ELSEVIER

Shugoshin: guardian spirit at the centromere

Yoshinori Watanabe

A recently emerging protein family, shugoshin, plays a crucial role in the centromeric protection of cohesin, which is responsible for sister chromatid cohesion. This is especially important at the first meiotic division, where cohesin is cleaved by separase only along chromosome arms while the centromeric cohesin must be preserved. In vertebrate cells, arm cohesion is largely lost during prophase and prometaphase in order to facilitate sister chromatid resolution, whereas centromeric cohesion is preserved until the bipolar attachment of sister chromatids is established. Vertebrate shugoshin plays an essential role in protecting centromeric cohesin from prophase dissociation. In yeast, shugoshin also has a crucial role in sensing the loss of tension at kinetochores and in generating the spindle checkpoint signal.

Addresses
Laboratory of Chromosome Dynamics, Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi1-1-1, Bunkyo-Ku, Tokyo 113-0032, Japan; SORST, Japan Science and Technology Agency, Yayoi1-1-1, Bunkyo-Ku, Tokyo 113-0032, Japan

Corresponding author: Watanabe, Yoshinori (ywatanab@iam.u-tokyo.ac.jp)

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Introduction

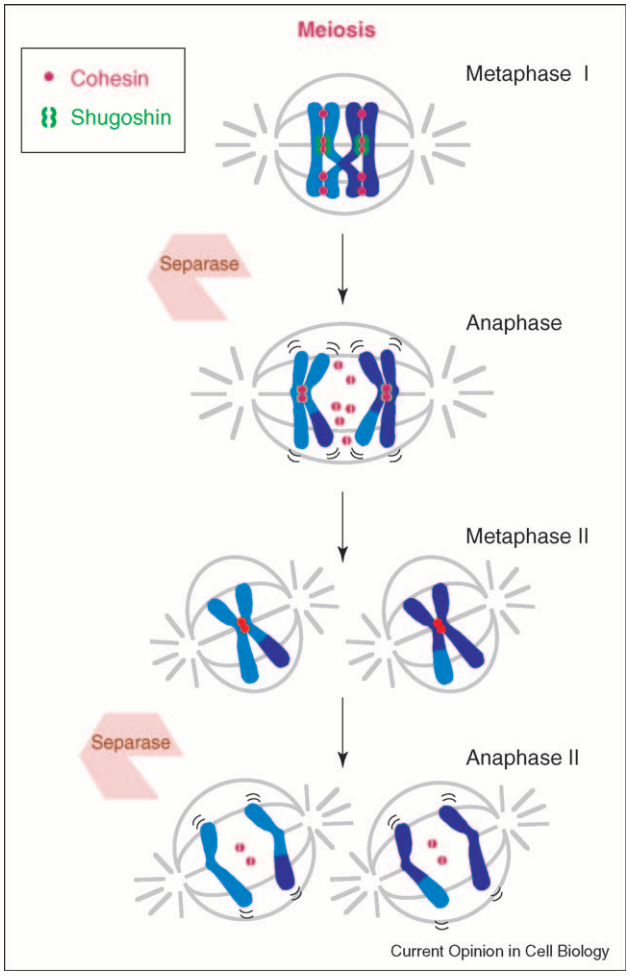
During the cell cycle, chromosomes are replicated in S-phase, and all pairs of replicated chromosomes (sister chromatids) are segregated to two daughter cells at mitosis. Sister chromatids must not come apart before metaphase, when the spindle microtubules capture their kinetochores, because the proper capture of sister chromatids depends on their association as a pair. The association of sister chromatids — cohesion — is carried out by a multi-subunit complex, cohesin, comprising two SMC (structural maintenance of chromosome) family proteins, Smc1 and Smc3, and two accessory subunits, Scc1 (also called Mcd1 in *S. cerevisiae* and Rad21 in *S. pombe*) and Scc3 [1,2]. Several lines of evidence support the notion that both ends of the Smc1–Smc3 rods interact with the single protein Scc1, thereby forming a ring structure that entraps sister chromatids [3]. At the onset of anaphase, when sister chromatids start to separate, Scc1 is cleaved by a specific endo-peptidase, separase, thus opening the cohesin ring to release the entrapped sister chromatids.

To reduce their chromosome number by half as part of the process of sexual reproduction, eukaryotic cells undergo a specific chromosome segregation called meiosis, which consists of two rounds of chromosome segregation following a single round of DNA replication. During the first meiotic division (meiosis I), homologous chromosomes (homologs) pair to recombine, forming chiasmata in which one sister chromatid from one homolog is covalently attached to a sister chromatid from the other homolog. Hence, in order for homologs to segregate at meiosis I, sister chromatid cohesion must be released along the chromosome arms to resolve the chiasmata. However, sister chromatid cohesion is retained at the centromeres until meiosis II, when sister chromatids segregate as they do in mitosis, utilizing the residual centromeric cohesion. Thus, meiotic divisions require sister chromatid cohesion to be released in two steps, first along the chromosome arms and second at the centromeres [1,4–6] (see Figure 1). This complex pattern of meiotic chromosome segregation is remarkably conserved from yeast to human. However, the molecular basis for the protection of centromeric cohesion during meiosis I has long been the subject of debate, although several factors, including MEI-S332, Spo13 and Bub1, have been shown to be required for this pathway [7–10]. Recently, it was revealed that the yeast protein shugoshin (Sgo) contributes to this process by protecting centromeric cohesin Rec8 complexes from cleavage [11••,12•,13•]. It turns out that shugoshin, which shows limited similarity to *Drosophila* MEI-S332 as well as to many uncharacterized proteins in various eukaryotes, constitutes a conserved protein family. In this review, I summarize what has emerged about the roles of shugoshin, not only during meiosis but also during mitosis, in various organisms.

Shugoshin confers a conserved mechanism to protect centromeric cohesion at meiosis I

Cohesin complexes are modified in meiosis. The most important modification is that the Rad21(Scc1) subunit is largely replaced by its meiotic counterpart, Rec8. During anaphase of meiosis I, Rec8 is cleaved only along the chromosome arms by separase, while centromeric Rec8 is preserved until meiosis II. If Rec8 is replaced by Rad21 during meiosis, sister chromatid cohesion, but not protection at the centromeres, is restored, leading to the separa-

Figure 1



Shugoshin protects centromeric cohesin from separase cleavage during meiosis I. Homologs are connected by recombinational exchange of chromosomes during prophase I. At the onset of anaphase I, cohesin complexes are cleaved only along the arm regions, while centromeric complexes are protected by Sgo1. This allows separation of the homologs but not of the sister chromatids. Sgo1 is degraded, presumably by APC, prior to meiosis II in fission yeast. At the onset of anaphase II, centromeric cohesin is cleaved by separase, thereby segregating the sister chromatids.

tion of sister chromatids at meiosis I. Therefore, an intrinsic property of the Rec8 subunit that is absent from Rad21 contributes to centromeric protection at meiosis I [14,15]. Centromeric heterochromatin plays a crucial role in enriching cohesin complexes and thereby strengthens centromeric cohesion in mitosis [16–18]. Fission yeast heterochromatin mutants, which fail to enrich Rec8 complexes specifically in the pericentromeric regions, lose centromeric cohesion during meiosis I, underscoring the importance of pericentromeric Rec8 for preserving meiotic centromeric cohesion [19].

A functional screening of fission yeast identified the Rec8 protector as a gene that causes the disjunction of chromosomes, and thus that is toxic during mitotic growth only when co-expressed with Rec8 and not when co-expressed with Rad21 [11••]. This gene encodes a meiosis-specific protein named shugoshin (Sgo1), which means 'guardian spirit' in Japanese. Sgo1 localizes exclusively at pericentromeric heterochromatin regions, the site at which Rec8 was predicted to play a role in centromeric protection at meiosis I [19]. Independent knockout screening in fission yeast and budding yeast also identified the *sgo1/SGO1* gene [12•,13•] as a Rec8 protector in meiosis. Remarkably, it turns out that shugoshin shares a hitherto unperceived limited similarity to MEI-S332, a *Drosophila* protein that was previously shown to be required for the persistence of centromeric cohesion during meiosis I [4,7,20] but had lost favor as a Rec8 protector because of an apparent lack of homology. Moreover, shugoshin shows similarity to uncharacterized proteins in most eukaryotes, although the homology is restricted to the coiled-coil sequences located near the N terminus and basic sequences near the C terminus [11••,13]. Thus, shugoshin/MEI-S332 constitutes a conserved protein family in eukaryotes (Figure 2). In *sgo1* mutants of both fission yeast and budding yeast, Rec8 cohesin complexes fail to persist at the centromeres during meiosis I, causing premature separation of sister chromatids prior to metaphase II. As a result of this lack of cohesion, the sister chromatids undergo random segregation at meiosis II. The *Drosophila* Rec8-like molecule C(2)M seems not to function in chromosome cohesion at metaphase I; therefore, it remains unclear whether MEI-S332 indeed protects cohesin complexes in meiosis [21]. Recently, maize shugoshin (ZmSgo1) was identified by studying sterile mutants in which centromeric cohesion is released precociously before metaphase II [22]. As with fission yeast Sgo1, maize Sgo1 localizes at centromeres only during meiosis I and is not detected during mitosis or meiosis II. Because of the phenotypic similarity of shugoshin mutants in yeast, fly and plant, eukaryotic shugoshin is believed to have a conserved role in protecting centromeric cohesion at meiosis I, presumably by protecting the cleavage of centromeric Rec8 from separase (Figure 1). Rec8 complexes co-precipitate with Sgo1 *in vivo* in fission yeast [11••], and maize Sgo1 requires Rec8 for centromeric localization [22], suggesting that the protection might be directly executed by the close interaction of these proteins. Nevertheless, the precise mechanisms of protection remain elusive.

Mitotic chromosomes are protected at centromeres by shugoshin in vertebrate cells

Cytological observations of metazoan chromosomes indicate that by metaphase sister chromatid cohesion is reduced along the arm regions, but not at the centromeres, and that prolonged arrest at this stage by the addition of a microtubule destabilizing drug such as nocodazole leads to the complete separation of chromosome arms, thereby producing 'X- shaped' chromosomes.