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Sister chromatid segregation in meiosis II
Deprotection through phosphorylation

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Abbreviations: APC/C, anaphase promoting complex/cyclosome; Bub1, Budding uninhibited by Benomyl 1; Cdk, cyclin-dependent kinase; CSF, cytostatic factor; I2PP2A, inhibitor 2 of PP2A; MPF, M-phase promoting factor; PP2A, protein phosphatase 2A; SAC, spindle assembly checkpoint; Sgo, shugoshin/MEI-S332

Meiotic divisions (meiosis I and II) are specialized cell divisions to generate haploid gametes. The first meiotic division with the separation of chromosomes is named reductional division. The second division, which takes place immediately after meiosis I without intervening S-phase, is equational, with the separation of sister chromatids, similar to mitosis. This meiotic segregation pattern requires the two-step removal of the cohesin complex holding sister chromatids together: cohesin is removed from chromosome arms that have been subjected to homologous recombination in meiosis I and from the centromere region in meiosis II. Cohesin in the centromere region is protected from removal in meiosis I, but this protection has to be removed—deprotected—for sister chromatid segregation in meiosis II. Whereas the mechanisms of cohesin protection are quite well understood, the mechanisms of deprotection have been largely unknown until recently. In this review I summarize our current knowledge on cohesin deprotection.

Introduction

Haploid gametes are derived from diploid germ cells through two rounds of specialized cell divisions, meiosis I and II, without intervening S-phase. Prior to entry into meiosis I, homologous chromosomes (originating from each parent) pair and undergo meiotic recombination, thereby generating new genetic combinations in the offspring. Excellent reviews on meiotic recombination have been published and are beyond the scope of this review (for example, see refs. 1–4). After resolution of recombination products in prophase, entry into meiosis I takes place. During meiosis I, homologous chromosomes, and in meiosis II, sister chromatids are segregated into daughter cells. Whereas meiosis II can be compared with a mitotic division, meiosis I is fundamentally different due to the fact that sister chromatids are segregated to the same pole of the bipolar spindle.[3]

Errors in chromosome segregation during the meiotic divisions have dire consequences, because they lead to the generation of aneuploid embryos harboring the wrong number of chromosomes. In humans, female meiosis is surprisingly error-prone, and furthermore, the high error rate drastically increases with age.[5-7] To get insights into what might go wrong so frequently in human oocytes, both age-related and independent of age, we need to understand the basic mechanisms and their limits in the control of chromosome and sister chromatid segregation. In this review, I will focus mainly on recent work dealing with sister chromatid segregation in meiosis II.

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Meiotic Divisions

Prior to meiosis I, meiotic recombination takes place between chromosomes of maternal and paternal origin. Recombination events between non-homologous sister chromatids that have been resolved by double-Holliday junctions become visible as chiasmata upon entry into the first meiotic division, and they constitute essential structures holding the condensed chromosomes (bivalents) together.[3,8] Each chromosome consists of two sister chromatids that are held together through cohesion formed by cohesin proteins that are entrapping sister chromatids through a ring-like structure, according to the widely accepted "ring model."[9,10] Cohesins are also thought to stabilize chiasmata and thereby maintain chromosomes together.[5] Therefore at entry into meiosis I, bivalents are held together through chiasmata, and sister chromatids by cohesion. Crucially, both paired sister chromatids are oriented toward the same pole in a monopolar fashion.[11,12] At the metaphase-to-anaphase transition, cohesin along chromosome arms, where recombination has taken place, has to be removed to allow the separation of chromosomes. Importantly, cohesion has to be maintained in the centromere region, where no recombination takes place, to prevent the precocious separation of sister chromatids. Meiosis II takes place immediately after the first meiotic division without intervening S-phase. Here, sister chromatids are oriented toward opposite spindle poles in a bipolar fashion, such as in mitosis. It is during meiosis II, and only then, that centromeric cohesion is removed, and sister chromatids are segregated.[3,13]

In vertebrate mitosis, cohesin is first removed from chromosome arms by the so-named prophase pathway. This requires the cohesin-associated proteins Wapl and Pds5 and phosphorylation

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of the cohesin subunit SA2 by Plk1 kinase.[10,14-20] Remaining cohesin (mainly in the centromere region) has to be removed by the thiol-protease separase, which cleaves Scc1, the α-kleisin subunit of the cohesin complex.[21-23] Separase-dependent cleavage is essential for mitotic cell cycle progression.[24,25] In metaphase, when all kinetochores (the attachment sites for microtubules on chromosomes) are correctly attached to the opposite poles of the spindle, a checkpoint, the so-named spindle assembly checkpoint (SAC), is inactivated (for SAC control please refer to existing excellent reviews in refs. 26 and 27). The SAC keeps the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin kinase, inactive toward its substrates Cyclin B and Securin. Once the SAC has been satisified, APC/C-dependent ubiquitination targets Cyclin B1 and Securin for degradation by the 26S proteasome.[28] Both proteins inhibit separase,[29-32] and therefore separase can only be active and remove cohesins when the SAC has been satisfied, ensuring that chromosomes are correctly attached to the spindle. In mammalian meiosis, no prophase-dependent removal of cohesin was shown to take place, and only separase-dependent cleavage is required for chromosome segregation.[33] As in mitosis, separase activation requires inactivation of the SAC, and the degradation of Cyclin B and Securin.[34-38] Importantly, the mitotic cohesin subunit Scc1 is substituted with a meiotic form, named Rec8, which is a substrate of separase.[33,39,40] Crucially, centromeric Rec8 is protected from separase cleavage in meiosis I, and therefore cohesion is not removed at centromeres, so that sister chromatids remain associated throughout the first division. In meiosis II, separase acquires the capacity to cleave centromeric Rec8 and therefore allows the separation of sister chromatids.[3] In other words, Rec8 is deprotected.[41] So how is this deprotection of centromeric Rec8 brought about in meiosis II?

Centromeric Cohesin Protection

Most of what we know about the molecular mechanisms of chromosome segregation during the meiotic divisions stems from pioneering work in yeast. Combining genetics, biochemistry and, more recently, live imaging in this simple organism provided a more complete picture of meiotic chromosome segregation than in any other model organism. I will therefore describe our current knowledge concerning cohesin protection in yeast first.

In budding and fission yeast, Rec8 has to be phosphorylated at multiple sites by two kinases, Cdc7-Dbf4 and casein kinase 1, for cleavage by separase.[41-43] Protection of centromeric cohesin requires Shugoshin (Sgo1)-dependent recruitment of PP2A phosphatase (containing the regulatory subunit Rts1)[44,45] to the centromere in meiosis I. In contrast to the unique Sgo1 in *S. cerevisiae*, *S. pombe* harbors two Shugoshin proteins (Sgo1 and Sgo2), with Sgo1 being required for centromeric cohesin protection in meiosis.[46,47] In both budding and fission yeast, PP2A counteracts phophorylation of Rec8 at the centromere and thereby prevents Rec8's cleavage by separase at the centromere, but not on chromosome arms.[41-44,46-49] Accordingly, phosphomimicking mutants of Rec8 are not protected from cleavage at the centromere, whereas non-phosphorylatable mutants of Rec8 cannot be cleaved by separase.[41,43] The requirement of Rec8 phosphorylation by Cdc7-Dbf4 and casein kinase 1 for separase-dependent cleavage is meiosis-specific and different from the situation in mitosis, where Scc1 is phosphorylated by Cdc5 (Plk1 in mammalian cells) for efficient cleavage.[50,51]

So how is this protective mechanism removed in meiosis II? The question is intriguing, given the fact that in budding yeast, Drosophila and mammals the respective Shugoshin proteins[52] required for Rec8 protection are still found in the vicinity of centromeres in meiosis II.[48,49,53-57] Is de novo phosphorylation of Rec8 indeed required for meiosis II sister chromatid segregation? And if yes, which kinases are responsible for this phosphorylation, and how do they overcome the counteracting effect of PP2A?

In mammalian meiosis the molecular mechanisms underlying cohesin protection have been less well characterized, but seem to be similar to yeast. Also, in mouse oocytes Rec8 has to be cleaved by separase.[33,58-60] Sgo2 clearly is required for protection of centromeric cohesin in male and female meiosis, as has been demonstrated by analyzing meiosis in Sgo2 (Sgol2) mutant mice: Sgo2 is essential for correct chromosome segregation in male and female meiosis I, but is not required during the mitotic divisions.[61] Knockdown of Sgo2 equally leads to loss of centromeric cohesin protection in oocyte meiosis I and loss of PP2A from centromeres.[53] Localization of the catalytic subunit of PP2A to the centromere region in oocytes,[53] and of the regulatory PP2A subunit B56 to mitotic centromeres,[45] strongly suggests that, as in yeast, PP2A-B56 is required for chromosome segregation in meiosis I. Inhibiting PP2A (but not only PP2A complexes interacting with Sgo2!) with okadaic acid indeed induces precocious sister chromatid segregation in meiosis I.[62,63] A caveat of using a general PP2A inhibitor as an experimental tool is the fact that presumably all PP2A complexes present in the cell are inhibited. Given the multitude of roles occupied by different PP2A complexes during cell division,[64] these experiments as well as experiments using a dominant-negative form of the PP2A catalytic subunit[63] are therefore difficult to interpret. Mapping Rec8 phosphorylation sites or determining whether Rec8 is phosphorylated in mammalian meiosis I and II has not been possible for technical reasons. Therefore, the formal proof for the conservation of the mechanism for centromeric cohesin protection in meiosis is still missing in mammals. Importantly though, it has been shown that all three PP2A subunits (scaffold, catalytic and regulatory B56 subunit) required for PP2A-B56 activity[65] are localized to centromeres in oocyte meiosis I, but once again, also in meiosis II.[57]

Centromeric Cohesin Deprotection

So how is centromeric cohesin deprotection regulated in meiosis II, if PP2A is still localized to centromeres? Two not necessarily mutually exclusive models have been proposed for mammalian meiosis: in the first model, differences in kinetochore attachment between meiosis I and II (monopolar or bipolar, respectively) lead to subtle changes of Sgo2 localization that would pull associated PP2A away from centromeric cohesin and therefore allow Rec8's phosphorylation to take place.[53,55] Indeed, in fission yeast mutants that are defective in monopolar attachment due to a mutation in the SAC protein Bub1, and which attach sister chromatids in a

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bipolar fashion, centromeric cohesin is not protected, even when Sgo1 is correctly localized to the kinetochore.[66] It seems that also in mouse oocytes, a univalent chromosome in meiosis I whose sisters are attached in a bipolar manner can separate the two sister chromatids at the first meiotic division.[67-69] On the other hand in budding yeast, monopolin mutants that biorient sister chromatids in meiosis I cannot separate sisters, because centromeric cohesin is still protected in a Sgo1-dependent way.[70] Furthermore in *S. pombe* the absence of chiasmata leads to a bipolar attachment of sister chromatids in meiosis I and, in contrast to the situation observed in Bub1 mutants,[66] also to a failure in removing centromeric cohesin and separating sisters.[71-73]

In mammalian meiosis, subtle changes in the localization of Sgo2 in meiosis I and II are visible on squashes of spermatocytes and whole-mount immunofluorescence of oocytes.[53,55] In short, in meiosis I, a colocalization of cohesin with Sgo2 is observed, whereas in meiosis II, Sgo2 is relocalized—apparently in a tension-dependent manner—toward the outside of the centromere, and colocalization with centromeric cohesin is therefore lost. According to the first model, relocalization of Sgo2 takes place in late metaphase II in oocytes that are competent to undergo metaphase II-to-anaphase II transition upon fertilization. It is intriguing that earlier in metaphase, when paired sister chromatids are already aligned at the metaphase plate, centromeric Rec8 and Sgo2 still colocalize, even though kinetochores are already attached in a bipolar manner and oriented toward the opposite poles.[53] Maybe in early metaphase I, the tension applied on paired kinetochores by the newly formed metaphase II spindle is not as strong as later in metaphase II, when oocytes are competent to undergo anaphase II? Indeed, displacement of Sgo2 from Rec8 occurred in parallel with an increase in interkinetochore distance between sisters. On the other hand, PP2A has been shown to colocalize with centromeric Rec8 in late metaphase II mouse oocytes, competent to undergo the metaphase-to-anaphase II transition in a recent study.[57] Differences in stainings may be due to different staining protocols used and differences in the amount of tension maintained on kinetochores throughout the staining procedure. Adding to the complexity is the fact that recently it has been shown that PP2A-B56 can be localized to the centromeres in a Sgo-independent manner in mitotic cells, insinuating that Sgo2 may not always reflect PP2A's localization.[74]

The second model of how centromeric cohesin deprotection is brought about proposes that a PP2A inhibitor at the centromere is counteracting PP2A exactly where Rec8 is localized in metaphase II. Indeed, a known PP2A inhibitor named I2PP2A[75,76] (also named Setβ) was recently identified as an interaction partner of Shugoshin proteins,[44,57,77] and in a PP2A-associated complex after chemical crosslinking.[77] In mouse oocytes, endogenous I2PP2A is colocalizing with PP2A and Rec8 in meiosisII, in agreement with a potential role in inhibiting PP2A exactly where centromeric Rec8 is found in metaphase II.[57] Endogenous I2PP2A is also found in the centromere region in meiosis I but does not colocalize with Rec8. Morpholino-mediated knockdown of I2PP2A prevents sister chromatid segregation in meiosis II, even though metaphase-to-anaphase transition takes place,[57] and overexpression of I2PP2A in meiosis I induces precocious sister

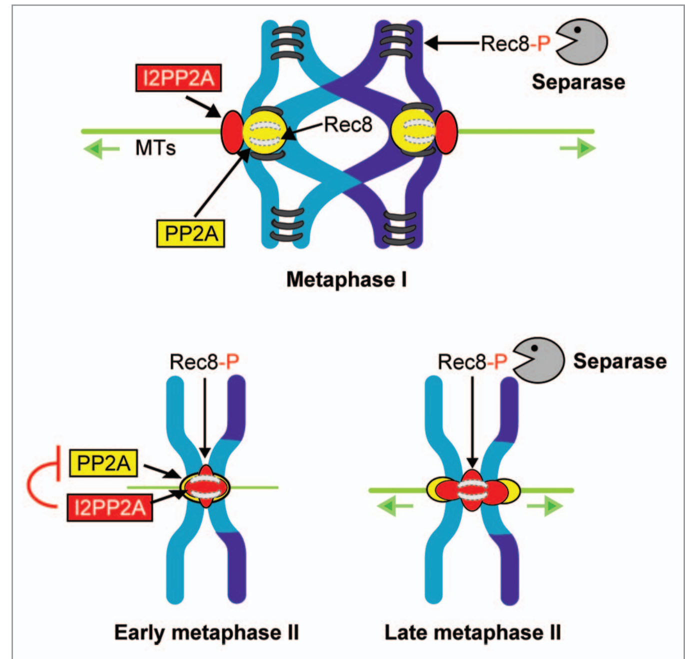

Figure 1. Scheme of how deprotection of centromeric cohesin is brought about through a combination of PP2A inhibition by I2PP2A and bipolar tension applied on sister kinetochores in meiosis II. In metaphase I, I2PP2A (in red) is localized to the centromere region, but does not colocalize with the three PP2A subunits constituting active PP2A (yellow). In metaphase II, I2PP2A is found exactly where centromeric cohesin (gray bars) remains. It is therefore localized exactly where PP2A has to be inhibited to avoid dephosphorylation of Rec8. In late metaphase II, bipolar tension applied on sister kinetochores moves potentially remaining PP2A complexes that are still free of inhibitory I2PP2A further away from Rec8. Cohesins, black bars; cohesins not visible due to PP2A or I2PP2A localization, gray bars; Rec8, unphosphorylated Rec8; Rec8-P, phosphorylated Rec8 that can be cleaved by separase; MTs, microtubules.

separation.[78] Importantly though, the change in I2PP2A localization at meiosis I and meiosis II centromeres does not depend on monopolar vs. bipolar tension applied on sister kinetochores.[57]

How can we reconcile the two models? Far from opposing each other, we can imagine that two different mechanisms are at work to ensure that no active PP2A is remaining between sister centromeres at the same place as Rec8. We propose that I2PP2A inhibition of PP2A is required to permit efficient phosphorylation of Rec8 in metaphase II, whereas physical removal of Sgo2 just before anaphase II onset is a back-up mechanism that ensures that no phosphatase activity in the vicinity of Rec8 is remaining (**Fig. 1**).

I2PP2A has also been identified as Set/TAF-Iβ, a component of the INHAT (inhibitor of acetyltransferases) complex, which masks histones from being acetyltransferase substrates.[79] Therefore, it was also possible that I2PP2A's role in meiosis was independent of its inhibitory activity on PP2A and, alternatively, due to its role as a component of the INHAT complex. In mitosis, sister chromatid cohesion is lost in a separase-independent manner upon knockdown of HDAC3 (histone deacetylase 3), which deacetylates centromeric histone H3K4.[80] Knockdown

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of HDAC3 therefore induces precocious sister separation,[80] and more generally, histone hyperacetylation was shown to interfere with chromosome segregation in mammalian oocyte meiosis I.[81-83] If I2PP2A had a role as a component of the INHAT complex in meiosis II by preventing acetylation of histone H3K4, I2PP2A knockdown in oocytes were expected to relieve inhibition of histone acetylation and thereby induce loss of sister chromatid cohesion, such as observed upon knockdown of HDAC3. Importantly, this is not what has been observed: morpholino-oligo-mediated knockdown of I2PP2A prevents sister separation in meiosis II,[57] strongly suggesting that I2PP2A functions as an inhibitor of PP2A and not as a component of the INHAT complex on meiotic centromeres.

Cyclin A2 is Required for Sister Chromatid Segregation in Meiosis II

It is fascinating that in the same cytoplasm, two completely different segregation patterns take place in meiosis I and II. In budding yeast, the meiotic program with monopolar attachment, suppression of S-phase between meiosis I and II and chromosome segregation before sister chromatid segregation depends on the suppression of mitotic cell cycle regulators in meiotic prophase.[84] Progression through mitosis and meiosis is regulated through rise and fall of MPF (M-phase promoting factor) activity and counterbalance by phosphatase activities.[64] How do mitotic kinases support the correct pattern of chromosome and sister chromatid segregation during the meiotic divisions? Inappropriate expression during oocyte prophase arrest of Cyclin A2 in Drosophila[85] and of Cyclin E in *C. elegans*[86] perturbs the meiotic cell cycle and leads to the separation of sister chromatids. In *S. cerevisiae*, untimely expression of the B-type cyclin Clb3 in prophase I causes failures in monopolar attachment and therefore sister chromatid segregation.[87,88] In mouse oocytes, constitutive presence of Cyclin A2-associated kinase activity leads to the loss of centromeric cohesion protection in meiosis I and sister separation, but in contrary to budding yeast with correct monopolar attachments of sisters.[89] This mouse oocyte-specific phenotype of stable Cyclin A2-expressing oocytes allowed the discovery of an essential role that Cyclin A2 plays in mammalian female meiosis II, namely its requirement for the separation of sister chromatids, which cannot come appart without functional Cyclin A2. Cohesin remains protected in metaphase II when Cyclin A2 is inhibited, and constitutive presence of Cyclin A2-associated kinase activity leads to spontaneous separation of sister chromatids in a separase-dependent manner in meiosis I.[89] This meiosis-specific role of Cyclin A2 is intriguing and appears specific to mammalian oocytes.

In accordance with a role in the deprotection of centromeric cohesin in meiosis II, endogenous Cyclin A2 is localized to centromeres throughout the metaphase-to-anaphase transition of meiosis II. To make matters more complicated, endogenous Cyclin A2 is also found at centromeres in meiosis I but, importantly, not during the metaphase-to-anaphase I transition[89] (**Fig. 2A**). How is Cyclin A at centromeres protected from APC/C dependent degradation beyond prometaphase, and what are Cyclin A2's substrates? At the metaphase-to-anaphase transition, the APC/C is active to ubiquitinate and induce degradation of the APC/C substrates Cyclin B1 and Securin upon spindle assembly checkpoint satisfaction, and even before in prometaphase to target Cyclin A for degradation in mitotic cells, so there has to be some protective mechanism prohibiting the APC/C from targeting Cyclin A2 at centromeres in meiosis.[28] Concerning CyclinA2's substrates at the centromere, we can only speculate as to their identity: Cyclin A2 may directly or indirectly mediate phosphorylation of centromeric Rec8, and thereby render Rec8 cleavable for separase. Cyclin A2 may phosphorylate I2PP2A so that it can interact with PP2A (it has been shown previously in a different context that phosphorylation of I2PP2A is required for its interaction with the catalytic subunit of PP2A).[90] PP2A itself may be a target of Cyclin A2. A recent study has identified Ppp2r1a (which corresponds to a B56 regulatory subunit of PP2A) as an interaction partner of Cyclin A2 in G_2 cells by immunoprecipitation and mass spectrometry.[91] It is therefore possible that Cyclin A2 influences PP2A's phosphatase activity (either directly, or indirectly) at the centromere in meiosis II. Sgo2 and PP2A localization were not affected in stable Cyclin A2-expressing oocytes that were maintained in a metaphase I arrest, excluding that CyclinA2 removes PP2A from the centromere.[89] Moreover, Cyclin A2 inhibition cannot prevent sister separation induced by PP2A inhibition by okadaic acid. With the reserve that inhibition of total PP2A activity has other pleiotropic effects, this result may indicate that Cyclin A2 functions upstream of PP2A and requires PP2A to induce sister separation.[89]

So how does Cyclin A2 induce sister chromatid segregation only in meiosis II, if it is localized to centromeres in meiosis I as well? As mentioned above, Cyclin A2-associated kinase activity is required for its function in meiosis II. One obvious question concerns the identity of the Cdk that Cyclin A2 is associated with. It has been shown that only Cdk1 and not Cdk2 is required for meiosis in mouse oocytes[92] and therefore Cyclin A2 is expected to be associated with Cdk1 for sister chromatid separation in meiosis II. Now it will be important to address whether Cyclin A2 is found in association with Cdk1 only on metaphase II and not metaphase I centromeres, and therefore capable of phosphorylating its targets only in metaphase II. Alternatively, association of Cdk1 with Cyclin A2 may not be stable at metaphase I centromeres due to missing T-loop phosphorylation.[93] We can also imagine that removal of Cyclin A2 shortly before anaphase onset in meiosis I is sufficient for maintaining protection of centromeric Cohesin, whereas in meiosis II, the presence of Cyclin A2 at centromeres throughout the metaphase-to-anaphase transition induces removal of centromeric Cohesin. Accordingly, inhibition of Cyclin A affects only the second meiotic division and has no effect on meiosis I (**Fig. 2B**).[89] We can speculate that exogenously expressed stable Cyclin A2 associates with Cdk1 before being recruited to the meiosis I centromere. This and stable Cyclin A's centromere localization throughout the metaphase-to-anaphase transition in meiosis I are probably required to induce precocious sister separation in meiosis I (**Fig. 2C**).[89] Likely, a combination of Cyclin A's localization and local regulation of associated kinase activity is responsible for inducing loss of Cohesin protection only in meiosis II.

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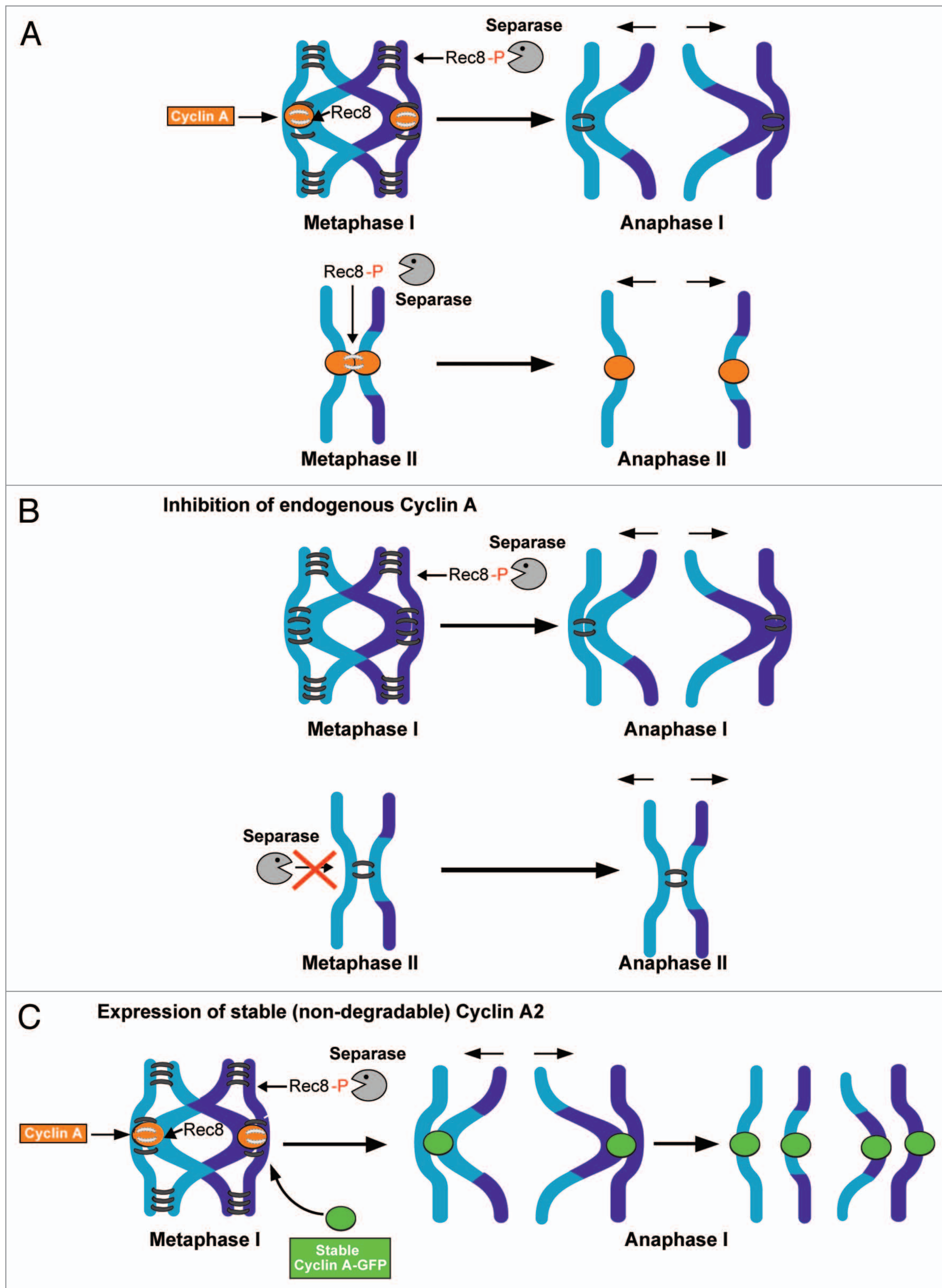

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Figure 2. Cyclin A2 is required for sister chromatid segregation in meiosis II in mouse oocytes. (**A**) Endogenous Cyclin A (orange) is localized in the centromere region in metaphase I and II. In meiosis II, Cyclin A remains associated with centromeres throughout the metaphase-to-anaphase transition, whereas in meiosis I Cyclin A is lost from centromeres at anaphase onset. (**B**) Inhibition of endogenous Cyclin A-associated kinase activity does not interfere with chromosome segregation in meiosis I, but prevents sister chromatid segregation in meiosis II, even though metaphase-to-anaphase transition takes place. (**C**) Expression of stable Cyclin A2 in meiosis I induces sister chromatid segregation in oocytes that remain blocked in an anaphase I-like state due to high Cdk1 kinase activity. Stable Cyclin A2 (in green) is localized to centromeres at the metaphase-to-anaphase transition in meiosis I. Cohesins, black bars; cohesins not visible due to Cyclin A colocalization, gray bars; Rec8, unphosphorylated Rec8; Rec8-P, phosphorylated Rec8 that can be cleaved by separase.

Generating Oocytes of the Correct Ploidy

It is estimated that a staggering 20–40% of all human oocytes are aneuploid.[6,94] Errors in chromosome segregation during the meiotic divisions lead to either spontaneous abortions or the development of trisomies, with trisomy 21 being the most frequent.[6,94] Furthermore, the incidence of missegregations in oocytes augments with the age of the mother, which has led to an increase of clinically recognized trisomy 21 pregnancies by more than 70% in the UK in the past 20 y, due to the fact that today women get their first child on average later in life than 20 y ago.[95] The reasons for this high error rate are still unknown and are probably due to multiple factors, such as weakening of the SAC, failures to maintain a functional cohesin complex throughout the several-decades-long prophase arrest and environmental factors.[5,6] Excellent reviews have been published on this topic,[5-7] and I will therefore only briefly outline how loss of cohesins with age is thought to affect oocyte ploidy.

Cohesion holding sister chromatids together is generated in the immature oocytes of the female embryo, and has to be maintained until entry into the first meiotic division upon hormonal stimulation and fertilization in the adult. Prior to entry into meiosis I, oocytes undergo a lengthy growth phase that takes up to nearly 3 mo in human oocytes. In the mouse, it has been shown that no Rec8 cohesin turnover takes place during the growing phase of the oocyte.[60] Cohesin complexes are therefore extremely stable and long-lived, but probably for this reason they also constitute the weak point of mammalian female meiosis. Indeed, diminished levels of cohesin proteins have been described in oocytes of aged mice.[68,96,97] Not only are cohesins required for keeping sister chromatids together, but also for the maintenance of chiasmata.[33] Therefore, less cohesin is expected to have severe consequences, leading both to failures to maintain sisters and homologous chromosomes together. Indeed, this loss of cohesin leads to the destabilization of chiasmata and, therefore, the presence of unpaired chromosomes in meiosis I[5]. Diminished levels of cohesin proteins in the centromere region may also be responsible for the age-dependent loss of Sgo2 that has been observed in mouse oocytes.[96] We can hypothesize that this loss of Sgo2 further increases precocious sister chromatid separation in oocytes from older mice.

So named "cohesin fatigue" has been shown to affect mitotic cells kept in metaphase for prolonged periods of time.[98] The force applied by the bipolar spindle leads to a gradual loss and rupture of the cohesive forces holding sister chromatids together, and thereby contributes to the generation of aneuploid daughter cells. Mammalian oocytes are arrested in metaphase II (cytostatic factor or CSF-arrest) for a prolonged period of time to await fertilization.[99,100] It is only upon fertilization that metaphase-to-anaphase transition and exit from meiosis II takes place. During this CSF-arrest paired sister chromatids are attached to the bipolar spindle and under tension. In combination with the age-dependent loss of cohesin in oocytes, cohesin fatigue may additional make matters worse and contribute to the high aneuploidy rate of human oocytes.

Concluding Remarks

Protection of centromeric cohesin has been studied in a wide variety of model organisms, and it seems that the protective mechanisms are conserved from yeast to man. But as important as it is to understand how protection takes place, it is as important to know the mechanisms of deprotection. Not being able to get rid of centromeric cohesin protection in meiosis II will have the same fatal consequences as not being able to protect centromeric cohesin in the first place, with the generation of aneuploid gametes that will give rise to embryos with the wrong number of chromosomes. It is striking that proteins involved in protection and deprotection (Sgo2, PP2A, I2PP2A, Cyclin A) are localized to the centromere region in both meiosis I and II, with only subtle changes. Therefore it is reasonable to expect that posttranslational modifications further regulate activities and specificities of these proteins to confer protection in meiosis I and deprotection in meiosis II. I believe that future work will help us better understand chromosome segregation in meiosis by identifying the signaling pathways involved in regulating these proteins during meiotic progression. This will also help us understand why oocytes missegregate their chromosomes so frequently.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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