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Acetylation regulates monopolar attachment at multiple levels during meiosis I in fission yeast

Ayano Kagami[1,2], Takeshi Sakuno[1,3], Yuya Yamagishi[1], Tadashi Ishiguro[1], Tatsuya Tsukahara[1,4], Katsuhiko Shirahige[5], Koichi Tanaka[1] & Yoshinori Watanabe[1,2+]

[1]Laboratory of Chromosome Dynamics, Institute of Molecular and Cellular Biosciences, [2]Graduate Program in Biophysics and Biochemistry, Graduate School of Science, [3]Promotion of Independence for Young Investigators, [4]Department of Biological Sciences, Graduate School of Science, and [5]Laboratory of Genome Structure and Function, Research Center for Epigenetic Diseases, University of Tokyo, Tokyo, Japan

In fission yeast, meiotic mono-orientation of sister kinetochores is established by cohesion at the core centromere, which is established by a meiotic cohesin complex and the kinetochore protein Moa1. The cohesin subunit Psm3 is acetylated by Eso1 and deacetylated by Clr6. We show that in meiosis, Eso1 is required for establishing core centromere cohesion during S phase, whereas Moa1 is required for maintaining this cohesion after S phase. The *clr6-1* mutation suppresses the mono-orientation defect of *moa1Δ* cells, although the Clr6 target for this suppression is not Psm3. Thus, several acetylations are crucial for establishing and maintaining core centromere cohesion.
Keywords: cohesin; acetylation; meiosis; chromosome segregation

INTRODUCTION

Duplicated chromosomes (sister chromatids) become connected during S phase through the action of a multisubunit complex called cohesin, which consists of four core subunits: two SMC (structural maintenance of chromosome) family ATPase proteins, Smc1 and Smc3, a kleisin family protein, Scc1, and Scc3 (called Psm1, Psm3, Rad21 and Psc3, respectively, in fission yeast; Onn *et al*, 2008; Peters *et al*, 2008; Nasmyth & Haering, 2009). Sister chromatid cohesion must be maintained throughout G2 phase until metaphase to identify the pair of chromosomes that must be separated at division. At the onset of anaphase, a protease called separase cleaves the Rad21 subunit, leading to the separation of

sister chromatids. In meiosis, the Rad21 subunit is replaced by the meiosis-specific subunit Rec8, which is indispensable for meiosis-specific chromosome events, including monopolar attachment of sister chromatids (Watanabe *et al*, 2001). Whereas mitotic Rad21-containing cohesin localizes preferentially to the pericentromeric regions, meiotic Rec8-containing cohesin localizes additionally to the core centromere (Watanabe *et al*, 2001). The establishment of cohesion at the core centromere conjoins the two kinetochore domains and, thus, promotes mono-orientation at meiosis I, whereas the core regions might open to opposite sides when biorientation is favoured as in mitosis or meiosis II (Sakuno *et al*, 2009). Fission yeast Moa1, a meiosis-specific kinetochore protein, also has a crucial role in creating core centromere cohesion, presumably by assisting Rec8 action, although the molecular details of Moa1 function remain largely elusive (Yokobayashi & Watanabe, 2005).

During the mitotic cell cycle, the replication fork-associated acetyl transferase Eco1 has a crucial role in establishing cohesion in S phase (Uhlmann, 2009). Studies in budding yeast and humans have shown that a key function of Eco1 is the acetylation of two lysine residues of the Smc3 subunit of the cohesin complex (Ben-Shahar *et al*, 2008; Unal *et al*, 2008; Zhang *et al*, 2008; Rowland *et al*, 2009). Mutations of both lysine residues to non-acetylatable arginine cause cell lethality because of a cohesion defect as seen in *eco1*-deficient cells. Conversely, mutations of both lysine residues to asparagine or glutamine, which mimic the acetylated state, can sustain cell viability even in the absence of the *ECO1* gene, which is otherwise an essential gene. A similar regulation has been shown between human Esco1 (an Eco1 orthologue) and Smc3 (Zhang *et al*, 2008). In budding yeast, class I histone deacetylase (HDAC), Hos1, removes the acetylation of Smc3 mostly at anaphase (Beckouet *et al*, 2010; Borges *et al*, 2010; Xiong *et al*, 2010). Because the *de novo* acetylation is crucial for cohesion establishment, its deacetylation at anaphase might enable the recycling of cohesin in the next cell cycle. A recent study in fission yeast also shows that K105 and K106 of Psm3 (corresponding to budding yeast Smc3-K112/K113) is

[1]Laboratory of Chromosome Dynamics, Institute of Molecular and Cellular Biosciences,
[2]Graduate Program in Biophysics and Biochemistry, Graduate School of Science,
[3]Promotion of Independence for Young Investigators,
[4]Department of Biological Sciences, Graduate School of Science, and
[5]Laboratory of Genome Structure and Function, Research Center for Epigenetic Diseases, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
[+]Corresponding author. Tel: +81 3 5841 1466; Fax: +81 3 5841 1468;
E-mail: ywatanab@iam.u-tokyo.ac.jp

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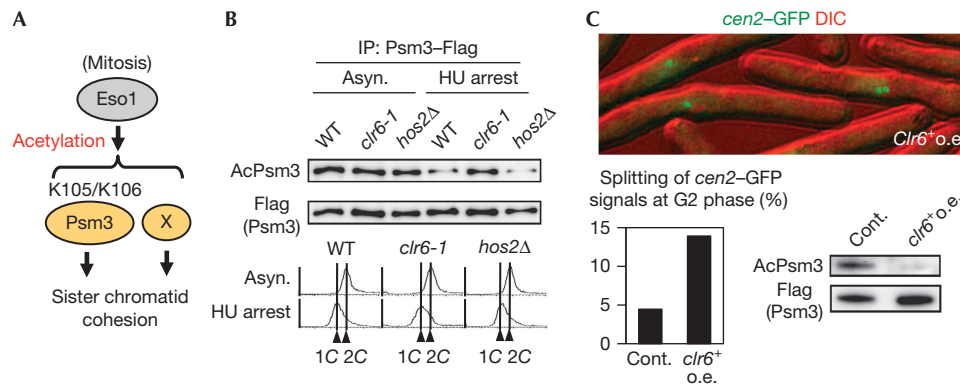
Fig 1 | Clr6 is a lysine deacetylase for the Psm3 subunit of cohesin. (A) Schematic depiction of the acetylation targets of Eso1 in establishing cohesion. X represents a putative acetylation target of Eso1 required for sister chromatid cohesion. **(B)** The indicated cells were cultured at 30 °C and arrested by HU for 4 h. Psm3–Flag protein was immunopurified from the indicated asynchronous (asyn.) or HU-arrested cells. Samples were analysed by immunoblot using anti-AcPsm3 and anti-Flag antibodies (top). DNA content was measured by flow cytometry (bottom). **(C)** *cdc25-22 cen2*-green fluorescent protein (GFP) cells carrying pREP1 (Cont.) or pREP1-*clr6*$^{+}$ (*clr6*$^{+}$ o.e.) were cultured at 25 °C in the absence of thiamine for 24 h and shifted to 36 °C for 4 h to arrest at G2 phase. A photograph of *clr6*$^{+}$ o.e. cells is shown at the top. The number of cells with two *cen2*–GFP dots was counted ($n > 220$). Acetylation status of Psm3 was analysed by immunoblot as in **B** (supplementary Fig S3 online). Cont., control; DIC, differential interference contrast; HU, hydroxyurea; IP, immunoprecipitation; o.e., overexpression; WT, wild type.

acetylated by Eso1 (Eco1 orthologue; Feytout *et al*, 2011; supplementary Fig S1A online). The growth defect of *eso1-H17* (temperature-sensitive allele of *eso1*$^{+}$) or even *eso1Δ* cells is largely restored by expressing Psm3-K105Q, Psm3-K106Q or Psm3-KKQQ, in which K105 and/or K106 are mutated to the acetyl-mimic residue glutamine (supplementary Fig S1B online). Strikingly, fission yeast *psm3-KKRR* cells, in which both K105 and K106 on Psm3 are mutated to arginines, retain substantial viability and sister chromatid cohesion during mitosis (Feytout *et al*, 2011; supplementary Fig S1C–E online). Thus, Eso1 might have an additional acetylation target(s) that promotes the establishment of cohesion in a redundant capacity with Psm3-K105/K106 acetylation (Fig 1A). This second acetylation target might be another site(s) on Psm3 or completely distinct protein. Although the acetylation of cohesin has been studied during the mitotic cell cycle, its role in meiosis is totally unknown. Here we show that acetylation functions in the establishment and maintenance of cohesion at the core centromere in meiosis, which is crucial for setting up mono-orientation of sister kinetochores.

RESULTS AND DISCUSSION
Clr6 is the deacetylase of Psm3-K106 acetylation
As class I HDAC functions in the deacetylation of Smc3 in *Saccharomyces cerevisiae*, we envisaged the possibility that fission yeast class I HDAC (Clr6 or Hos2) might control cohesin deacetylation (Ekwall, 2005). Whereas *hos2Δ* cells are viable, *clr6*$^{+}$ is indispensable for cell growth; thus, we used the temperature-sensitive mutant allele, *clr6-1*, for this assay (Grewal *et al*, 1998). Although the acetylation status of Psm3 was indistinguishable among the asynchronous cultures of wild-type and HDAC mutants, acetylation was significantly increased in *clr6-1* cells compared with others if cells were arrested in early S phase (Fig 1B). Given that Psm3 acetylation declines during anaphase towards G1 phase (Feytout *et al*, 2011; supplementary Fig S2 online), these results indicate that *clr6-1* cells show defects

in Psm3 deacetylation mainly during anaphase. To examine whether Clr6 has an activity to antagonize Psm3 acetylation *in vivo*, we overexpressed Clr6 from a plasmid and examined Psm3 acetylation in G2-arrested cells. Indeed, acetylation levels of Psm3-K106 decreased substantially by the overexpression of Clr6, leading to defects in sister chromatid cohesion (Fig 1C; supplementary Fig S3 online). These results support the notion that Clr6 has the potential to antagonize the Eso1 function by removing Psm3 acetylation. Although the *clr6-1* mutation did not suppress the growth defect in *eso1-H17* cells (supplementary Fig S1F online), this might be tenable because *clr6-1* itself impairs cell growth in a different context from Psm3 deacetylation.

Psm3 acetylation is required for mono-orientation
In fission yeast, sister chromatid cohesion at the core centromere has an essential role in the cosegregation of sister chromatids (mono-orientation) at meiosis I, and is prevented from being established during mitosis (Yokobayashi *et al*, 2003; Yokobayashi & Watanabe, 2005; Sakuno *et al*, 2009). In meiosis, cohesin is acetylated depending on Eso1 also during late S phase and persists until prophase (Fig 2A). To examine the requirement of cohesin acetylation for mono-orientation, we analysed meiotic chromosome segregation in the *eso1-H17* mutant. We marked centromere 2 (*cen2*-green fluorescent protein) on only one of the two homologous chromosomes and monitored its segregation during meiosis I in recombination-deficient (*rec12Δ*) zygotes, as the linkage between homologous chromosomes indirectly affects chromosome orientation (Yokobayashi & Watanabe, 2005). Although *eso1-H17* cells show intact biorientation of sister kinetochores in mitosis at the permissive temperature (supplementary Fig S4 online), mono-orientation of sister kinetochores is entirely abolished in meiosis I at the same temperature (Fig 2B). These results indicate that the acetylation of cohesin is crucial for mono-orientation at meiosis I, and might be the target for regulation of kinetochore orientation. We next examined whether acetylation of Psm3 is required for mono-
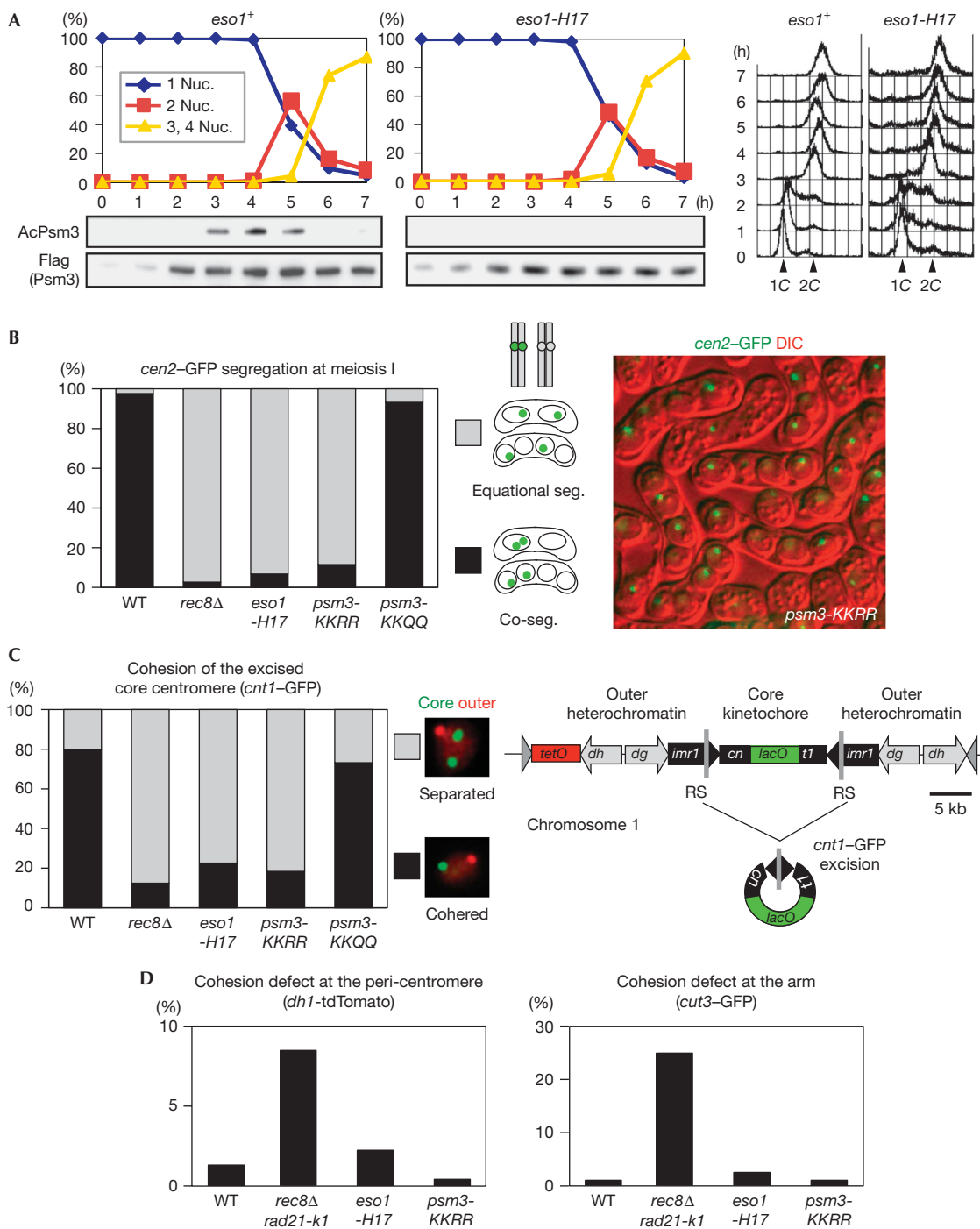
Fig 2 | Eso1-dependent acetylation of Psm3-K105/K106 is required for mono-orientation at meiosis I. (A) Haploid wild-type (WT) and *eso1-H17* cells were induced to undergo synchronous meiosis by inactivating *pat1-114* (Iino & Yamamoto, 1985). Cells were fixed and stained with 4,6-diamidino-2-phenylindole to monitor meiotic nuclear divisions. DNA content was measured by flow cytometry. Acetylation status of Psm3 was analysed by immunoblot. **(B)** Segregation (seg.) of heterozygous *cen2*-GFP at meiosis I was examined in the indicated *rec12Δ* zygotes at 26 °C (*n* > 230). Representative picture showing the *cen2*-GFP segregation patterns in *psm3-KKRR* cells. **(C)** Cohesion of the excised core centromere 1 in prophase I was examined in the indicated zygotes at 30 °C (*n* > 69). Schematic representation of centromere 1, in which a central core (*cnt1*) is surrounded by innermost repeats (*imr1*) and outer repeats (*dg* and *dh*), and its engineered version designed for excision (Sakuno *et al*, 2009). The split of *cnt1* by an insertion is designated *cn* and *t1*. **(D)** Cohesion defect at pericentromeric and arm regions was examined in the indicated cells by arresting at prophase I (by the *mei4Δ* mutation) at 26 °C. Strains marked with *dh1*-tdTomato or *cut3*–GFP were crossed with unmarked strains and the number of cells with two dot signals in a horsetail nucleus was counted (*n* > 150). We used *rec8Δ rad21-K1* as a cohesion defective control (Yokobayashi *et al*, 2003). DIC, differential interference contrast; nuc., nucleus.

orientation. Accordingly, mono-orientation is largely abolished in *psm3-KKRR* cells, but preserved intact in *psm3-KKQQ* cells (Fig 2B).

We next examined whether the acetylation of Psm3 by Eso1 is indeed crucial for cohesion at the core centromere, the canonical mono-orientation pathway in fission yeast. To monitor this cohesion, we popped out the core centromere from the chromosome during prophase I and visualized the cohesion of the excised centromeres (Sakuno *et al*, 2009; Fig 2C). The results indicate that cohesion at the core centromere is abolished in *psm3-KKRR* cells or *eso1-H17* cells as in *rec8Δ* cells, whereas it remains intact in *psm3-KKQQ* cells (Fig 2C). Chromatin immunoprecipitation assays indicate that the cohesion defect at the core centromere is not caused by displacement of Rec8 or Moa1 (supplementary Fig S5 online), suggesting that cohesion establishment itself is impaired in *psm3-KKRR* or *eso1-H17* cells. By observing centromere-marked *dh1*-tdTomato in meiotic prophase, we confirmed that the cohesion at pericentromeres is preserved in *psm3-KKRR* or *eso1-H17* cells (Fig 2D), consistent with the fact that sister chromatids segregate equationally rather than randomly in these cells (Fig 2B). Moreover, arm cohesion also remained largely intact during prophase in *psm3-KKRR* or *eso1-H17* cells (Fig 2D). We conclude that the requirement of Psm3 acetylation for sister chromatid cohesion is most pronounced at the core centromere, which is essential for the mono-orientation of kinetochores at meiosis I.

Eso1 and Moa1 act at different stages in prophase I

It is unknown how the meiosis-specific kinetochore protein Moa1 contributes to core centromere cohesion (Yokobayashi & Watanabe, 2005; Sakuno *et al*, 2009). Considering the fact that acetylation of cohesin might be involved in this regulation, we next examined the functional relevance of Moa1 to the acetylation pathway. The Eso1 acetyltransferase is expressed throughout meiosis (Fig 3A), whereas acetylation of cohesin is detected during prophase I (Fig 2A, 3–5 h). In contrast, Moa1 is induced during late S phase (Yokobayashi & Watanabe, 2005; also see Fig 3C). By expressing *eso1*+ using the *moa1*+ promoter (P_{moa1}), we could eliminate Eso1 expression during meiotic G1–S phase (Fig 3A, 0–3 h). We then expressed this P_{moa1}–*eso1*+ allele in *eso1-H17* cells, in which mono-orientation is intrinsically abolished. Consequently, the P_{moa1}–*eso1*+ allele failed to restore the full level of mono-orientation in *eso1-H17* cells, whereas the control P_{eso1}–*eso1*+ allele fully restored mono-orientation (Fig 3B). These results indicate that the acetylation of cohesin by Eso1, which occurs mainly at the late S phase (Fig 2A), is important in establishing cohesion, at least, at the core centromere. Partial activity of the P_{moa1}–*eso1*+ allele indicates that Eso1 was not completely abolished during S phase even in this allele, or that Eso1 could function also after S phase (see below).

Moa1 is produced during premeiotic S phase and loaded to kinetochores depending on DNA replication (Yokobayashi & Watanabe, 2005; Fig 3C). To examine whether Moa1 loading needs to be coupled to DNA replication for its function, we replaced the promoter of *moa1*+ with that of *spo6*+, which is activated long after premeiotic DNA replication but before meiosis I division (Watanabe *et al*, 2001). Indeed, the engineered P_{spo6}–*moa1*+ allele produced a physiological level of Moa1 protein after DNA replication (Fig 3C). Nevertheless, Moa1 localized properly at kinetochores before meiosis I division (Fig 3D), and

perfectly fulfilled its function (Fig 3E). These results indicate that Moa1 works only after DNA replication in the 'maintenance' of cohesion, rather than in its 'establishment', which couples with replication-dependent cohesin acetylation by Eso1.

The Clr6 deacetylase antagonizes Eso1 in meiosis

We next examined the contribution of cohesin deacetylation to mono-orientation by testing the genetic interaction between *clr6-1* and *eso1-H17* mutations during meiosis. The mono-orientation defect in *eso1-H17* cells was substantially (~50%) suppressed by *clr6-1* (Fig 4A). By performing the centromere excision assay, we confirmed that this suppression was the result of the recovery of cohesion at the core centromere (Fig 4B). Moreover, the mono-orientation defect in *eso1-H17* cells was largely suppressed by *psm3-KKQQ* (~95%) and again this suppression was mediated by the restored cohesion at the core centromere (Fig 4A,B). Because *psm3-KKRR* cells show complete impairment in mono-orientation as in *eso1-H17* cells (Fig 2B), these results indicate that the defect of *eso1-H17* in mono-orientation originates from the inability of Psm3 to be acetylated. To investigate whether the target of *eso1-H17* suppression by *clr6-1* is limited to Psm3 deacetylation, we examined the suppression in a *psm3-KKRR* background. *clr6-1* suppressed *eso1-H17* even in *psm3-KKRR* cells, albeit less efficiently than in *psm3*+ cells (Fig 4A). Thus, Clr6 antagonizes the Eso1 function in establishing mono-orientation by deacetylating not only Psm3 but also an unknown Eso1 target (see below).

Acetylation in Moa1-dependent mono-orientation

Because of the crucial importance of the Psm3 acetylation for mono-orientation, we wondered whether Moa1 might be required to sustain the Psm3 acetylation. To examine this possibility, we introduced the *psm3-KKQQ* mutation into *moa1Δ* cells and monitored chromosome segregation at meiosis I. In contrast to *eso1-H17* cells, the mono-orientation defect in *moa1Δ* cells was not suppressed at all by *psm3-KKQQ*. Strikingly, however, the *moa1Δ* defect was suppressed partially (~30%) by *clr6-1* (Fig 4C). The independence of this suppression and Psm3 acetylation was further validated by showing that *clr6-1* could suppress *moa1Δ* even in the background of *psm3-KKRR* (supplementary Fig S6 online). The centromere excision assay confirmed that the mono-orientation restored by *clr6-1* is mediated by the canonical cohesion pathway rather than another nonspecific effect on the kinetochores or spindle (Fig 4D). Consistently, suppression by *clr6-1* is not observed in *rec8Δ* cells (supplementary Fig S6 online). These results indicate that an acetylation target(s) other than Psm3-K105/K106 contributes to cohesion at the core centromere at meiosis I, and that this acetylation might be decreased in *moa1Δ* cells by the action of Clr6 (Fig 5). Because *eso1Δ* is not completely suppressed by *psm3-KKQQ* in meiosis (supplementary Fig S7 online), Eso1 might be responsible for the acetylation of this non-Psm3-K105/K106 substrate (Fig 5). Accordingly, *clr6-1* does not restore mono-orientation in *eso1Δ psm3-KKQQ moa1Δ* cells, whereas it suppresses *eso1*+ *psm3-KKQQ moa1Δ* cells (supplementary Fig S8 online), indicating that the acetylation of the non-Psm3-K105/K106 substrate counteracted by *clr6-1* in a *moa1Δ* background is indeed dependent on Eso1. Overall, these results imply that the antagonistic interaction between Eso1 and Clr6 in regulating cohesion is much more
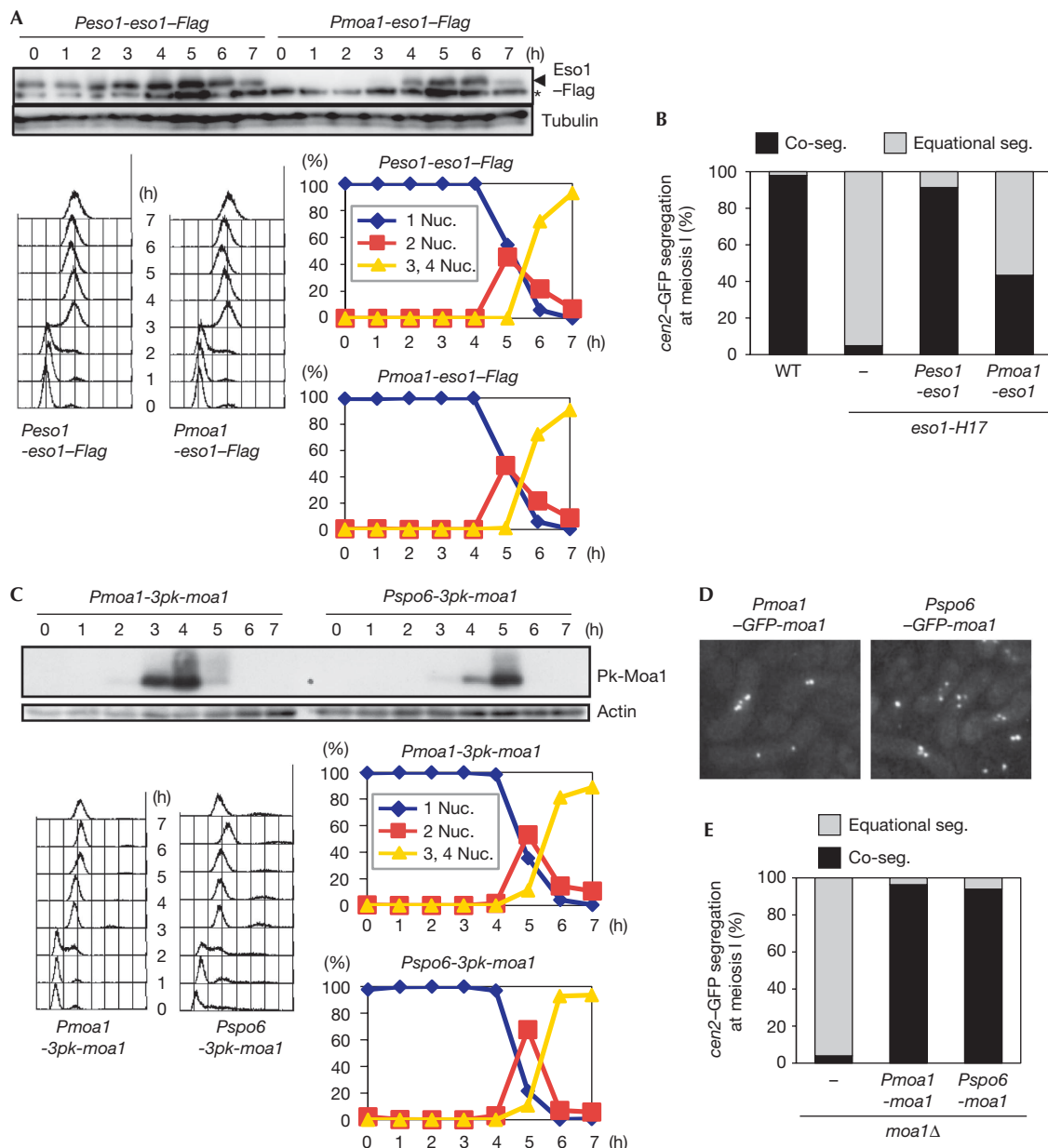
Fig 3 | Eso1–Psm3 acetylation functions during premeiotic S phase, whereas Moa1 functions after DNA replication. (**A**) Immunoblotting of Eso1–Flag using anti-FLAG antibody (top). The asterisk indicates a nonspecific band. The indicated cells were induced to undergo synchronous meiosis by *pat1-114* inactivation. The progression of meiosis was monitored by measuring DNA content by flow cytometry (left bottom) and the number of nuclei (right bottom). (**B**) Segregation (seg.) of heterozygous *cen2*–GFP at meiosis I was examined in the indicated *rec12Δ* zygotes at 26 °C (*n* > 150). (**C**) Immunoblotting of 3Pk-Moa1 using anti-Pk antibody (top). The indicated cells were induced to undergo synchronous meiosis and examined as in **A**. (**D**) Representative pictures showing GFP–Moa1 localization at meiosis I in the indicated strains. (**E**) Segregation of heterozygous *cen2*–GFP at meiosis I was examined in the indicated *rec12Δ* zygotes at 30 °C (*n* > 150). Nuc., nucleus; WT, wild type.

obvious in meiosis than in mitosis; the meiotic situation surrounding Eso1 and acetylation targets is reminiscent of that of mitosis (Figs 1A and 5).

It has been shown that the requirement of cohesin acetylation is counteracted by the Wapl protein (Ben-Shahar *et al*, 2008; Rowland *et al*, 2009; Sutani *et al*, 2009; Uhlmann, 2009; Feytout *et al*, 2011). We then examined whether deletion of the *wpl1* gene (encoding Wapl homolog) can suppress the mono-orientation

defect in Psm3 acetylation-defective or *moa1Δ* cells. Although the mono-orientation defect in *eso1-H17*, *eso1Δ* and *psm3-KKRR* cells was largely suppressed by *wpl1Δ*, that of *moa1Δ* cells was hardly suppressed (Fig 4E). These results reaffirm that cohesion defects in *moa1Δ* do not originate through Psm3 acetylation.

In summary, our results indicate that cohesion at the core centromere is established primarily by the Eso1-dependent acetylation of Psm3, but that the maintenance of this cohesion

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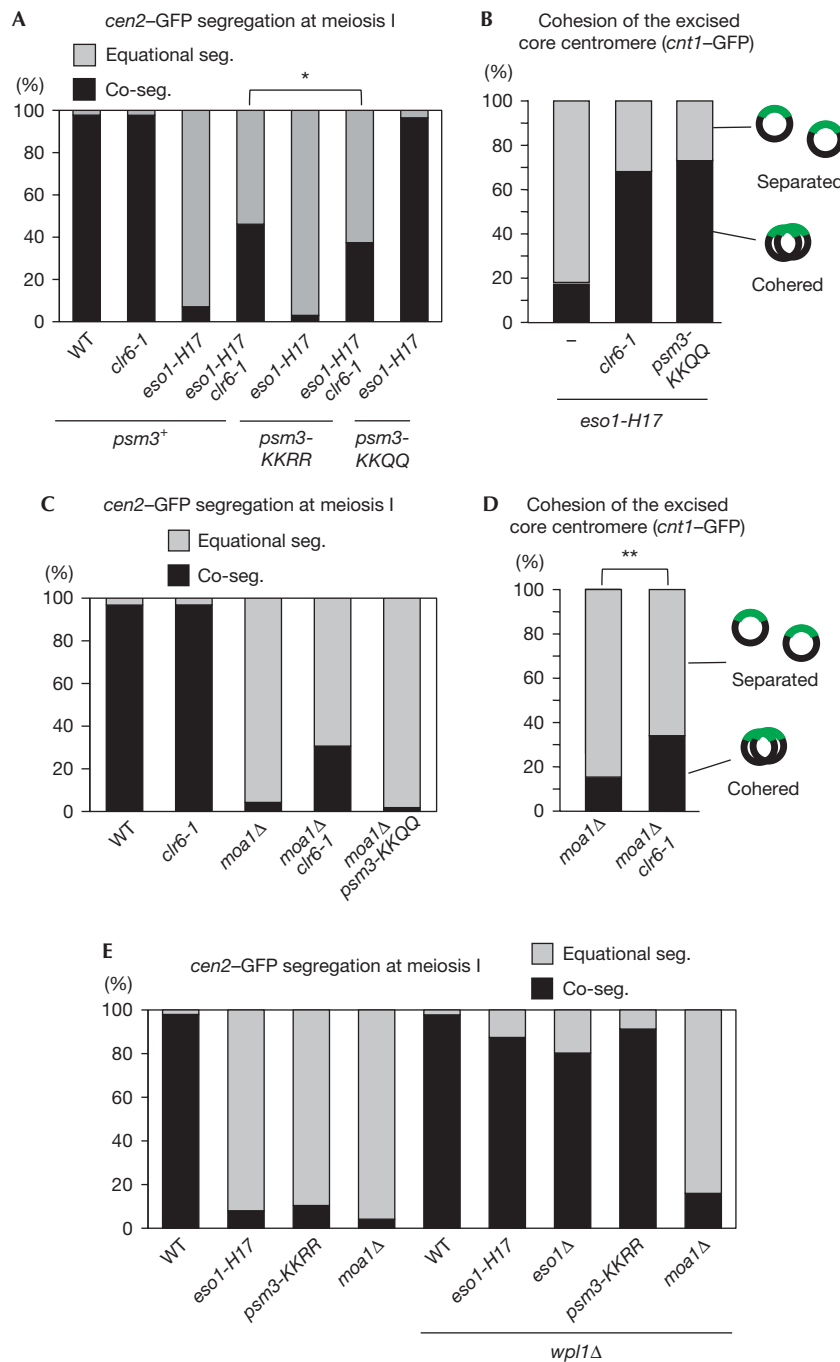
Fig 4 | The *clr6-1* mutation suppresses the mono-orientation defect in *eso1-H17* and *moa1∆* cells. (A,C,E) Segregation (seg.) of heterozygous *cen2*-GFP at meiosis I was examined in the indicated *rec12∆* zygotes (*n* > 150). (B,D) Cohesion of the excised core centromere 1 in prophase I was examined in the indicated zygotes (*n* > 79). Experiments in **A**, **B** and **E** were performed at 26 °C, whereas those in **C** and **D** were performed at 30 °C. *$P < 0.05$; **$P < 0.01$ (χ^2-test). WT, wild type.

requires an additional acetylation of unidentified substrate(s) that can be antagonized by deacetylase Clr6 but might be protected by the meiosis-specific kinetochore factor Moa1 (Fig 5). Although further studies are required to validate this model, our study suggests that protein acetylation is an important target for the regulation of kinetochore orientation during meiosis I.

METHODS

Yeast strains, plasmids and antibodies. Plasmids and antibodies are described in the supplementary information online; the genotypes of the strains are listed in supplementary Table S1 online. Methods used to generate the strains are described in supplementary methods online.
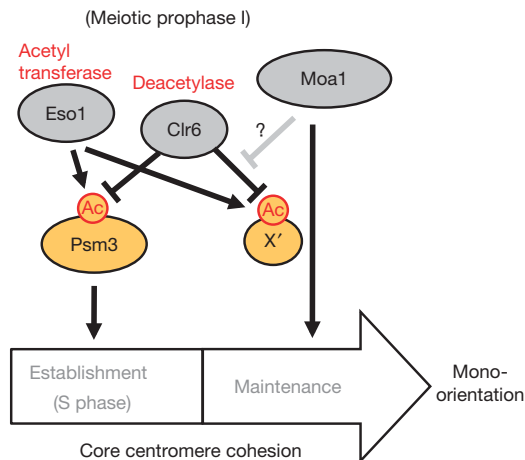
(Meiotic prophase I)

Fig 5 | Schematic depiction of the regulation of core centromere cohesion by acetylation during meiotic prophase I. X′ represents a putative acetylated protein required for core centromere cohesion. Moa1 might function to maintain the acetylation of X′ partly by antagonizing Clr6 and/or might function in parallel with this acetylation to maintain the cohesion.

Medium. Complete medium yeast extract or minimal medium (MM) was used for the culture of *Schizosaccharomyces pombe* strains. Sporulation agar plate was used to induce meiosis and for microscopic examination. MM and MM-N (lacking nitrogen) containing 1% glucose were used for synchronous meiosis and for expressing $clr6^+$ from the pREP1 plasmid.

Flow cytometry. Methanol-fixed cells were washed twice with 50 mM Na-citrate (pH 7.0) and treated with 100 μg/ml RNaseA for 3 h at 37 °C. Cells were incubated with 10 μg/ml propidium iodide for 1 h at 4 °C, and then analysed by FACS Calibur (BD Biosciences) after brief sonication.

Detection of Psm3 acetylation. To analyse the acetylation status of Psm3, anti-AcPsm3 antibodies were generated using acetylated peptides (TIGLK(AcK)DEY) spanning the Psm3 acetylation site at amino acid 106 of *S. pombe*. The Flag-tagged Psm3 was immunoprecipitated from cell extracts using anti-Flag M2 monoclonal antibody-conjugated agarose (Sigma), and analysed by immunoblot probed with anti-Flag M2 (Sigma) and anti-AcPsm3 antibodies.

Protein preparation and immunoblotting. Cells were boiled in homogenization buffer for 5 min and then disrupted with glass beads using a Multi-bead shocker (Yasui Kikai). Total cell extracts were boiled in SDS-sample buffer and subjected to immunoblotting. The following antibodies were used: mouse monoclonal antibodies against Flag (1:1,000, M2; Sigma), Pk (1:1,000, MCA1360; Serotec) and TAT-1 (1:5,000), and goat polyclonal antibodies against actin (1:1,000, Santa Cruz).

Assay for sister chromatid cohesion at the core centromere. Cohesion of the excised core centromere 1 in prophase I (arrested by *mei4Δ*) was examined as previously described (Sakuno et al, 2009).

Chromosome segregation assays. To observe sister chromatid segregation during meiosis I, we cultured opposite mating-type cells, one marked with green fluorescent protein or tdTomato and the other unmarked, and mixed them before spotting them onto sporulation agar plate.

Supplementary information is available at EMBO *reports* online (http://www.emboreports.org).

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