

somes are needed for IL-1 $\beta$  maturation, whereas others are involved in caspase-1-dependent cell death. Would some inflammasomes activate caspase-1 more efficiently than others? Or do certain complexes inhibit the secretion of active caspase-1 to the extracellular space? Do higher levels of active caspase-1 inside the cell result in a broader spectrum of substrate processing, leading to apoptosis? Finally, during infections, how much can lipids protect us? The authors show that, when using live bacteria instead of pure recombinant pore-forming toxins, cells underwent apoptosis, albeit at lower levels than when lipid metabolism was blocked by an inhibitor of SREBP activation. Do lipids slow down the death caused by invading pathogens and provide the cell with a survival win-

dow, giving it time to secrete proinflammatory cytokines, repair itself, and resist the infection? And is it only when the infection is persistent that the cell maintains caspase-1 in a hyperactivated state and commits suicide? Answering these questions will significantly enhance our understanding of the multifaceted roles of caspase-1 in host defense.

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## A One-Sided View of Kinetochores Attachment in Meiosis

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**Meiosis includes a reductional division in which homologous chromosomes, rather than sister chromatids, are segregated to opposite poles of the spindle. In this issue of *Cell*, Petronczki et al. (2006) report that casein kinase 1 contributes to this process by promoting the attachment of both kinetochores of a homolog to only one pole of the meiotic spindle in budding yeast.**

When proliferating cells divide, kinetochores—proteinaceous structures that form on the centromeres of sister chromatids—are captured by microtubules emanating from both spindle poles (bipolar attachment). This bipolar attachment ensures that sister chromatids are faithfully segregated to daughter cells: a process called equational division (Figure 1). Dur-

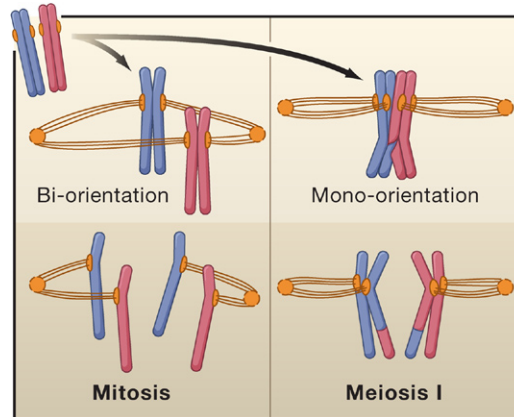
ing meiosis, however, one round of DNA replication is followed by two rounds of cell division, which results in four daughter cells, each with half the number of chromosomes. The first round of cell division, meiosis I, is characterized by the fact that homologous chromosomes, and not sister chromatids (that are observed in mitosis and meiosis II), are segregated

to opposite poles of the spindle. During this “reductional” division, sister kinetochores are always attached by spindle microtubules that originate from the same pole (monopolar attachment; Figure 1). A key question that remains is how monopolar attachment occurs at the kinetochores in meiosis I. In this issue of *Cell*, Petronczki et al. (2006) address this question

and identify a protein that is important for monopolar attachment in budding yeast *Saccharomyces cerevisiae*.

The regulation of kinetochore orientation and attachment to microtubules is strictly regulated during mitotic division, which is considered the “prototype” of chromosome segregation. One of the crucial mechanisms at work is the stabilization of kinetochore-microtubule attachment through tension. Unstable spindle microtubules repeatedly attach and release kinetochores until paired kinetochores are captured by microtubules from opposite poles, which generates tension across the centromeres of sister chromatids that are held together by cohesion (Tanaka, 2002). In addition to being required to maintain tension, close cohesion of centromeres might also play an important role to orient the two centromeres in opposite directions or to establish centromere architecture (Hauf and Watanabe, 2004).

During meiosis I, exchange of genetic material between maternal and paternal chromosomes is accomplished by recombination between homologous chromosomes. Recombination also serves to hold homologous chromosomes together at sites called chiasmata. Therefore, tension can be generated not only when sister chromatids are captured by spindle microtubules from opposite poles but also when homologous chromosomes are pulled toward opposite poles (Figure 1). Indeed, the latter occurs in meiotic cells during the first meiotic division to achieve reductional chromosome segregation. To ensure this process, bipolar attachment of sister kinetochores must be suppressed. Interestingly, if recombination is genetically abolished during meiosis, sister kinetochores still do not undergo bipolar attachment. Therefore, the structure of sister



**Figure 1. Kinetochore Orientation during Mitosis and Meiosis I**

Different segregation patterns of one pair of chromosomes in mitosis and meiosis I are depicted. In mitosis, spindle microtubules from opposite poles capture the kinetochores of sister chromatids, thereby allowing the separation of sister chromatids (equational division) during anaphase. In meiosis I, however, kinetochores on homologous chromosomes are captured by microtubules from the same pole to ensure separation of homologs (reductional division) during anaphase I.

kinetochores itself may be modified to orient toward the same pole at this stage of meiosis.

One plausible model for the molecular mechanism of mono-orientation of kinetochores came from the analysis of the sister chromatid cohesion molecule (cohesin) in fission yeast *Schizosaccharomyces pombe*. This analysis revealed that mutation of Rec8, a meiosis-specific cohesin subunit, results in equational rather than reductional division at meiosis I (Watanabe and Nurse, 1999). Additionally, although mitotic cohesin localizes preferentially to regions close to the centromere, meiotic cohesin localizes to the core centromere as well. Based on these observations, the model predicted that establishing cohesion at the central core of centromeres joins the two kinetochores together at meiosis I, whereas in the absence of this cohesion during mitosis, the core regions open to allow attachment from opposite poles. Crucially, when Rec8 cohesin is inactivated specifically at the core centromere at meiosis I but its other functions are preserved, kinetochore orientation becomes bipolar. This result illuminates a specific function of cohe-

sion at the core centromere to specify mono-orientation (Yokobayashi and Watanabe, 2005). Given that mutations in Rec8 homologs in maize or *Arabidopsis* similarly cause “equational” division at meiosis I, the cohesion-mediated regulation of mono-orientation seems to also operate in plants (Chelysheva et al., 2005; Yu and Dawe, 2000). Moreover, recent experiments in fission yeast have identified the meiosis-specific kinetochore protein Moa1, which is crucial for establishing mono-orientation of kinetochores. Moa1 interacts with Rec8 and localizes at the core centromere only at meiosis I. Circumstantial evidence suggests that Moa1 assists Rec8 cohesin to establish or maintain cohesion at the core centromere in meiosis I (Yokobayashi and Watanabe, 2005).

In budding yeast, the involvement of cohesin in the regulation of mono-orientation of kinetochores is not clear. Mitotic cohesin, if expressed in place of meiotic-specific cohesin, can support the establishment of mono-orientation, which contrasts with the results in fission yeast. Instead, in budding yeast a different set of proteins, called the monopolin complex, are required for mono-orientation. Monopolin includes Mam1, Csm1, and Lrs4 and localizes to centromeres specifically at meiosis I (Rabitsch et al., 2003; Toth et al., 2000). Whereas Mam1 is a meiosis-specific protein, Csm1 and Lrs4 usually form a complex that localizes to the nucleolus and move to centromeres only at meiosis I by associating with Mam1. These factors mutually depend on each other for their localization to centromeres. To identify new subunits of the monopolin complex, Petronczki et al. (2006) used a tandem affinity purification strategy. Through this approach, they identified a highly conserved casein kinase 1  $\delta/\epsilon$  (CK1  $\delta/\epsilon$ ) called Hrr25 as a subu-

nit of this complex. Given that CK1  $\delta/\epsilon$  participates in multiple cellular processes in many organisms including budding yeast, deletion of *HRR25* causes severe defects in cell growth and meiotic progression, making it difficult to analyze its role in kinetochore orientation at meiosis. To identify mutations in *HRR25*, Petronczki and colleagues (2006) used an ingenious genetic screen that showed a defect in mono-orientation but not in other cellular processes. They then generated an allele called *hrr25-zo*, which integrated two such mutations. Interestingly, *Hrr25-zo* specifically could not interact with Mam1 and, concomitantly, the monopolin complex could not localize to centromeres. However, using another allele of *HRR25* that is sensitive to a kinase inhibitor, they demonstrated that the kinase activity of *Hrr25*—although dispensable for the assembly of the monopolin complex at centromeres—is importantly required for the mono-orientation of kinetochores. Based on the integration of this data, Petronczki et al. (2006) suggest that phosphorylation of some kinetochore proteins by *Hrr25* is a crucial step to set up mono-orientation of kinetochores in budding yeast.

To examine the conservation of this finding, Petronczki et al. (2006) also analyzed the function of CK1  $\delta/\epsilon$  in fission yeast. By repressing the activity of fission yeast CK1  $\delta/\epsilon$  during meiosis, they demonstrated that chromosome segregation at meiosis I was somewhat impaired. However, these phenotypes could be caused by merotelic attachment (one kinetochore being attached to two spindle poles), rather than by a specific defect in the mono-orientation of kinetochores. Previously, Rabitsch et al. (2003) found that *Pcs1*, a *Csm1* homolog in fission yeast, is dispensable for mono-orientation but required to

repress merotelic attachment of kinetochores. Thus, although two putative homologs of monopolin components have been found in fission yeast, their function is likely not conserved. Moreover, it is difficult to detect any traces of homology between fission yeast *Moa1* and monopolin components (or other proteins) in budding yeast. Why have the molecules required for mono-orientation diverged so much between budding yeast and fission yeast? The budding yeast centromere is exceptionally small and forms a kinetochore that attaches to only a single microtubule in mitosis. Remarkably, a recent analysis of the three-dimensional ultrastructure of the meiotic spindle in budding yeast indicates that a pair of sister kinetochores in meiosis I is attached by a single microtubule rather than two (Winey et al., 2005). This is in contrast with other eukaryotes in which both kinetochores are attached to microtubules (Hauf and Watanabe, 2004). Thus, one can argue that the monopolar attachment in budding yeast is caused by the “fusion” of point centromeres but in other organisms by “cohesion” of two centromeric regions. However, it is still possible that the fundamental mechanisms of mono-orientation are conserved, but we are still far from understanding them. The identification of crucial substrates of *Hrr25* in budding yeast would be important to address this problem. In this regard, Petronczki et al. (2006) envisage two proteins, Mam1 and Rec8, as potential substrates. Both associate with *Hrr25* and are phosphorylated in an *Hrr25*-dependent manner. The significance of Mam1 phosphorylation has not been tested. However, the fact that *Hrr25* associates and phosphorylates the meiotic cohesin Rec8 but not its mitotic counterpart *Sccl* seems more intriguing because meiotic cohesin

plays a crucial role in mono-orientation in other organisms. But the story is not so simple, as the *Hrr25*-dependent phosphorylation occurs in the entire cellular pool of Rec8 (not only in centromeric Rec8). Moreover, budding yeast can establish mono-orientation even in cells where Rec8 is replaced with *Sccl*, which is not bound to and phosphorylated by *Hrr25*. In spite of such drawback, it is still tenable that the monopolin complex regulates cohesin at centromeres to promote the fusion of the sister kinetochores, which ultimately might be required to promote mono-orientation. To examine this possibility, it would be important to specifically inactivate cohesin at the kinetochore in meiosis I in budding yeast, as has been done in fission yeast, and to examine the consequences.

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