How separated sisters get bad connections

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Accurate chromosome segregation depends on chromosomes acquiring correctly configured attachments to microtubules of the spindle apparatus via multi-protein super-complexes that assemble on centromeric DNA called kinetochores.[1] In the correct attachment configuration, kinetochore pairs attach exclusively to opposite spindle poles (**Fig. 1**). Mis-attachments usually lead to imbalanced forces acting on chromosomes that manifest as misalignment on the spindle and, if left uncorrected, as aberrant separation at anaphase.

Chromosome segregation during meiosis I—which involves separating homologous chromosomes—is notoriously error-prone in human oocytes, especially with advancing female age, and accounts for the overwhelming majority of human aneuploidy that underpin adverse events such as miscarriage and birth defects. During meiosis I, sister kinetochores of each homolog should function as a coherent unit and not as independent entities as in mitosis or meiosis II (**Fig. 1**).

The fraction of the molecular glue known as cohesin that is located in the centromere region constrains sister kinetochores to act as a functional unit during meiosis I and is therefore important for enabling each homolog to become attached to only one spindle pole (monopolar attachment).[2] Cohesin has become a hotbed of interest, since cohesin levels were found to decay in oocytes with aging and to be associated with resolution of meiosis I sister kinetochores into distinct units.[3] The expectation was that relaxation of constraints would lead to uncoupled sister kinetochore behavior and to chaotic attachments to opposite spindle poles (see **Fig. 1**), thereby markedly increasing the risk for aberrant chromosome segregation and accounting for female age-related increases in aneuploidy.

This has not been an easy problem to tackle, because visualizing kinetochore–microtubule (kMt) attachments at the resolution required for meaningful analysis is an extremely challenging prospect in oocytes due to their large volumes and high spindle microtubule density. Shomper et al. have taken on this challenge and meticulously compared kMt attachments in oocytes from younger female mice (6 wk) with those in aged oocytes from females 15–17-mo-old, when sister kinetochore separation had become a prominent feature indicative of substantial deterioration of centromeric cohesion.[4] They found that aged oocytes had increased chromosomal misalignment defects. Also more pronounced in aged oocytes were mis-attachment configurations—lateral attachments and attachments of sister kinetochores to both spindle poles (which the authors termed meiotic-merotelic)—with concomitant reductions in correct monopolar attachment. Interestingly, although separated sisters formed meiotic-merotelic attachments (see **Fig. 1**) more often than unified sisters, their overall involvement in such mis-attachments was surprisingly modest whether oocytes were young (7.8%)

or aged (12.4%).[4] Furthermore, within each age group, unified sisters were equally at risk, as separated sisters, of forming lateral mis-attachments, and both exhibited comparable ability in forming correct monopolar attachments.[4] Together, these data indicate that sister separation, while contributing to, was not the main driver for age-related increases in mis-attachment during meiosis I. In meiosis II, however, misaligned chromosomes and mis-attachments were restricted to chromosomes that had undergone premature division, reflecting premature loss of cohesion. Overall, therefore, these findings show that the majority of erroneous meiosis I attachments that arise with aging are not primarily the consequence of sister separation. In contrast, in meiosis II attachment errors are due to cohesin defects that lead to premature chromosome division.

One interpretation of this work is that meiosis II is more acutely vulnerable to defective cohesion than meiosis I. These results are based on a snapshot taken within a highly
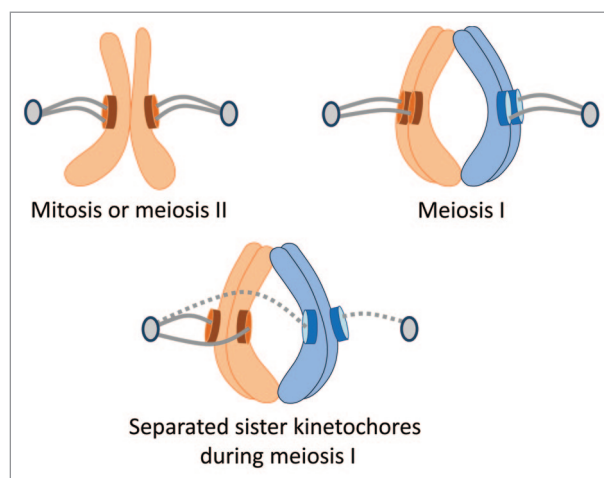

Figure 1. Sister kinetochore geometry and attachment configurations. Shown are the back-to-back geometry of sister kinetochores during mitosis or meiosis II and constrained side-by-side kinetochore geometry during meiosis I important for promoting monopolar attachment of homologs (brown and blue). Shown also are possible attachment patterns when sisters separate in meiosis I due to cohesin decay: blue homolog has sisters attached to both poles (so-called meiotic-merotelic attachments [dashed lines]), while brown homolog has monopolar attachments (solid lines).

dynamic process,[4] so it is possible that at least some of these errors would be corrected before anaphase I onset. It seems very likely, however, that the defect that allowed errors to persist to this late stage in meiosis I would leave many of them permanently uncorrected.

The underlying mechanisms will require further investigation, but an obvious focal point would be the Aurora kinase-mediated error-correction mechanism that dissolves erroneous connections in mitosis[5] and, via the oocyte-specific Aurora kinase C, is also active in mouse oocytes.[6] Interestingly, in human oocytes, Aurora kinase C localizes to chromosomes and centromeres,[7] and its transcript abundance declines markedly as women get older.[8]

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