Genome Biology

RESEARCH HIGHLIGHT

Pushing the (nuclear) envelope into meiosis

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Abstract

A recent study shows that a short isoform of a mammalian nuclear lamin is important for homologous chromosome interactions during meiotic prophase in mice.

Meiosis is the specialized cell division process required for sexual reproduction. As cells enter meiotic prophase, a relatively long period preceding the two chromosome divisions, nuclei and chromosomes undergo remodeling to promote interactions between homologous chromosomes. Each chromosome must find and identify its unique partner within the volume of the nucleus, a process that obviously involves large-scale chromosome movements.

Over 100 years ago, cytological analysis of meiotic cells revealed a unique chromosome configuration termed the meiotic 'bouquet', in which chromosome ends seem to be attached to the nuclear periphery, frequently in a tight cluster. The presence of the bouquet was found to coincide with the stage during which homologous chromosomes undergo pairing and synapsis. This was the first indication that interactions between the chromosomes and the nuclear envelope might be important for meiotic pairing. More recent analysis in diverse model systems has revealed that the bouquet is a consequence of interactions between chromosomes and cytoskeletal elements - microtubules or actin cables - via a protein bridge that spans the nuclear envelope. A study recently published in *PLOS Genetics* [1] has shed further light on the role of the nuclear lamina in meiotic progression by studying the role of a meiosis-specific isoform of a nuclear lamin protein.

In metazoans the nuclear envelope is fortified by the nuclear lamina, a meshwork of intermediate filament proteins (lamins) and associated proteins that underlies the inner nuclear membrane. The lamina confers structural rigidity to nuclei and also interacts with a wide variety of nucleoplasmic, transmembrane and chromosome-associated proteins. The composition of the lamina in metazoans shows tissue-specific variability and developmental regulation. Most differentiated mammalian cells express both A-type lamins (lamins A and C, which are generated by alternative splicing of the *LMNA* gene) and B-type lamins (encoded by two different genes), whereas some invertebrates express only a single lamin protein. Stem cells typically lack A-type lamins, which are also dispensable for early development in mice.

Among the nuclear envelope components that interact with lamins are LINC (linker of nucleoskeleton and cytoskeleton) complexes. These versatile networks involve a pair of SUN/KASH proteins that bridge both membranes of the nuclear envelope. SUN domain proteins traverse the inner membrane, with their amino termini projecting into the nucleus and their SUN domains in the lumen between the two membranes. Their partners have membrane-spanning regions adjacent to their carboxy-terminal KASH domains, short peptides that bind to the SUN domains. Using a variety of interaction modules, LINC complexes create connections between nuclear structures such as the lamina or chromosomes and cytoskeletal elements such as actin filaments or microtubules. Throughout the eukaryotes, they have essential roles in diverse processes, including the positioning and migration of nuclei within cells and anchorage of centrosomes to the nuclear envelope. During meiosis, specific LINC complexes are recruited to interact with chromosomes through the expression of meiosis-specific proteins that bind to telomeres or, less frequently, to other specialized loci [2]. These connections, probably in conjunction with meiosis-specific modifications to the cytoskeleton and motor proteins, lead to large-scale chromosome motions that facilitate homologous chromosome pairing. These movements involve dramatic motion of the LINC proteins within the nuclear membrane, sometimes involving movements of up to several micrometers that occur within a few seconds [3]. This stands in sharp contrast to the behavior of some of the same protein complexes in somatic or premeiotic cells, in which they show highly constrained motion and minimal turnover [3].

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In the new *PLOS Genetics* study [1], groups led by Manfred Alsheimer and Ricardo Benavente, both of the University of Würzburg, have now engineered a disruption of an exon in the mouse *LMNA* gene that is specific to the meiotic isoform lamin C2 to generate C2-deficient mice (*C2*$^{-/-}$ mice). These collaborators have previously provided important insights into the regulation and functions of cell-type specific lamin isoforms, particularly during meiosis. Using antibodies, they characterized the lamin isoforms present in rat spermatocytes [4]. Immunolocalization revealed that a truncated isoform of lamin C (lamin C2) was localized in a patchy pattern along the nuclear envelope, along with a short B-type lamin (lamin B3) [4]. Because these short isoforms lack domains implicated in interactions between lamin subunits, they and others proposed that these proteins might form a more flexible network. This idea was supported by experiments in which meiosis-specific lamin C2 was ectopically expressed in fibroblasts and found to be more mobile within the nuclear envelope than full-length lamin C [5]. Expression of lamin C2 also resulted in aberrant localization of Sun1 in these cells. The collaborators also demonstrated that spermatogenesis was disrupted in *Lmna*$^{-/-}$ mice, although oocyte meiosis was not obviously perturbed [6]. Although defects in meiosis-specific processes were observed in the knockout mice, it was not possible to rule out an indirect effect of lamin depletion in somatic cells on meiosis in spermatocytes, prior to the new study.

An important feature of the new research [1] is that the *C2*$^{-/-}$ mice show normal expression of all other A-type lamins. The *C2*$^{-/-}$ males recapitulate the meiotic failure seen in *Lmna*$^{-/-}$ mice. Nevertheless, their chromosomes frequently fail to synapse and they engage in heterologous associations or show aberrant telomere-telomere interactions; all of these defects are rare in wild-type spermatocytes. As a result of extensive apoptosis and failure of sperm maturation, the males are completely infertile. However, females are fertile, despite some evidence for pairing defects in *C2*$^{-/-}$ oocytes.

These sex-specific differences in the effects of lamin C2 loss are somewhat surprising. They could in part reflect differential implementation of meiotic checkpoints, which cull defective spermatocytes more ruthlessly than oocytes [7]. However, analysis of homologous pairing and synapsis in the *C2*$^{-/-}$ mutant mice also revealed more severe defects in males. Both male and female mice lacking Sun1 protein are completely sterile and show synaptic failure during meiotic prophase [8]. This suggests that LINC-mediated chromosome dynamics are essential for homolog interactions during meiosis in both sexes. The milder defects caused by loss of lamin C2 in both male and female meiosis suggest that it has a less direct role in mediating chromosome movement than Sun1. This is consistent with the idea that expression of short lamin isoforms during meiosis acts primarily to increase the mobility of proteins within the nuclear envelope, relative to somatic cells. It seems likely that the dynamics of pairing, synapsis and recombination differ dramatically between spermatocytes, which are produced continually during the adult life of the male, and oocytes, which undergo meiotic prophase during fetal development. Such differences might render male meiosis more sensitive to changes in nuclear envelope organization or dynamics.

The modifications made to the mouse nuclear envelope during meiosis are likely to be conserved in concept, if not in detail, in other taxa. As mentioned above, the isoforms and expression patterns of lamin proteins have diverged rapidly among the metazoa, as have the structures and functions of LINC complexes. For example, amphibians lack lamin C (and lamin C2), suggesting that its meiotic role in mammals is a recent innovation. Furthermore, the mouse Sun1 protein has a C2H2 zinc finger lacking in primate orthologs, which might suggest that it has evolved a distinct way to connect with meiotic chromosomes. It is thus not currently clear which aspects of meiotic lamina remodeling in mice can be extrapolated to other species.

In *Caenorhabditis elegans*, meiotic chromosome dynamics are probably mediated by post-translational modification of the amino-terminal (nucleoplasmic) domain of *sun-1* [9]. It is not yet known how this modification contributes to the function of the meiotic LINC complex. Direct observation has indicated that the motion of LINC complexes within the nuclear envelope becomes much less constrained as cells enter meiosis [3]. Phosphorylation of *sun-1* may weaken interactions between the LINC complexes and the lamina to increase their mobility within the nuclear envelope, and/or promote interactions between LINC complexes to create high load-bearing aggregates of these proteins necessary to drive chromosome movement. It is not currently known whether the lamina itself is modified in *C. elegans* meiotic nuclei, but it is easy to imagine that phosphorylation could also be used to tweak protein-protein interactions within the lamina to optimize its properties during meiosis and other specialized cellular processes. It is likely that metazoans have evolved a wide range of mechanisms to modify their nuclear envelopes to meet the special demands of meiotic prophase.

Homologous chromosome pairing remains one of the most mysterious aspects of meiosis. This new work in mice [1] adds an important piece of the puzzle by illuminating how the nuclear lamina can be modified to facilitate meiotic chromosome dynamics. To understand this process will clearly require looking beyond the chromosomes, and even beyond the nucleus, to the cellular networks connected by LINC complexes.

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Published: X Month 2013

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doi:10.1186/gb-2013-14-3-110
Cite this article as: Dernburg AF: **Pushing the (nuclear) envelope into meiosis.** *Genome Biology* 2013, **14:**110.