisions in many eukaryotes (Dultz et al., 2008; Markossian et al., 2015; Suresh et al., 2017), separation of the nuclear basket from the NPC core may be necessary to disrupt interactions between NPCs and chromosomes that would otherwise prevent NPC core sequestration. Further, basketless pores may become disorganized and clustered, enhancing their sequestration, as basket members have previously been shown to regulate NPC distribution (Niepel et al., 2013). Any association of the nuclear basket with chromatin could then facilitate its return to gamete nuclei, where amphipathic helices in Nup60 and Nup1 would allow it to dock onto and curve the nuclear envelope (Meszaros et al., 2015). Given the increased evidence that nuclear pore insertion takes place via an inside-out mechanism when the nuclear envelope is intact (Otsuka et al., 2016), the sites of nuclear basket binding might initiate insertion of new NPCs in bulk. Meanwhile, core subcomplexes – some of which are extraordinarily long-lived and stable (D'Angelo et al., 2009; Rabut et al., 2004; Toyama et al., 2013) – are eliminated, allowing clearance of any age-induced damage. Consistent with a functional importance for nuclear basket return, deletion of the non-essential nuclear basket member Nup60 causes meiotic defects and gamete inviability (Chu et al., 2017). Determining the consequences of disrupting NPC modularity is therefore likely to provide fundamental insights into nuclear basket function.

Conclusions

In budding yeast, the nuclear periphery is far from a passive participant in closed cell divisions. Its compartmentalization is critical to ensure that offspring are born young in both mitosis and meiosis (Figure 1). Dramatic remodeling of its core constituents, including

nuclear pore complexes, occurs during meiosis in young cells with possible consequences to gamete health (Figure 2). Our work contributes to an increasing body of evidence that the nuclear periphery is highly dynamic, with its own dedicated quality control systems (Khmelinskii et al., 2014; Miller et al., 2015; Mochida et al., 2015; Smoyer and Jaspersen, 2019; Smoyer et al., 2019; Webster et al., 2014) and active lipid metabolism (Romanauska and Kohler, 2018). Studying the exceptional changes that take place to the nuclear periphery during budding yeast meiosis will improve our understanding of healthy nuclear organization in yeast and metazoans.

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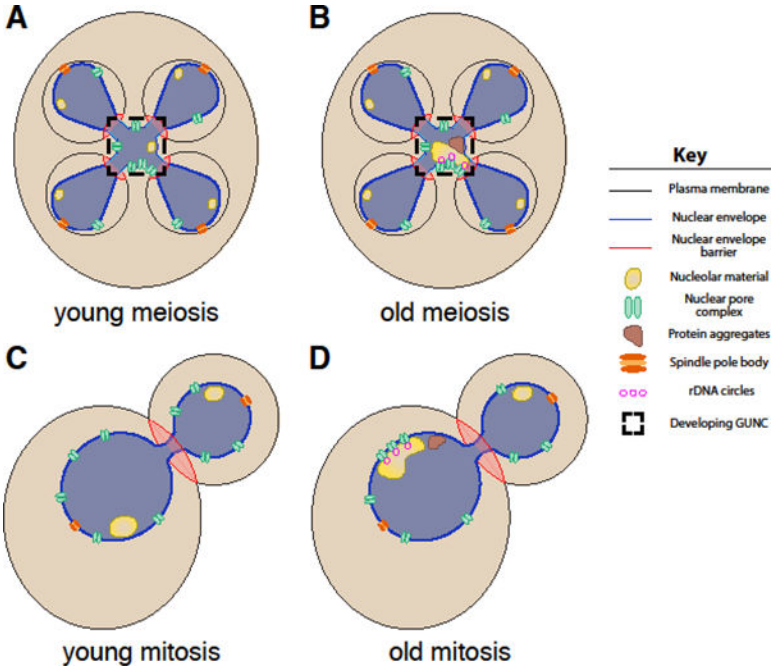

Figure 1. Nuclear compartmentalization in budding yeast meiosis and mitosis.

A-B. Gamete plasma membranes result in nuclear compartmentalization during meiosis via an unknown mechanism (King and Goodman et al., 2019). **A.** In young cells, the gametogenesis un-inherited nuclear compartment (GUNC) contains core NPC subcomplexes and some nucleolar material. **B.** In old cells, the GUNC also contains non-chromosomal rDNA circles, protein aggregates, and abnormal nucleolar material. **C-D.** The bud neck organizes a septin-mediated outer nuclear envelope diffusion barrier during mitosis in both **C.** young and **D.** old cells (Chao et al., 2014; Clay et al., 2014). In old cells, the diffusion barrier contributes to the asymmetric inheritance of nuclear pore complexes and associated non-chromosomal rDNA circles (Denoth-Lippuner et al., 2014). The narrow constriction of the nucleus at the bud neck also limits diffusion between the mother and daughter nucleoplasm (Boettcher et al., 2012; Gehlen et al., 2011).

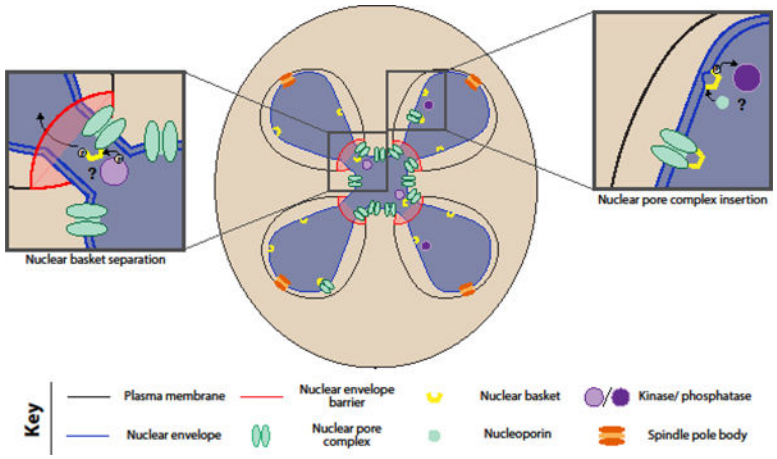

Figure 2. Nuclear pore complex modularity during budding yeast meiosis.

During meiosis II in budding yeast, the core of the nuclear pore complex is sequestered away from dividing chromosomes, while the nuclear basket returns to gamete nuclei (King and Goodman et al., 2019). We postulate that phosphorylation mediates separation of basket from the core, allowing the basket to return to gamete nuclei despite the diffusion barrier created by nascent gamete membranes. Once inside the gamete nuclei, the basket might mediate the insertion of new nuclear pore complexes, via its constituents' membrane-binding amphipathic helices (Meszaros et al., 2015).