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Condensin(g) Crossover Control to a Few Breaks

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Meiotic chromosome pairs must receive at least one crossover to ensure proper segregation at the first meiotic division. Mets and Meyer (2009) now present compelling evidence that the establishment of higher-order chromosome structure by a condensin complex regulates crossover recombination by controlling the distribution and frequency of meiotic double-strand breaks.

Formation of a crossover on each homologous chromosome pair during meiosis is obligatory and strictly dependent on the formation and subsequent repair of meiotic DNA double-strand breaks (DSBs). Aided by the close juxtaposition of homologous chromosomes during meiotic prophase, DSBs are repaired by homologous recombination using the intact homologous duplex as a template. How homologous recombination intermediates are processed directly determines whether the DSB is repaired to produce a crossover or noncrossover product (Figure 1). Evidence suggests that crossovers are most likely produced after resolution of a double Holliday junction intermediate, although crossovers can be produced by other means. In contrast, meiotic noncrossover products are thought to arise primarily from processing of homologous recombination intermediates distinct from double Holliday junctions. However, the mechanisms that execute the crossover/noncrossover decision to ensure that each chromosome pair receives at least one crossover remain enigmatic (Bishop and Zickler, 2004). In this issue of *Cell*, Mets and Meyer (2009) identify a novel condensin complex whose inactivation increases and redistributes meiotic DSBs in the worm *Caenorhabditis elegans*. Evidence in budding yeast suggested that the crossover/noncrossover decision can occur at or prior to the establishment of a stable strand exchange intermediate. The work of Mets and Meyer reveals, however, that crossover control can occur very early, during formation of meiotic DSBs.

Condensin complexes, known to promote restructuring of global chromosome architecture, are critical for processes such as X chromosome dosage compensation and accurate chromosome segregation during mitosis and meiosis. Recent studies of the dosage compensation complex, which resembles condensin, also revealed an unexpected role for condensin in controlling crossover number and distribution during meiosis in *C. elegans* (Tsai et al., 2008). In the current study, Mets and Meyer embarked on a detailed biochemical and genetic characterization to investigate the contribution of condensin complexes to crossover control in the worm. Surprisingly, they identified three biochemically distinct condensin complexes (condensin I, I^{DC}, and II). The complexes contain a number of common subunits (see also Csankovszki et al., 2009), but the condensin I complex is the primary regulator of meiotic crossover frequency and distribution.

C. elegans exhibits remarkable crossover control; wild-type worms invariably produce only one crossover per homologous chromosome pair (Hillers and Villeneuve, 2003). In contrast, disruption of any one of the condensin I complex subunits (but not components unique to condensin I^{DC}) resulted in a striking change in the location of crossovers along chromosomes as well as the occurrence of double and triple crossover events on a single homolo-

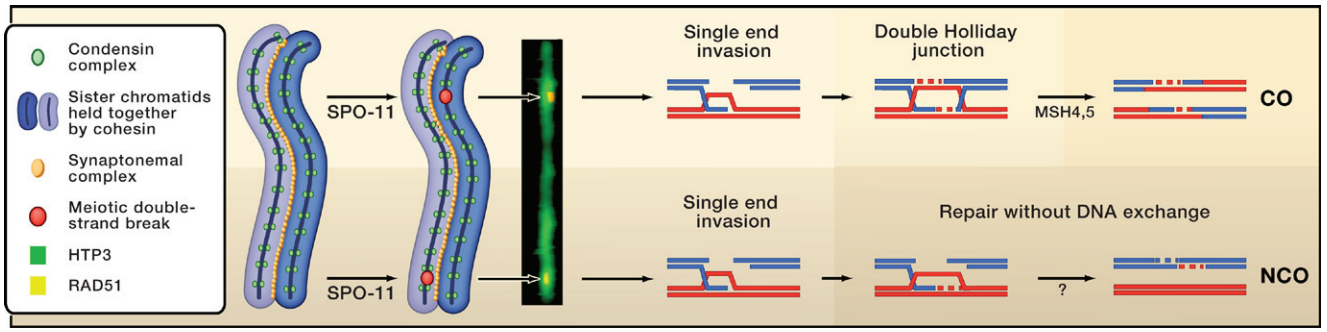

Figure 1. Crossover Control in *C. elegans*

Chromosome axis length is determined by condensin, which in turn controls the number of meiotic DSBs produced by the action of the topoisomerase-related protein SPO-11. On average, two meiotic DSBs are produced on a single chromosome pair (or bivalent). Shown is a representative image of a bivalent; the axis is stained with HTP-3 (green), and meiotic DSBs are marked by RAD-51, a key recombination factor that binds to DSBs (yellow). Since only one of the DSBs is repaired as a crossover, the "extra" DSB must be repaired to give a noncrossover. Crossover formation is absolutely dependent on the mismatch repair-related proteins MSH-4/5 and most likely results from the resolution of a double Holliday junction intermediate. Conversely, repair without reciprocal DNA exchange produces noncrossovers (most likely by synthesis-dependent strand annealing), but the proteins that execute this pathway remain unknown. Image courtesy of D. Mets and B. Meyer.

gous chromosome pair. The authors proceeded to investigate whether the elevation in crossover events in worms with Condensin I complex mutations was attributable to an increase in the formation of meiotic DSBs. Indeed, meiotic DSBs were found to be elevated in the condensin I complex mutants relative to the wild-type. By assessing the position of meiotic DSBs relative to the chromosome axis in condensin I complex mutants, the authors were able to establish a direct correlation between DSB and crossover position. They found that DSBs and crossovers on the left end of the X chromosome were both decreased, whereas DSBs and crossovers on the right end of the X chromosome were both increased.

How might the condensin I complex regulate meiotic DSB formation? The authors reasoned that this function may be linked to its role in controlling chromosome architecture. Indeed, cytological analysis of condensin I complex mutants revealed a striking expansion in the length of the X chromosome axis (1.3- to 1.6-fold increase in axis length). Introducing extra DSBs with ionizing radiation or eliminating meiotic DSB formation altogether using a *spo-11* mutation (SPO-11 is a topoisomerase required to generate meiotic DSBs; Figure 1) had no effect on axis length in either the wild-type or in the condensin I complex mutants, indicating that axis length is not influenced by DSBs per se. Rather, the authors propose that the expansion of axis length in condensin I complex mutants contributes directly to the alteration in meiotic DSB frequency and location (Figure 1). This view was reinforced by the observation that axis expansion and increased meiotic DSB formation in condensin I complex mutants were both suppressed by mutations in the axis component HIM-3. How might alterations in axis length directly influence meiotic DSB formation? Chromatin relaxation may simply improve the accessibility of SPO-11 to its potential targets leading to the generation of more DSBs. Axis changes could also alter the epigenetic status of the chromosome; DNA methylation is known to be a contributing factor in regulating crossovers (Maloisel and Rossignol, 1998). Given that DSBs are known to occur within DNA loops emanating from the DNA axis (Blat and Kleckner, 1999; Gerton et al., 2000), the authors favor the idea that condensin I controls DSB formation by regulating axis attachment sites, which control the frequency, position, and size of DNA loops.

A safe and logical means to ensure that each chromosome pair receives at least one crossover would be to generate a significant excess of meiotic DSBs relative to crossovers. Yet the authors discovered that wild-type *C. elegans* produce surprisingly few breaks: 38% of bivalents (chromosome pairs) had only one DSB, and 61% of bivalents had two to six DSBs (overall, an average of 2.1 DSBs per bivalent). Thus, an active distribution mechanism ensures that each chromsome pair receives a DSB. Crossovers are believed to be produced via a double Holliday junction intermediate (although direct evidence for double Holliday junctions in *C. elegans* is lacking), which can be resolved in one of two possible orientations to give either a crossover or a noncrossover product. For bivalents that receive only one DSB, a mechanism must exist to ensure that repair always produces a crossover. One intriguing possibility is that the MSH4/5 complex, which consists of mismatch repair-related proteins and is absolutely required for crossover formation in worms (Kelly et al., 2000; Figure 1), may present the double Holliday junction in a configuration that can only be resolved to produce crossovers. Alternatively, the obligate crossover in *C. elegans* may be produced from a homologous recombination intermediate (distinct from double Holliday junction) that can only be processed to give crossovers. As only one crossover is produced per bivalent in *C. elegans*, "extra" DSBs (for bivalents with two to six DSBs) must be repaired to produce noncrossovers. The noncrossovers could be produced via dissolution of double Holliday junction by the DNA helicase HIM-6/BLM complex or, more likely, via a meiotic synthesis dependent strand annealing mechanism (repair without reciprocal DNA exchange). However, the factors

that promote meiotic synthesis dependent strand annealing remain unknown in any organism (Figure 1).

Overall, the Mets and Meyer study reveals that crossover formation in *C. elegans* is controlled at two levels: at the level of meiotic DSB production by a new condensin complex, and at the level of the crossover/noncrossover decision, the control and execution of which remains to be defined.

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It's All about Timing

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In the formation of long-term memories, a "spaced" distribution of study sessions is more beneficial than closely spaced "massed" study sessions. Pagani et al. (2009) examine the molecular basis of this spacing effect in *Drosophila* and find a role for the SHP2 homolog, corkscrew, an activator of Ras/MAPK signaling, in establishing optimal spacing intervals.

Increasing the amount of time spent studying improves memory retention, but the distribution of study sessions across time is equally critical for memory formation. The *spacing effect* refers to the benefit to enduring memory retention of a "spaced" distribution of study sessions compared to a continuous study session of the same total duration, or more closely spaced "massed" sessions. Although the benefits of this spacing effect in both humans and animal models have been known for over a century, the underlying molecular mechanisms are still poorly understood. From studies in a wide range of experimental systems, we now have an extensive list of candidate molecules and cellular correlates that can, at least in principle, contribute to this sensitivity to training patterns (Figure 1). Recent work has implicated the Ras/MAPK pathway in regulating the optimal spacing intervals for long-lasting memory formation (Ajay and Bhalla, 2004; Philips et al., 2007; Ye et al., 2008). In this issue of *Cell*, Pagani et al. (2009) characterize a role in long-lasting memory formation for a *Drosophila* tyrosine phosphatase called corkscrew (SHP2 in vertebrates), a potent activator of Ras/MAPK signaling. They show that corkscrew activity regulates the appropriate training intervals for the induction of long-term memory in flies.

Memory formation in *Drosophila* is sensitive to both the number and pattern of training sessions. In response to multiple spaced training sessions, two forms of enduring memory can be formed. One type of memory does not require protein synthesis and lasts about 4 days (also called anesthesia-resistant memory). A second type of memory, long-term memory, lasts at least 1 week and requires both protein synthesis and CREB-dependent gene transcription. The Ras/MAPK signaling pathway, which regulates many cellular processes, also plays a role in the formation of long-term memory, through its effects on both protein synthesis and CREB-dependent transcription.

The SHP2 tyrosine phosphatase is an activator of the Ras/MAPK pathway. In humans, dominant mutations in the gene encoding SHP2, *ptpn11*, are associated with the development of Noonan's and LEOPARD syndromes. These syndromes belong to a family of Ras/MAPK-related disorders associated with mental retardation. Most clinically relevant mutations in *ptpn11* are associated with prolonged SHP2 phosphatase activity that promotes the conversion of the MAPK activator Ras from its inactive state to its active state. Thus, gain-of-function SHP2 mutants lead to prolonged activation of the Ras/MAPK pathway.

In their new work, Pagani et al. (2009) examine the role of corkscrew, the fly homolog of SHP2, in the formation of long-term memory. The authors use a common aversive olfactory memory task, in which flies are first given an electric shock in the presence of a specific odor. Later, they demonstrate memory for that experience in a two-choice apparatus by avoiding a chamber containing the odor