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INVITED RESEARCH HIGHLIGHT

Sperm Biology

Which one is the real matchmaker for the pair?

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A fundamental question for meiosis is how homologous chromosomes (homologs) find each other and pair together to ensure homologous recombination and segregation. Intuitively, the answer to the question is related to the interaction between homologous sequences. However, that is not the whole story according to some studies on the role of cohesins in homolog pairing. The most recent one by Ishiguro *et al.*[1] of the Watanabe group indicates that chromosome architecture defined by a meiosis-specific cohesin protein RAD21L is the key to homology searching. Moreover, they report that homologous pairing is dependent on neither SPO11, an evolutionarily conserved type 2 isomerase responsible for generating DNA double-strand breaks (DSBs), nor SUN1, which tethers the ends of chromosomes to the nuclear envelop (NE) and facilitates chromosome movement and bouquet formation. These discoveries are quite some surprises!

Recombination and segregation of homologs are two hallmark events of meiosis in most species despite that recombination does not occur in certain organisms. Both of these two events require homolog pairing, which culminates with the formation of synaptonemal complex (SC). Whether pairing depends on homologous recombination remains controversial for long. It has been believed that, in most organisms, pairing is initiated by DSBs, which are resected into single strands that invade homologous sister-chromatids for homology search. However, homologs can pair and synapse in a DSB-independent manner in some species such as *Schizosaccharomyces pombe*, plants, *Caenorhabditis elegans*, *Dipterans*, and *Lepidopterans*. Some DSB-defective mutants of *C. elegans* and *Drosophila* undergo normal synapsis.[2–4] In natural condition, homolog recombination does not occur in some organisms such as *Drosophila melanogaster* males and *Bombyx mori* females. Pairing is maintained by SC in *B. mori* but by sequestration of homolog pairs into distinct territories of the prophase nucleus in *Drosophila* males.[5] During meiosis, telomeres attach to NE to form clusters and result in the bouquet structure of chromosomes. This process, depending on nuclear proteins SUN/KASH, has been believed to be essential for both DSB-dependent and DSB-independent homolog pairings.[6] However, homologous pairing precedes telomere grouping in both *Sordaria macrospora* and rye.[7]

Premeiotic pairing in germ cells and somatic pairing has also been known for long although controversial evidences exist. Importantly, closeness need not imply homologous pairing and can simply be explained by the chromosomal arrangement defined by the clustering of centromeres and/or telomeres. Because of these clustering, allelic loci of similar distances from their centromeres/telomeres are close to each other. Indeed, some fluorescent *in situ* hybridization (FISH) studies indicate that somatic pairing does not occur in budding yeast,[8] while other studies using green fluorescent protein-tagging show that tagged chromosomal domains of yeast cells do associate irrespective of their genomic location with preferences for similar positions.[9] Somatic pairing in *D. melanogaster* is an established phenomenon.[10] It is involved in X-choromosome inactivation in mammals.[11] Specialized sites along DNA, known as pairing centers, maintain homologous pairing during meiosis. Work from McKee's laboratory has identified a 240 bp intergenic spacer located between ribosomal DNA repeats and its binding proteins – SNM and MNM – at the pairing centers in male flies.[12] SNM share homology with SCC3, a sister-chromatid cohesin subunit. The two proteins are involved in the maintenance of homolog pairing although it is unknown whether they have a role in initiating the pairing. The paring centers of *C. elegans* locate to the ends of chromosomes. A zinc-finger protein, HIM-8, which binds to these sites and facilitate their colocalization at the NE, is probably involved in both initiating and stabilizing presynaptic alignment.[13] Centromeres and pericentric heterochromatic regions are also important pairing centers that mediate nonexchange segregation.[14]

Cohesin is a protein complex, which binds to sister-chromatids to prevent premature separation of sister kinetochores both in mitosis and meiosis. It consists of four proteins: SMC1, SMC3, SCC1/RAD21 and SCC3. Cohesin is loaded onto chromosomes prior to or during S-phase, and its SCC1/RAD21 subunit is proteolysed at anaphase to trigger chromatid separation. The SCC1/RAD21 subunit in the mitotic cohesion is replaced by a meiotic counterpart, REC8, in the meiotic cohesin. Meiotic cohesin also functions as a structural basis for SC assembly. A novel SCC1/RAD21 meiotic counterpart, RAD21L, has been identified lately.[15] RAD21L and REC8 form distinct cohesin complexes, and spermatogenesis of their knockout mice are arrested at the zygotene stage.

Just one year earlier, the presence of premeiotic pairing in mammals was observed as early as at late premeiotic S-phase by Boateng *et al.*[16] and it was reported to be dependent on an enzymatic-inactive SPO11 and the SUN1 protein. However, the results by the Watanabe group were different in the following three aspects: (1) homolog pairing was not observed until early leptotene stage; (2) homolog pairing depends on neither SPO11 nor SUN1. Ishiguro *et al.*[1] argued that the reason for the first discrepancy

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was not clear though some experiments in the earlier study by Boateng *et al.*[16] used fluorescence-activated cell sorting, but they did not, while the reason for the second discrepancy was that the earlier study considered a 1.00 μm distance between FISH probes as "paired" whereas theirs used a cut-off value of 1.35 μm. It has been noted that 22% of zygotene-arrested spermatocytes of SUN1 knockout mice undergo synapsis. Therefore, SUN1 facilitates pairing but is dispensable for pairing initiation. (3) Homolog pairing occurs at multiple interstitial sites along the entire chromosome length instead of just the telomeres. One novel discovery by the Watanabe group was that RAD21L but not REC8 was essential for the pairing. This is consistent with the expression patterns of these two meiotic cohesin subunits – REC8 is present throughout prophase while RAD21L appears mostly after DNA replication, peaks at the leptotene/zygotene stage. Despite of these differences, both study support the presence of DSB-independent homolog pairing in mammals.

After decades of research in meiosis, we still know little about this mysterious process, in which so many players are involved. Especially, we do not know how homologs get together although some theories have been proposed.[7] This study by Ishiguro *et al.*[1] together with the one by Boateng *et al.*[16] represent the most current advances of our understanding of this question although many issues await to be resolved.

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