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RESEARCH HIGHLIGHT

# Meiotic crossover: what controls the breaks?

**Katherine Ewen[1] and Peter Boag[2]**

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Meiotic crossover (CO) formation establishes the physical linkages between duplicated meiotic chromosomes. These COs are required for the segregation of chromosomes into the developing gametes and subsequent exchange of genetic material between maternal and paternal chromosomes. Ultimately, meiotic CO recombination represents the fundamental advantage of sexual reproduction and helps drive genetic diversity. Abnormalities in meiotic CO can have dire consequences including meiotic non-disjunction and concomitant aneuploidies.[1] The biological importance of meiotic CO dictates that it be tightly controlled and that the basic function of CO regulators be conserved across sexually reproducing species. Although we have learnt a significant amount about the molecular mechanisms that regulate CO formation and resolution, there is a major gap in understanding how these events are distributed across the meiotic chromosomes. The 'CO distribution' question was the subject of a recent paper in *Nature* led by Judith Yanowitz.[2] In this study, Wagner and colleagues identify a previously uncharacterized gene in the nematode *Caenorhabditis elegans*, *xnd-1*, that directs meiotic CO formation potentially by modulating the acetylation of histone H2A on lysine 5 and thereby affecting chromatin structure. This work has identified not only a novel architect of CO formation, but also a new histone post-translational modification (HPTM) regulatory site in *C. elegans*. This new information will hopefully shed light on meiotic recombination events in higher order species.

Wagner *et al.* used a highly sophisticated series of *in vitro* and *in vivo* experiments to demonstrate that *xnd-1* regulates CO events in *C. elegans*. First, by screening 350 known and putative chromatin binding proteins by RNA interference, they identified *xnd-1* as a potential candidate CO regulator. Next, they examined the global CO landscape by conducting single nucleotide polymorphism analysis of wild type and worms lacking *xnd-1*. In *xnd-1* mutants, a striking shift in CO placement was observed, with placement away from chromosomal ends and into the central region of autosomes and the X chromosome. Interestingly, the number of CO events was also halved only on the mutant X chromosome. The authors conclude that *xnd-1* has a genome-wide influence on CO distribution, and an additional function where it influences CO frequency on the sex chromosome. They go on to show that the frequency is decreased due to a defect in the formation of COs, suggesting that *xnd-1* is required for X-chromosome CO formation. In an unexpected result, XND-1 protein was enriched on autosomes, and essentially absent from the X chromosome. How XND-1 affects the X-chromosome CO frequency remains to be elucidated.

What controls CO formation? CO formation begins with the introduction of meiosis-specific double-strand breaks (DSBs) by the conserved endonuclease Spo11.[3] Additional genes and accessory factors have been identified in other model systems that are also required for Spo11 function and DSB formation. Wagner and colleagues add to this growing list of genes required for DSB formation by showing that *xnd-1* is needed to recruit DSBs to the X chromosome in *C. elegans*.

Both DNA sequence and higher order DNA structure regulate protein accessibility to, and activity at, DSB sites and thus influence CO formation and location. Indeed, COs cluster in discrete chromosomal locations, called hotspots, which are typically associated with open chromatin. Unlike autosomes, the X chromosome is transcriptionally silent in the *C. elegans* germ line,[4] and during the CO formation period, the X chromosome is full of HPTMs which confer a closed chromatin (heterochromatic) state to the entire chromosome. This unique feature makes *C. elegans* an excellent model organism for analyzing the relationship between higher order DNA structure and CO regulation.[5] By taking advantage of worms that are defective in silencing genes on the X chromosome, Wagner and colleagues show that *xnd-1* acts at the level of chromatin structure to ensure that COs form on the X, but is independent of the X-chromosome gene silencing pathway.

HPTMs can have either region-specific functions or genome-wide affects on meiotic CO formation. Recently, trimethylated histone H3 (H3K4me3) has been shown to mark a majority of hotspot-associated DSB initiation sites in yeast and mice.[6,7] Moreover, PRDM1, a zinc-finger containing H3K4 histone methyltransferase, has been identified as a mammalian hotspot-associated protein.[8–10] In this study, Wagner and colleagues show that histone 2A lysine acetylation (H2AK5ac) levels are elevated in *xnd-1* mutants, suggesting that *xnd-1* may regulate this acetylation site. Moreover, they propose that the H2AK5ac mark may be a crucial new regulator of meiotic COs in *C. elegans*.

This study further extends the importance of HPTMs in regulating the meiotic CO landscape, and has revealed H2AK5ac as a novel marker required for normal distribution of DSBs on chromosomes. These revelations may help explain the variation in hotspot locations observed within and between individuals and may provide insight into how environmental factors can influence CO formation. The molecular mechanism of how *xnd-1*/H2AK5ac and other HPTMs regulate Spo11-mediated DSB formation remains to be determined. It will be interesting to see how broadly the *xnd-1*/H2AK5ac pathway is conserved in higher eukaryotes. Future research using advanced genomic technologies, such as deep sequencing, as well

[1]Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark and [2]Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia
Correspondence: Dr K Ewen (kate.ewen@gmail.com)

as proteomics, is sure to address these questions and to generate new clues in the control of meiotic CO events.

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