CELL CYCLE
2016, VOL. 15, NO. 5, 609–610
http://dx.doi.org/10.1080/15384101.2015.1131524

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EDITORIALS: CELL CYCLE FEATURES

How to pre-pair chromosomes for meiosis

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ARTICLE HISTORY Received 23 November 2015; Accepted 3 December 2015

Meiosis is a special type of cell division specific to germ cells, whereby diploid germ cells produce haploid gametes for sexual reproduction. At the beginning of meiosis, chromosomes need to pair with their homologous partner and initiate recombination events that will ensure exchange of genetic information and proper segregation during anaphase I. Pairing events differ significantly between species.[1] Indeed it is initiated at telomeres in mammals, at specific sequences called pairing centers in *C. elegans*, and at centromeres in *Drosophila*. In most species studied, chromosomes adopt a specific configuration upon entry into meiosis called the telomere bouquet where telomeres aggregate on one side of the nucleus. Finally, divergent dynamic chromosome movements take place that promote pairing. *C. elegans* pairing centers and budding yeast telomeres display rapid saltatory movements, while fission yeast meiotic nuclei undergo horsetail motions and telomeres of mouse spermatocytes perform rotational movements.[1]

In *Drosophila* the dynamic events that drive homologous pairing were unknown. Indeed, it was always thought that meiotic pairing was a continuation of a phenomenon observed in several insects called somatic pairing whereby homologous chromosomes are paired in both somatic and germline cells. So, chromosomes were expected to be always paired in every cell. We and others have recently shown that homologous chromosomes are not paired in primordial germ cells (PGCs), which are the first germ cells to be formed in the embryo; and that this absence of pairing is maintained for the autosomes until PGCs become germline stem cells (GSCs) in the adult.[2-3] Paradoxically, of all cells in the adult, the only cells with unpaired chromosomes are the ones bound for meiosis. We were surprised to find that pairing takes place in premeiotic cells originating from GSCs and which undergo 4 rounds of mitosis before entering meiosis. Nonetheless, in agreement with previous studies, we found that chromosomes are already paired when entering meiosis.[2] In a recent study, we have characterized by live imaging the dynamic movements of chromosomes that occur mostly in premeiotic cells where homologous pairing takes place.[4] We found that premeiotic nuclei perform full rotations, which depend on microtubules and the motor protein Dynein. Inhibiting rotations led to strong defects in pairing and synapsis between homologs, strongly suggesting that nuclear rotations are very important for proper meiosis progression. We also found for the first time that nuclear rotations also depend partially on centrosomes, which are one of the microtubule organizing centers. Finally SUN and KASH domain proteins (Klaroid and Klarsicht respectively) at the nuclear envelope are also important for proper nuclear rotations. We have uncovered that Mud (NuMA in mammals) localizes at the nuclear envelope with SUN and KASH domain proteins. Mud is not critical for nuclear rotations but is rather required for maintaining the integrity of the nuclear membrane when cytoplasmic forces are exerted on it. On the one hand, our work revealed cytoplasmic factors regulating nuclear rotations that in turn are required for homolog pairing and synapsis; and on the other hand, it identified a new factor that regulates nuclear membrane integrity.[4]

As mentioned above several studies have shown that chromosomes in germ cells perform dynamic movements that diverge between species.[1] These movements are thought to be required for homolog pairing, for prevention of non-homologous pairing, for removal of chromosome entanglements and finally for maturation of recombination intermediates. Nuclear rotations have also been described in somatic cells but their function is not well understood. Indeed, these events were seen in different cultured cell types [5] and more recently in the follicular cells of the developing *Drosophila* egg primordia.[6] This last study suggested that nuclear rotations are correlated with nuclear positioning as they stop when the nucleus accomplishes migration and is anchored by the actin cytoskeleton.[6] Recently, another function for SUN/KASH and microtubules has been proposed in vertebrate nuclei for DNA repair.[7] It was known for some time, that DNA damages, such as double strand breaks (DSBs), induce an increase mobility of chromatin. The recent study by de Lange and colleagues demonstrates that in MEF cells, this mobility depends on SUN/KASH, microtubules and microtubule motors, and promotes DNA repair. Interestingly, we have also observed that centromeres are often clustered in somatic follicle cells, as in germ cells. Moreover, we found that Mud and Koi (SUN) also formed a dot at the nuclear envelope juxtaposed to the clustered centromeres. It

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Feature to: Christophorou N, et al. Microtubule-driven nuclear rotations promote meiotic chromosome dynamics. Nat Cell Biol 2015;17(11):1388-400; PMID: 26458247; http://dx.doi.org/10.1038/ncb3249.

will be interesting to test whether these proteins also play a role in the spatial organization of chromosomes in somatic cells. As DSBs caused by external damages can trigger chromosome motions through SUN/KASH and microtubules, it will also be interesting to test whether meiotic DSBs can trigger nuclear movements and how these nuclear events are signaled to cytoplasmic components. These are exciting lines of future research.

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