Chromosoma (2016) 125:321–335
DOI 10.1007/s00412-015-0536-7

REVIEW

How oocytes try to get it right: spindle checkpoint control in meiosis

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Received: 10 April 2015 / Revised: 9 July 2015 / Accepted: 20 July 2015 / Published online: 11 August 2015

Abstract The generation of a viable, diploid organism depends on the formation of haploid gametes, oocytes, and spermatocytes, with the correct number of chromosomes. Halving the genome requires the execution of two consecutive specialized cell divisions named meiosis I and II. Unfortunately, and in contrast to male meiosis, chromosome segregation in oocytes is error prone, with human oocytes being extraordinarily "meiotically challenged". Aneuploid oocytes, that are with the wrong number of chromosomes, give rise to aneuploid embryos when fertilized. In humans, most aneuploidies are lethal and result in spontaneous abortions. However, some trisomies survive to birth or even adulthood, such as the well-known trisomy 21, which gives rise to Down syndrome (Nagaoka et al. in Nat Rev Genet 13:493–504, 2012). A staggering 20–25 % of oocytes ready to be fertilized are aneuploid in humans. If this were not bad enough, there is an additional increase in meiotic missegregations as women get closer to menopause. A woman above 40 has a risk of more than 30 % of getting pregnant with a trisomic child. Worse still, in industrialized western societies, child birth is delayed, with women getting their first child later in life than ever. This trend has led to an increase of trisomic pregnancies by 70 % in the last 30 years (Nagaoka et al. in Nat Rev Genet 13:493–504, 2012; Schmidt et al. in Hum Reprod Update 18:29–43, 2012). To understand why errors occur so frequently during the meiotic divisions in oocytes, we review here the molecular mechanisms at works to control chromosome segregation during meiosis. An important mitotic control mechanism, namely the spindle assembly checkpoint or SAC, has been adapted to the special requirements of the meiotic divisions, and this review will focus on our current knowledge of SAC control in mammalian oocytes. Knowledge on how chromosome segregation is controlled in mammalian oocytes may help to identify risk factors important for questions related to human reproductive health.

Keywords Meiosis · Spindle assembly checkpoint · Mouse oocytes · Cohesin protection · Aneuploidy · Monopolar attachment

Introduction

Sexual reproduction serves to mix the genome of the parents to create new genetic combinations in the offspring. Two haploid gametes, the oocyte and the spermatocyte, fuse to give rise to a diploid cell, the zygote. Haploid gametes are generated through two successive specialized cell divisions named meiosis I and II, which take place without intermediate S-phase, thereby halving the genome (Petronczki et al. 2003). In mammals, female meiosis is error prone, with an estimated 20–25 % of oocytes not harboring the correct number of chromosomes and being aneuploid. Aneuploid oocytes can still be fertilized and give rise to an aneuploid embryo, which in most cases is not viable and therefore aborted. In humans, the most frequently occurring viable aneuploidy is trisomy 21, which is due to chromosome 21 missegregation in female meiosis, with

This article is part of a Special Issue on "Recent advances in meiotic chromosome structure, recombination and segregation" edited by Marco Barchi, Paula Cohen and Scott Keeney.

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65 % occurring in meiosis I and 23 % in meiosis II. Trisomy 16 (which is incompatible with life) is in close to 100 % of cases due to missegregation in female meiosis I (Hassold et al. 1996; Hassold and Hunt 2001; Nagaoka et al. 2012).

Human male meiosis is by far not as error prone as female meiosis in oocytes. One important difference is the fact that, in females, meiosis starts in the fetus, and oocytes have to remain arrested before entry into the first meiotic division for sometimes more than 40 years until onset of menopause in humans. Male gametes are continuously produced from male germ cells (spermatogonia) that are mitotically dividing in the sexually mature adult before entering meiosis. Male gametes are therefore under much less temporal strain, and sperm production is maintained throughout lifetime. Most aneuploidies in male gametes concern the sex chromosomes because during male meiosis, XY chromosomes that harbor only a limited region of homology have to pair and segregate, in contrary to female meiosis where the XX chromosome pair does not create additional challenges. It is estimated that, on average, 2 % of sperm are aneuploid in humans compared to the above mentioned 20–25 % of oocytes (Hassold and Hunt 2001; Vera et al. 2012).

There is an exponential increase in trisomic pregnancies with the age of the mother. A woman in her 20s has a risk of less than 3 % of carrying a trisomic embryo, whereas in women 40–42 years old, the risk lies at a staggering 30 % (Hassold and Hunt 2001). In industrialized countries, women get their first child later in life due to societal changes, which has since significantly increased the occurrence of trisomic pregnancies (Davie 2012). Several factors have been shown to determine oocyte quality, and excellent reviews (Handyside 2012; Hassold and Hunt 2001; Nagaoka et al. 2012) exist on this topic. Here, we will mainly focus on the role and mechanisms of an important control mechanism, namely the spindle assembly checkpoint, or SAC, for the accuracy of the first meiotic division in female meiosis. Given the fact that most errors occur during female meiosis, we will refrain from discussing problems associated with male meiosis and refer the reader to a review treating also the male perspective (Vera et al. 2012). Unless stated otherwise, we will mainly discuss studies done in the mouse.

Meiotic divisions in oocytes

Maturation of mammalian oocytes

Oogenesis starts in the female fetus, where mitotically dividing primordial germ cells undergo premeiotic S-phase, enter meiosis, and pair homologous chromosomes that undergo recombination to generate new genetic combinations in the gametes of this female not yet born. Upon finalization of recombination, oocytes remain arrested in diplotene or prophase I of the 1st meiotic division. This protracted arrest is called dictyate or germinal vesicle (GV) arrest. Around birth of the female, primordial follicles are formed due to preganulosa cells that reside around each oocyte. Only a fraction of oocytes form primordial follicles, the remaining oocytes are lost during folliculogenesis. Oocytes remain dormant until hormonally stimulated to grow and progress through meiosis I in the sexually mature female. Surprisingly, only around 400 oocytes can be ovulated during the entire life in humans, even though around 50,000 oocytes have been present at puberty, starting from an estimated 7 million germinal cells in the fetus (Darribère 2003).

Diploid, GV arrested oocytes enter meiosis I upon luteinizing hormone (LH) stimulation. Meiosis I is a reductional division, with the separation of paired chromosomes that have recombined and are still held together by chiasmata formed at sites of meiotic recombination, and cohesin which is holding sister chromatids together. Meiosis I takes very long in mammals: around 8–10 h in mice and more than 24 h in humans (Gemzell 1962). It is thought that this is due in part to the fact that spindles are formed without centrosomes in oocytes. It is also likely that the meiosis I specific attachment (paired chromosomes instead of sister chromatids) poses challenges to the oocyte that requires a much longer prometaphase I to correctly attach chromosomes to the bipolar spindle (Terret and Wassmann 2008).

At exit of meiosis I, a small polar body (PB) is extruded to discard half of the genetic material and keep a huge oocyte with a cytoplasm containing all maternal stock to support the development of the future embryo. Oocytes enter meiosis II and remain arrested with aligned sister chromatids in metaphase of meiosis II to await fertilization. Fertilization allows metaphase II oocytes to resume meiosis, separate sister chromatids, extrude a second small PB, and form a female pronucleus, which fuses with the male pronucleus to from a diploid cell: the zygote, the first cell of the embryo.

Chromosome attachment and spindle stabilization in meiosis I

Correct spindle formation and attachment of chromosomes are prerequisites for the generation of oocytes of the correct ploidy. In meiosis I, sister chromatids of one chromosome are oriented towards the same pole; they are mono-oriented, in contrast to meiosis II or mitosis, where sister chromatids bi-orient (they are turned towards the opposite poles of the bipolar spindle). As a consequence, kinetochores (the attachment sites on chromosomes for the bipolar spindle) of sister chromatids are oriented side-by-side in meiosis I and in a back-to-back configuration in meiosis II or mitosis. This attachment allows the separation of chromosomes in meiosis I, and of sister chromatids in meiosis II (Fig. 1).

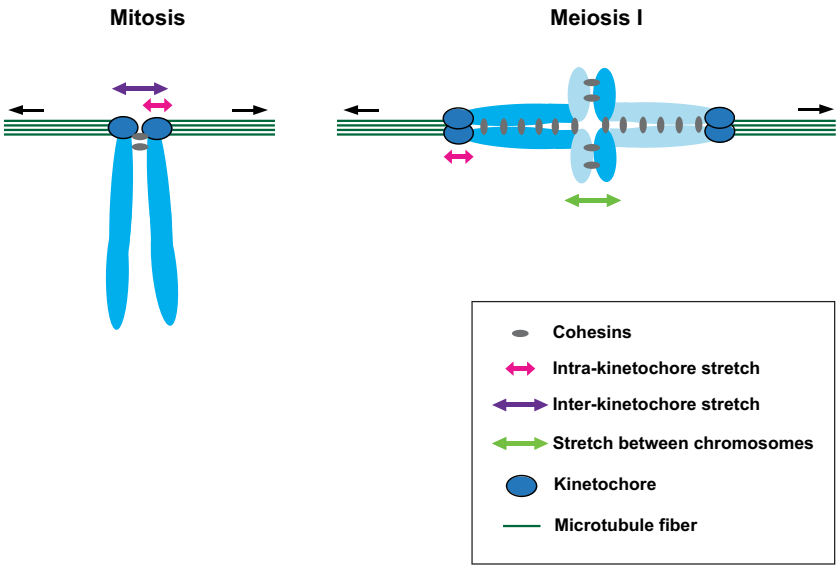

Fig. 1 Kinetochore-microtubule attachment and stretch applied on chromosomes in mitosis and meiosis I. In metaphase of mitosis, sister chromatids are held together by cohesin (in *grey*) in the centromeric region and are bioriented towards the opposite poles of the spindle. This type of attachment generates a stretch within each kinetochore (intra-kinetochore stretch) and between the kinetochores of sister chromatids which are oriented back-to-back (inter-kinetochore stretch). In metaphase I of meiosis, maternal and paternal chromosomes (depicted in *two different shades of blue*) are held together by chiasmata generated through recombination (visualized here by *change of blue color shade*) between sister chromatids of the two chromosomes, and sister chromatids are held together by cohesin. Homologous chromosomes, and not sister chromatids, are oriented towards the opposite spindle poles. Sister kinetochores are mono-oriented and side-by-side, facing the same pole. In this case, intra-kinetochore, but not inter-kinetochore stretch, is established. Moreover, chiasmata are stretched due to the tension applied between the maternal and paternal chromosome

Proper attachment of chromosomes in meiosis I is achieved through multiple rounds of microtubule attachments and removal until correct orientation is achieved. Individual chromosomes undergo on average three rounds of attachment/removal until proper attachments are stabilized (Kitajima et al. 2011). In human tissue culture cells in mitosis, wrong attachments are corrected by the chromosomal passenger complex (CPC) through the activity of the kinase Aurora B. Aurora B localizes to the inner centromere and generates a gradient of kinase activity which destabilizes kinetochore–microtubule interactions on tensionless kinetochores by phosphorylating specific substrates at the kinetochore. Once microtubules emanating from both poles are attached to the kinetochores of two paired sister chromatids, tension can be applied. This tension stretches kinetochores towards the poles and thereby moves Aurora B substrates out of the Aurora B kinase activity gradient, preventing their phosphorylation and consequently allowing stabilization of kinetochore fibers (Liu et al. 2009; van der Waal et al. 2012; Watanabe 2012).

In mouse oocytes, AURORA B and its close homolog AURORA C are expressed. Expression of AURORA C in mitosis rescues loss of AURORA B; therefore, their roles are at least partially overlapping (Fernandez-Miranda et al. 2011; Sasai et al. 2004; Slattery et al. 2008, 2009). In prometaphase I oocytes, AURORA B localization is restricted to the centromere such as in mitosis, whereas AURORA C is localized to the centromere and also chromosome arms (Nguyen et al. 2014; Tang et al. 2006; Yang et al. 2010) and more specifically the interchromosomal region, depending on HASPIN-dependent phosphorylation of HISTONE H3 (Nguyen et al. 2014). Interestingly, chromosome alignment in meiosis I seems to depend mostly on AURORA C (Balboula and Schindler 2014). It is attractive to speculate that due to the specific localization of AURORA C to chromosome arms, AURORA C has a meiosis I specific role in chromosome alignment related to the fact that attachments are monopolar. However, for now, no defects in monopolar orientation of sister kinetochores or precocious sister separation have been observed in meiosis I upon loss of AURORA C or inhibition of HASPIN kinase in oocytes. AURORA C may also recognize missing tension along chromosome arms in meiosis I, instead of at the inner centromere region, as in mitosis, and thereby induce correction (Nguyen et al. 2014).

Successful execution of metaphase-to-anaphase transition requires correct attachments and the establishment of stable spindles. In oocytes, slowly increasing CYCLIN B-CDK1 activity leads to progressive stabilization of attachments. Accordingly, inhibition of CYCLIN B-CDK1 kinase activity delays the formation of stable kinetochore-microtubule attachments, and high levels of CYCLIN B-CDK1 activity lead to premature stabilization of attachments (Davydenko et al. 2013). In mitosis, on the other hand, it is the degradation of CYCLIN A in early prometaphase that permits the switch from unstable to stable attachments (Kabeche and Compton

2013). Accordingly, expression of non-degradable CYCLIN A2 in mitosis prevents the establishment of stable attachments, whereas in oocyte meiosis I the presence of non-degradable CYCLIN A2 does not perturb the formation of stable attachments (Touati et al. 2012). Degradation of CYCLIN A2 is therefore not required for stabilization of microtubule fibers in mouse oocytes, either because CYCLIN A2 activity is restrained in meiosis through specific subcellular localization or because of different mechanisms of spindle attachment and stabilization in mitosis and oocyte meiosis.

Once robust kinetochore-microtubule attachments have been formed, the spindle migrates to the cortex. This movement is mediated by an F-actin network and is essential to bring about the very asymmetric cell division with the extrusion of a small PB (Almonacid et al. 2014; Chaigne et al. 2015; Li and Albertini 2013). Oocytes then progress into meiosis II and form in a relatively short time frame compared to meiosis I, the second meiotic spindle near the cortex. Instead of chromosomes, sister chromatids are now aligned at the metaphase plate. Oocytes remain arrested in metaphase II until fertilization occurs, and this arrest is mediated by CSF (Cytostatic Factor) activity (Wu and Kornbluth 2008). The mechanisms underlying sister chromatid orientation, spindle stabilization, and error correction in meiosis II are not well understood yet.

Holding sisters together

In meiosis I, chromosomes that have recombined are held together through chiasmata and sister chromatids by the cohesin complex. Even though chromosomes and not sisters are separated in meiosis I, cohesion has to be removed from arms, where recombination between homologous chromosomes has taken place, to allow separation of chromosome arms. On the other hand, cohesion has to be maintained in the centromere region, where no recombination takes place, to keep sisters together throughout the first division and to attach them correctly in meiosis II. If sisters are already separated in meiosis I, no tension-bearing attachments can be formed in meiosis II, leading to random segregation of sister chromatids. Accordingly, one key feature of meiosis is the step-wise removal of cohesion, from arms in meiosis I, and from centromeres in meiosis II (Petronczki et al. 2003) (Fig. 2).

The cohesin complex in budding yeast consists of the subunits Smc1, Smc3, and the α-kleisin subunit Scc1 or Rec8 (Peters et al. 2008; Uhlmann 2003). These subunits form a tripartite ring entrapping sister chromatids. Cleavage of the α-kleisin subunit Scc1 in metaphase of mitosis by the thiol-protease Separase allows the separation of sister chromatids and anaphase onset (Peters et al. 2008; Uhlmann 2003). In *Caenorhabditis elegans*, step-wise removal of cohesin is achieved through regulated maintenance of meiosis-specific cohesins, namely Rec8 and COH-3/4, on the long and short arm of bivalents, respectively. Both Rec8 and COH-3/4 are removed in a Separase-dependent and Separase-independent pathway, depending on phosphorylation of Rec8 (Rogers et al. 2002; Severson et al. 2009; Severson and Meyer 2014; Siomos et al. 2001). Rec8 is expressed in meiotic cells of different model systems and cleaved by Separase, but unlike Scc1, Rec8 has to be phosphorylated for cleavage by Separase, at least in yeast (Ishiguro et al. 2010; Katis et al. 2010; Rumpf et al. 2010). Maintaining Rec8 in its unphosphorylated stage at the centromere protects it from cleavage in meiosis I, and this is brought about by the localization of PP2A-B56 to the centromere region due to Shugoshin (Sgo)-dependent recruitment (Ishiguro et al. 2010; Katis et al. 2010; Kitajima et al. 2006; Riedel et al. 2006). Mammals express two Shugoshin proteins, SGO1 and 2, with SGO1 being required to protect cohesin from prophase pathway-dependent removal in mitosis and SGO2 being required in meiosis to prevent precocious centromeric cohesin removal. Accordingly, SGO2 loss of function in mice does not affect viability, but prevents correct sister chromatid segregation in meiosis II, the formation of viable gametes, and, consequently, leads to sterility (Llano et al. 2008; Rattani et al. 2013).

Sister separation in meiosis II requires deprotection of centromeric cohesin. In mammalian oocytes, this is brought about through the combined action of physical removal of PP2A-B56 through the bipolar tension now applied on sister kinetochores, and the action of I2PP2A/SET, and CYCLIN A2 (Chambon et al. 2013; Gomez et al. 2007; Lee et al. 2008; Touati et al. 2012; Wassmann 2013).

Activation of separase

The key event for anaphase onset in mitosis and meiosis in different model organisms is the activation of Separase. For activation, Securin, an inhibitor of Separase, has to be degraded, and Cyclin B-Cdk1 levels have to drop, as elevated Cyclin B-Cdk1 kinase activity maintains Separase inactive through inhibitory phosphorylation (Gorr et al. 2006). Both Cyclin B and Securin are substrates of the anaphase promoting complex/Cyclosome (APC/C), an E3 ubiquitin ligase, which in association with its activator Cdc20 ubiquitinates Securin and Cyclin B and thereby targets both proteins for degradation by the 26S proteasome (Sullivan and Morgan 2007) (Fig. 2). Activation of the APC/C underlies checkpoint control, and in mitosis, it is only upon establishment of correct, tension-bearing attachments on all kinetochores that the SAC is inactivated and metaphase-to-anaphase transition takes place (Sullivan and Morgan 2007) (Hauf 2013).

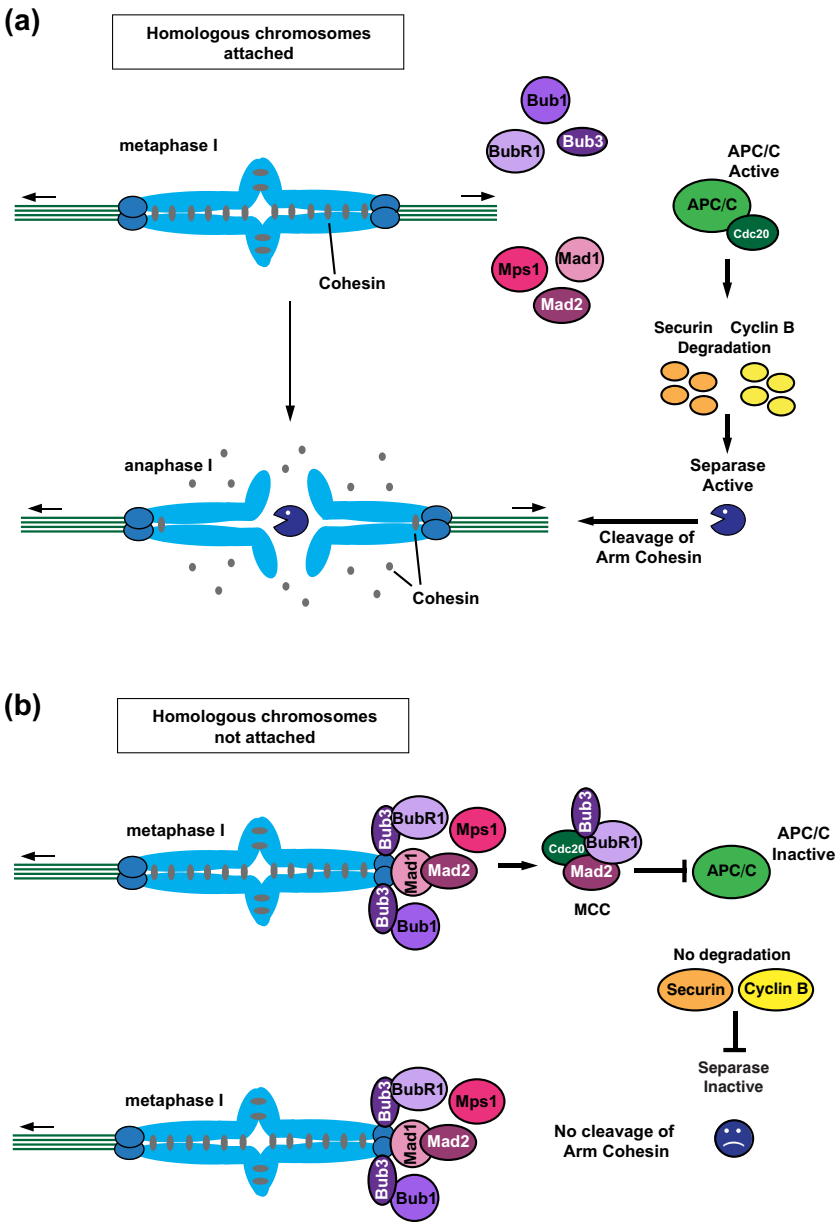

Fig. 2 SAC proteins localize to unattached kinetochores and prevent metaphase I-to-anaphase I transition in mouse oocytes. **a** In metaphase I, correct attachments lead to removal of SAC proteins from kinetochores. APC/C-CDC20 is activated and CYCLIN B and SECURIN are targeted for degradation by the 26S proteasome, allowing activation of SEPARASE. SEPARASE then cleaves the cohesin subunit REC8 on chromosome arms, leading to cohesin removal and metaphase I-to-anaphase I transition. **b** When homologous chromosomes are not, or not correctly, attached, SAC proteins are recruited to kinetochores and APC/C activity is inhibited. CYCLIN B and SECURIN levels remain high and SEPARASE is not activated. This prevents removal of cohesin, and metaphase I-to-anaphase I transition

The SAC in mammalian mitosis

In metaphase, paired sister chromatids are attached with their kinetochores to the bipolar spindle. Microtubules are stabilized because they are under tension, as sister kinetochores are attached to opposite poles. The spindle checkpoint detects errors in kinetochore attachment, and in the case of missing attachments or attachments that are not under tension, the checkpoint delays anaphase onset so that these faulty attachments can be corrected (Sacristan and Kops 2015). This is achieved through inhibition of the APC/C, and activation of Chromosomal Passenger Complex (CPC)-dependent error correction (London and Biggins 2014; Sacristan and Kops 2015).

The SAC recognizes microtubule occupancy. The more microtubules are bound to a given kinetochore, the less SAC signal is generated at this kinetochore, generating a graded checkpoint response (Collin et al. 2013). If microtubules are not under tension, they are unstable and therefore kinetochore occupancy decreases, which in turn can activate the checkpoint. The checkpoint detects whether attachments are under tension and, in the absence of tension, induces error correction through Aurora B phosphorylation dependent destabilization of microtubules (Foley and Kapoor 2013). Tension at kinetochores has been proposed to be detected by the stretch applied between the two sister kinetochores and within the kinetochore (inter- and intra-kinetochore stretch, respectively), in mitosis (Foley and Kapoor 2013) (Fig. 1). In mitosis with unreplicated genome (MUG) cells, which undergo mitosis without prior DNA replication and therefore unpaired single sister kinetochores, intra-kinetochore stretch seems on its own

sufficient for SAC satisfaction and anaphase onset. Importantly, these cells are still responsive to drugs affecting microtubule attachment or tension and therefore harbor a functional checkpoint. Nevertheless, this result does not exclude that interkinetochore stretch may still be recognized when two sister kinetochores are present (O'Connell et al. 2008).

Core proteins required for checkpoint response have been identified in budding yeast first, in a screen for mutants that could grow in the presence of Benomyl (Budding Uninhbited by Benomyl, or Bub proteins) or Nocodazole (Mitotic Arrest Deficient, Mad proteins). Monopolar spindle 1 (Mps1) was equally shown to be essential for SAC functionality (Maiato et al. 2004). The spindle checkpoint and its core components were found to be conserved in nearly all eukaryotes (Vleugel et al. 2012). Importantly, whereas yeast cells can grow just fine without a functional checkpoint as long as they are not challenged with spindle drugs, in mammalian somatic cells the SAC is active during each and every cell cycle and needs to be inactivated for APC/C activation (Foley and Kapoor 2013; Wassmann and Benezra 1998). Without the SAC, mitosis is accelerated and missegregations occur, even without challenging cells with spindle drugs (Meraldi et al. 2004). In mammalian cells, correct timing of mitosis does not require the kinetochore localization of SAC components (Meraldi et al. 2004; Rodriguez-Bravo et al. 2014). In *Drosophila melanogaster*, on the other hand, mitosis seems to be efficient enough that the acceleration observed upon loss of checkpoint function does not affect chromosome segregation, as long as cells are not additionally challenged with spindle drugs or mutations affecting spindle stability (Buffin et al. 2007). In short, whereas the checkpoint is functional in the different model systems studied so far, it is not always required for normal progression through mitosis, if cells are not additionally challenged.

Spindle checkpoint proteins accumulate on unattached kinetochores in a hierarchical order, as shown mostly in human tissue culture cells (Sacristan and Kops 2015; Stukenberg and Burke 2015). Mps1 phosphorylates the scaffold protein Knl1 within motifs called the MELT repeats. This allows recruitment of Bub3, the kinase Bub1, and BubR1, leading to further recruitment of Mad2 and Mad1 to unattached kinetochores, and cytosolic enrichment of the so-named MCC, or mitotic checkpoint complex. The MCC consists of Mad2, BubR1, Bub3, and Cdc20, and it directly inhibits the APC/C and cell cycle progression. The capacity of the SAC to change quickly from the SAC "on" stage to the SAC "off" stage is achieved through the simultaneous recruitment of phosphatases that counterbalance checkpoint activation and error correction (Foley and Kapoor 2013). First, BubR1 recruits PP2A-B56, which counterbalances Aurora B phosphorylation and thereby turns off error correction, allowing for stable kinetochore microtubule attachments to take place (Kruse et al. 2013; Suijkerbuijk et al. 2012). PP2A recruitment in turn promotes binding of the phosphatase PP1 to Knl1, which induces SAC silencing (Nijenhuis et al. 2014). The fast responsiveness of the checkpoint is mediated through the negative feedback loop activated upon stimulation of a SAC response at the kinetochore.

Still, up to quite recently, it was not clear how attachment of microtubules to kinetochores can rapidly turn off the checkpoint and how loss of attachments activates the checkpoint immediately. Three recent studies demonstrate that competition between Mps1 and microtubules at the kinetochore turns the checkpoint on and off (Aravamudhan et al. 2015; Hiruma et al. 2015; Ji et al. 2015). In human cells, Mps1 binding to the Ndc80 complex at the kinetochore occurs in the absence of microtubule binding to the same complex and is enhanced through Aurora B dependent phosphorylation. Once a microtubule is bound to an attachment module consisting of Ndc80 and Knl1, phosphorylations on Hec1 (an Ndc80 complex protein) and Knl1 are removed, and further binding and phosphorylation by Mps1 and binding of SAC proteins is prevented, thereby keeping the checkpoint inactive (Hiruma et al. 2015; Ji et al. 2015). Also, in budding yeast, end-on microtubule attachment prevents Mps1 dependent phosphorylation of the Knl1 homolog Spc 105 and inactivates the SAC through physical separation of Mps1 from its substrate by microtubule binding (Aravamudhan et al. 2015).

Differences in kinetochore recruitment of individual SAC proteins have been observed, and it is thought that Mad1 and Mad2 are foremost recruited at unattached kinetochores, whereas Bub1 and BubR1 are recruited when attachments are not under tension (Pinsky and Biggins 2005). However, this may also just reflect the fact that attachment is required for removing Mad1 and Mad2 from kinetochores through shedding along microtubules due to activity of the RZZ (Rod-Zwilch- ZW10) complex, and in the absence of any attachment, Mad1 and Mad2 cannot be removed efficiently (Musacchio and Salmon 2007). Bub1 and BubR1 on tensionless kinetochores may continuously activate and inactivate error correction through the above described negative feedback loop, leading to continuous re-recruitment of Bub1 and BubR1 when no tension can be established, as is the case upon treatment with drugs affecting stability of spindles, such as taxol. Differences in recruitment and removal of checkpoint proteins at kinetochores may therefore account for the observed differences in staining upon loss of attachment or only tension.

Mouse oocytes have a spindle checkpoint, too!

Whether the SAC functions in mammalian male meiosis is unknown, even though chromosome segregation is significantly less error prone than in female meiosis. In the mouse,

loss of one allele of *BUB3* or *MAD2* does not lead to an increase in aneuploid secondary spermatozoids and therefore does not affect male meiosis I and II, in contrary to splenocytes, where an important increase in missegregations in mitosis was observed (Jeganathan and van Deursen 2006). Only BUBR1 is required for correct chromosome segregation in male meiosis, but this can also be due to BUBR1's role in stabilizing kinetochore-microtubule interactions, independently of its role in the SAC (see below) (Jeganathan and van Deursen 2006). Male mice harboring only a kinase dead mutant version of BUB1 are sub fertile, but this may also be due to defects unrelated to checkpoint control (see below) (Ricke et al. 2012). As mentioned above, missegregation rates in mammalian oocytes are high, and therefore, the existence of the checkpoint in female meiosis has been put into question in the past. Indeed, in *Xenopus laevis* oocytes, the SAC does not exist, and the rate of chromosome missegregations is by far not as high as in mammalian oocytes devoid of checkpoint control (Liu et al. 2014). The type of aneuploidy occurring is usually the loss of one chromosome at the first meiotic division. *X. laevis* oocytes undergo metaphase-to-anaphase transition of meiosis I in the presence of nocodazole, which destabilizes spindles and activates the spindle checkpoint in cells harboring a functional SAC (Shao et al. 2013). In *D. melanogaster* oocytes, loss of checkpoint components does not affect Cyclin B degradation, as expected in the presence of a functional spindle checkpoint (Batiha and Swan 2012).

In mouse oocytes, a large body of evidence in recent years has shown that even though chromosome segregations go wrong so frequently, the SAC exists and is able to recognize unattached kinetochores, as in mitosis. All SAC components studied so far have been found to be expressed in mouse oocytes and are localized to kinetochores early in meiosis I when microtubules are not correctly attached to kinetochores yet (Fig. 2). Loss of SAC components leads to strong acceleration of the first meiotic division, severe chromosome missegregations, and, as a consequence, sterility. Table 1 shows a summary of different approaches used to study loss of core SAC components in oocytes. Low doses of nocodazole induce a SAC arrest, with recruitment of SAC components to kinetochores, and stabilization of CYCLIN B and SECURIN. This arrest is often only transient, and oocytes eventually undergo metaphase-to-anaphase transition, missegregate chromosomes, and exit meiosis I (Hached et al. 2011; Homer et al. 2005a, b, 2009; Leland et al. 2009; Li et al. 2009; McGuinness et al. 2009; Niault et al. 2007; Touati et al. 2015; Tsurumi et al. 2004; Wang et al. 2007; Wassmann et al. 2003b; Wei et al. 2009; Yin et al. 2006; Zhang et al. 2005).

Is the high error rate therefore due to a failure to keep the SAC arrest for long enough to repair faulty attachments? Probably, this contributes to the high error rate, but it additionally seems that the SAC is also not very efficient in meiosis compared to mitosis, where it recognizes a single, non-attached kinetochore and this is enough to maintain an arrest. Indeed, CYCLIN B and SECURIN start to be degraded before all chromosomes are properly aligned at the metaphase plate. This seems to indicate that the presence of one or a few not correctly attached kinetochores escapes checkpoint detection in oocytes (Gui and Homer 2012; Lane et al. 2012).

Checkpoint control in meiosis I poses important challenges: Monopolar attachments have to be recognized as correct, contrary to meiosis II or mitosis. A chromosome pair (bivalent) is held together by chiasmata, which allows the generation to tension bearing attachments, but this kind of attachment excludes that the checkpoint can recognize inter-kinetochore tension, as is supposedly the case in mitosis. The only tension signal that is conserved between mitosis and meiosis at the kinetochore upon correct attachment is intra-kinetochore tension. Indeed, loss of nuclear mitotic apparatus protein (NUMA), which is implicated in anchoring microtubules to the poles and leads to loss of tension between the two homologous chromosomes, does not provoke a metaphase I arrest in mouse oocytes, with the caveat that it is unknown whether the same mutation induces indeed a checkpoint arrest in mitosis (Kolano et al. 2012). The checkpoint may be "blind" against detection of inter-chromosome tension in oocytes, and this may contribute to the fact that the SAC is less sensitive in meiosis than mitosis.

In meiosis, chromosomes without chiasmata (univalents) may also escape checkpoint arrest if they are attached in a bipolar manner as in mitosis, with the kinetochores facing the opposite poles. This was confirmed by studies using XO mice, which harbor only one X chromosome that cannot form a bivalent, but nevertheless do not delay the first meiotic division (LeMaire-Adkins et al. 1997; Rieder et al. 1995). S*YCP3*$^{-/-}$ mice are another example of failures in correct checkpoint response in oocyte meiosis: SYCP3 is a component of the synaptonemal complex that maintains homologous chromosomes together for meiotic recombination. Without SYCP3, oocytes harbor, on average, one to three univalents (the remaining chromosomes are paired). These oocytes enter the first meiotic division, but again do not arrest in metaphase I or significantly delay anaphase I as expected upon checkpoint activation. Univalents biorient, MAD2, is lost from these bioriented sister kinetochores, and the spindle checkpoint is satisfied (Kouznetsova et al. 2007). It is possible that in this case, univalents biorient quickly enough on the meiotic spindle during the long prometaphase and are therefore "invisible" for the SAC. On the other hand, oocytes devoid of HORMAD1, a protein required for synaptonemal complex formation and recombination, do not show sister kinetochore splitting indicative of biorientation of univalents, even after extended times in meiosis I (Daniel et al. 2011). The number of univalents is probably too high for successful biorientation and may lead to SAC activation. These oocytes also rarely

Table 1 SAC loss of function studies in mouse oocytes

Prot.	Approach used	SAC functionality (response to nocodazole treatment)	Meiosis I timing	Mad2 kinetochore localisation	Chromosome alignment on metaphase plate	Additional phenotypes	Ref.
Mad1	Blocking antibody	–	Normal	–	Not aligned	–	(Zhang et al. 2005)
Mad2	Heterozygote mutant (1)	Not functional	Acceleration	–	–	–	(Niault et al. 2007)
	RNAi	–	Acceleration	–	Not aligned	–	(Wang et al. 2007)
	Morpholino	–	Acceleration	–	–	–	(Homer et al. 2005b)
	Morpholino	Not functional	–	–	–	–	(Homer et al. 2005a)
	Dominant negative mutant (2)	–	Acceleration	–	–	Not required for CSF arrest	(Tsurumi et al. 2004)
	Dominant negative mutant (3)	Not functional	–	–	Not aligned	–	(Wassmann et al. 2003a)
Bub1	Knockout	Not functional	Acceleration	–	Not aligned	Precocious sister chromatid separation (PSCS)	(McGuinness et al. 2009)
	Heterozygote mutant (4)	–	–	–	–	PSCS	(Leland et al. 2009)
	Blocking antibody	Not functional	Acceleration	–	Not aligned	–	(Yin et al. 2006)
	Dominant negative mutant (5)	–	Acceleration	–	Aligned	Not required for CSF arrest	(Tsurumi et al. 2004)
Bub3	RNAi	Not functional	Normal	–	Not aligned	–	(Li et al. 2009)
BubR1	Knockout	Not functional	Acceleration	No	Not aligned	Loss of spindle stability, entry into meiosis normal, not required for CSF arrest	(Touati et al. 2015)
	Morpholino	Not functional	Acceleration	–	Not aligned	Acceleration of meiosis entry (not confirmed in knockout)	(Wei et al. 2009)
	Morpholino	–	Meiosis I arrest	Yes	Not aligned	Spontaneous meiosis entry (not confirmed in knockout)	(Homer et al. 2009)
	Dominant negative mutant(6)	–	Acceleration	–	–	Not required for CSF arrest	(Tsurumi et al. 2004)
Mps1	Inhibitor (7)	Not functional	Acceleration	No	Not aligned	–	(Touati et al. 2015; Lane and Jones 2014)
	Loss of function mutant (8)	Not functional	Acceleration	No	Not aligned	Loss of Aurora B/C from chromosomes	(Hached et al. 2011)

The role of SAC components has been studied by transient knockdown and conditional knockout techniques and the expression of different mutants in mouse oocytes. This table summarizes the approaches that have been used up to date to study core SAC components and the results from these studies. For clarity, we only include the MAD and BUB proteins, and MPS1, and not proteins required for error correction (AURORA B, C,…) and for turning off the SAC (SPINDLY,…), which are also required for proper checkpoint response. (1) *MAD2* heterozygote mutant→Deletion of one *MAD2* allele, oocytes harbor only one copy of the *MAD2* gene. (2) MAD2 dominant negative mutant→Mutated form of MAD2 (lacks 10 amino acids in the C-terminus), which was shown to behave as a dominant negative in mitotic cells and abrogates the checkpoint (Luo et al. 2002), (3) MAD2 dominant negative mutant→MAD2 phospho-mimicking mutant (Wassmann et al. 2003a), mutant that was shown to behave as a dominant negative in mitotic cells, (4) *BUB1* heterozygote mutant→Truncated form of Bub1 (1–269) is expressed from one allele, (5) BUB1 dominant negative mutant protein→Truncated form of BUB1 (1–331), missing the kinase domain, is expressed, (6) *BUBR1* dominant negative mutant→Truncated form of BUBR1 (351–700) is expressed (Tang et al. 2001), (7) MPS1 inhibitor (Reversine)→Inhibitor of MPS1 kinase activity (Santaguida et al. 2010), (8) *MPS1* loss of function mutant→Only mutant of MPS1 that cannot localize to kinetochore is expressed. Abrogation of the checkpoint with different approaches leads to accelerated meiosis and severe missegregations in meiosis I. Kinetochore localized MPS1 is required for AURORA B/C localization to chromosomes. BUBR1 has an additional role in stabilizing kinetochore-microtubule attachments, and BUB1 is required to prevent precocious sister chromatid segregation in meiosis I

undergo metaphase-to-anaphase transition of meiosis I. Results from *MLH1*$^{-/-}$ mice indicate that robust activation of the spindle checkpoint in oocytes depends additionally on the strain background used: In the different strains, most chromosomes in *MLH1*$^{-/-}$ oocytes are univalents because MLH1 is required for recombination and chiasmata formation, but whether anaphase I onset is only delayed or inhibited due to checkpoint activation depends on the strain background (Nagaoka et al. 2011; Tachibana-Konwalski et al. 2013; Woods et al. 1999).

Mono-orientation and the spindle checkpoint

Contrary to the situation in meiosis II and in zygotes, mono-orientation of sister chromatids is the correct orientation in meiosis I. Single sister chromatids are not recognized as wrong in meiosis I and do not lead to a metaphase I arrest, as long as they are not maintained together with their sister through centromeric cohesin (Tachibana-Konwalski et al. 2013). A recent study has identified a novel, meiosis-specific mammalian protein, named MEIKIN, that is partly required for mono-orientation of sister kinetochores and cohesin protection in meiosis I (Kim et al. 2015). In the absence of MEIKIN, sister centromeres split, but are still mostly mono-oriented due to the presence of chiasmata, leading to a SAC-dependent delay of anaphase I onset. Importantly, the SAC arrest/delay observed in *MLH1*$^{-/-}$ oocytes is overturned by simultaneously knocking out Meikin. Univalents are bioriented in *MLH1*$^{-/-}$ *MEIKIN*$^{-/-}$ oocytes, and these results indicate that biorientation of univalents satisfies the checkpoint. The SAC response is therefore specific for the developmental context due to the orientation (bipolar or monopolar) of bivalents and dyads on the spindle.

Spindle checkpoint control in meiosis II

Missegregations in meiosis II have the same severe consequences as in meiosis I: They lead to the formation of aneuploid embryos (Yun et al. 2014). Missegregations may arise because sister chromatids are not correctly attached in a bipolar manner or because single sister chromatids have been generated during the first meiotic division and cannot be segregated correctly in meiosis II. Studies of spindle checkpoint control in meiosis II are hampered by the fact that vertebrate oocytes are arrested in metaphase to await fertilization due to CSF activity. Functionality of the checkpoint has to be analyzed under conditions of CSF release. Additionally, complicating matters, it was suggested in *X. laevis* oocytes that the checkpoint participates in establishment of CSF arrest (Tunquist et al. 2002, 2003). In mouse oocytes, on the other hand, it was shown that expression of a dominant negative BUB1 mutant did not affect CSF arrest, as was expected if the checkpoint was required for CSF arrest (Tsurumi et al. 2004). Very recently, the analysis of genetically modified mice that are deficient for SAC control unambiguously showed that CSF arrest and release per se do not required the SAC, at least in the mouse (Touati et al. 2015) .

Treatment of oocytes with nocodazole prevents exit from meiosis II, indicative of existing SAC control also in the second meiotic division (Madgwick et al. 2006). A recent study using *SYCP3* knockout mice demonstrates that single sister chromatids arising from the separation of bipolar attached univalents in meiosis I are not recognized by the SAC in meiosis II. Again, those single sisters are attached to both poles (merotelic attachment) and escape SAC surveillance. Upon treatment with spindle depolymerizing drugs, the same oocytes can mount a SAC response with localization of Mad2 to unattached kinetochores (Kouznetsova et al. 2014). It will be important to address whether the SAC can recognize meiosis I or meiosis II specific attachments because of factors present in the cytoplasm or only because of chromosome orientation due to the presence or absence of chiasmata. Also, it will be important to clarify how error correction takes place in meiosis I and II.

The role of SAC proteins for checkpoint response in mouse meiosis I

Just as in mitosis, SAC proteins localize to unattached kinetochores in meiosis (Sun and Kim 2012). The first protein, whose localization and role for the meiotic SAC were analyzed, was MAD2. Prometaphase I takes several hours in mouse oocytes. Initially, lateral attachments of microtubules to kinetochores, which do not silence the SAC, are established and correlate with strong MAD2 staining of kinetochores. During the second part of prometaphase, strong MAD2 staining disappears, and only kinetochores probably undergoing error correction are weakly positive for MAD2. Upon nocodazole treatment, strong re-recruitment of MAD2 to kinetochores occurs, and release from nocodazole correlates with loss of MAD2 from progressively attaching kinetochores. MAD2 therefore seems to behave as in mitotic cells and can be used as readout for SAC activation also in oocytes (Wassmann et al. 2003b). But as mentioned previously, the SAC is not able to induce a cell cycle arrest in the presence of a few wrongly attached kinetochores in meiosis, and therefore, weak MAD2 staining at some kinetochores does not mean that the SAC is strong enough to prevent activation of the APC/C (Gui and Homer 2012; Lane et al. 2012). It is important to mention here that, also in mitosis, the strength of the checkpoint response depends on the number of kinetochores that are not properly attached (Dick and Gerlich 2013), and on the amount of attachment sites that are free of microtubules, per kinetochore (Collin et al. 2013). Indeed, the APC/C has been shown to be active at around 50 % in late

prometaphase I with weak MAD2 staining at kinetochores (see further in the following) (Lane and Jones 2014).

First indications of the importance of checkpoint control for meiosis came from studies using heterozygote MAD2 mice: Even though loss of one allele of MAD2 does not significantly affect overall survival of mice except a predisposition to the development of certain tumors (Michel et al. 2001), missegregations in female meiosis I are increased and lead to an overall drop in fertility (Niault et al. 2007). RNAi-mediated knockdown of MAD2 abolishes SAC control and leads to precocious APC/C activation (Homer et al. 2005a, b; Wang et al. 2007). To address how the complete loss of checkpoint proteins affects meiosis, it was necessary to generate conditional loss of function mutants, as mice without a functional checkpoint are not viable. The checkpoint components BUB1 and BUBR1 were knocked out due to the generation of floxed alleles and expression of the Cre-recombinase in oocytes with the oocyte-specific Zp3 promoter. As expected, checkpoint control is lost without BUB1 and BUBR1, meiosis is strongly accelerated, the APC/C is activated prematurely, and oocytes are highly aneuploid after the first meiotic division leading to female sterility (McGuinness et al. 2009; Touati et al. 2015). The same conditional knockout approach was also used to target MPS1, but in this case, oocytes expressed exclusively a mutant form of Mps1 that retains its kinase activity but cannot localize to kinetochores anymore. MPS1 is required for localization of downstream checkpoint components to kinetochores, and removing MPS1 from kinetochores accordingly leads to complete checkpoint loss (Hached et al. 2011). The same phenotype of accelerated meiosis and checkpoint loss was also observed upon inhibition of Mps1 kinase activity with the drug Reversine (Touati et al. 2015). Up to now, the roles of the checkpoint proteins BUB3 and MAD1 were only analyzed through transient knockdown approaches, but as shown for other essential checkpoint components, they are required for SAC response and correct chromosome segregation in meiosis I (Li et al. 2009; Zhang et al. 2005) (Table 1).

Acceleration of prometaphase

In mitosis, cytosolic MCC inhibition of the APC/C delays prometaphase. In the absence of a functional checkpoint, not only metaphase-to-anaphase transition takes place in the presence of attachment errors, but also progression through the early steps of mitosis, from nuclear envelope breakdown to anaphase, is strongly accelerated (Maciejowski et al. 2010; Meraldi et al. 2004). This timer function of the checkpoint is conserved in oocyte meiosis, but as prometaphase I takes several hours in mouse oocytes, the acceleration is much more prominent and accounts for a shortening of meiosis I by on average 3 h upon loss of MPS1 or BUB1 (Hached et al. 2011; Lane and Jones 2014; McGuinness et al. 2009). Interestingly, and in contrast to mitosis, kinetochore localization of MPS1 is required for correct timing of prometaphase (Hached et al. 2011). This may indicate that the checkpoint-dependent timer in meiosis depends entirely on a kinetochore-generated signal, maybe due to the fact that the volume of the oocyte is too big to generate an MCC signal capable of inhibiting APC/C activity everywhere in the cell and, at the same time, allow rapid inactivation once the checkpoint has been satisfied.

Cyclin B/Cdk1 activity and the SAC in meiosis

It is intriguing that acceleration of prometaphase I upon checkpoint loss never exceeds 3 h (Hached et al. 2011; Lane and Jones 2014; McGuinness et al. 2009; Niault et al. 2007; Rattani et al. 2014; Touati et al. 2015). With or without checkpoint control, the APC/C does not seem to be active during the first hours of prometaphase (Lane and Jones 2014), which is not surprising, as APC/C activation requires high CYCLIN B CDK1 activity (Felix et al. 1990; Rattani et al. 2014; Yang and Ferrell 2013). Closer to metaphase, oocytes enter a state with APC/C activity at around 50 %, and abolishment of checkpoint control here leads to full APC/C activity, accelerates SECURIN degradation and anaphase I onset, with increased missegregation events as a consequence (Lane and Jones 2014). The authors of this study propose that slowing down prometaphase I by the SAC allows oocytes to repair faulty attachments, without the need for full checkpoint response in the presence of one or few attachment errors (Lane and Jones 2014). Still, the checkpoint can be fully activated in a kinetochore-dependent manner at this stage, and this also correlates with the fact that SAC activation requires high CDK1 levels (Lane and Jones 2014; Rattani et al. 2014). The following metaphase-to-anaphase I transition depends on a bistable switch, with a drop in CDK1 activity that prevents the reactivation of the SAC during anaphase I due to loss of tension (Rattani et al. 2014).

Oocytes without a functional checkpoint do not accumulate CDK1 activity to the same levels as oocytes with a functional checkpoint. They can undergo metaphase-to-anaphase transition with much lower CDK1 activity (Touati et al. 2015), probably because they do not have to overcome the SAC, which is dominant over CDK1-dependent APC/C activation. If SAC dominance depends on kinetochores as suggested (Lane and Jones 2014), this explains why prometaphase I is accelerated in oocytes only expressing a MPS1 mutant that cannot localize to kinetochores, in contrast to mitosis (Foijer et al. 2014; Hached et al. 2011). It will be important to determine exactly how many and what kind of attachment errors are required for the SAC to remain dominant over APC/C activation by CDK1.

Checkpoint-independent roles of SAC proteins in meiosis

SAC proteins have been shown to be expressed in oocytes of *X. laevis*, which do not harbor a functional meiotic checkpoint (Chen et al. 1996; Shao et al. 2013). Maybe some SAC proteins have other, checkpoint independent functions required for proper execution of meiosis. For example, the kinase Bub1 was shown to phosphorylate Histone H2A in mitotic human tissue culture cells, where this histone mark is required for localization of Sgo1 (Kawashima et al. 2010). Similar to Sgo2, Sgo1 protects centromeric cohesin from precocious removal, although not from Separase, but from the so-named prophase pathway (Kitajima et al. 2006). It is attractive to speculate that Sgo1 in mitosis and Sgo2 in meiosis are recruited through the same Histone mark, and indeed, BUB1-deficient oocytes precociously separate sister chromatids in meiosis I (McGuinness et al. 2009), as expected without centromeric cohesin protection. However, this is probably not the only mechanism required for SGO2 localization because oocytes without BUB1 do not precociously separate all sister chromatids in meiosis I, as would be expected in case of complete SGO2 loss from centromeres (Leland et al. 2009; McGuinness et al. 2009). Importantly, whereas male mice harboring only a kinase dead mutant version of BUB1 are sub fertile, females are perfectly fertile without BUB1 kinase activity, indicating that BUB1 kinase activity is not essential for female meiosis (Ricke et al. 2012). Also, loss of AURORA B and C function either by inhibiting AURORA kinase activity with an inhibitor or through a conditional knockout strategy leads to loss of BUB1 from kinetochores, but does not seem to induce sister chromatid segregation in meiosis I (Balboula and Schindler 2014; Lane et al. 2010; Yang et al. 2010). Therefore, it still remains to be determined how SGO2 is recruited to kinetochores in meiosis I.

MPS1 and BUBR1 also have additional roles in oocyte meiosis: MPS1 is required for the localization of Aurora B/C kinase and therefore CPC function and error correction (Foley and Kapoor 2013; Hached et al. 2011). The MCC component BUBR1 is essential for SAC control and timing of meiosis I and has an additional meiosis-specific role for the establishment of stable spindles in meiosis I, which does not depend on its kinetochore localization and is therefore independent of its known mitotic function in counterbalancing AURORA B substrate phosphorylation at the kinetochore, which destabilize attachments (Touati et al. 2015).

Age-related increase of meiotic missegregations due to failing SAC control?

In mice and especially humans, aneuploidies during the meiotic divisions increase with maternal age (Handyside 2012). The reasons are probably multifactorial. In the mouse, cohesins that hold sister chromatids together are not renewed during oocyte growth (Tachibana-Konwalski et al. 2010) and have been shown to decrease in older mice, leading to the destabilization of chiasmata (Chiang et al. 2010; Lister et al. 2010). As the SAC is less efficient in meiosis than mitosis, and additionally, bioriented chromosomes seem to escape SAC detection, loss of chiasmata with age will inevitably lead to increased chromosome missegregations (Jones and Lane 2013). SGO2 at the centromere decreases as well with age in mouse oocytes, which is expected to lead to loss of centromeric cohesin protection and the presence of single sisters in meiosis II (Lister et al. 2010). Again, these single sisters may not to be detected by the SAC.

However, is SAC control degenerating with age as well? The literature is contradictory on this issue, and different strain backgrounds used in these studies are probably, in part, the reason for this discrepancy (Danylevska et al. 2014; Duncan et al. 2009; Liu and Keefe 2002; Merriman et al. 2013; Sebestova et al. 2012; Yun et al. 2014). Importantly, though, the checkpoint protein BUBR1 has been shown to decrease with age in both human oocytes and mouse ovaries (Baker et al. 2004; Riris et al. 2014). Given the importance of BUBR1 for checkpoint control, in addition to its role in the formation of stable spindles, a decrease of BUBR1 levels is expected to have severe consequences for SAC function in mammalian oocytes. Combined with less cohesin proteins and less SGO2 in older oocytes, the consequences for mammalian oocytes from mothers close to the end of reproductive age are expected to be dire.

Concluding remarks

The special features of cell division in meiosis and the large size of oocytes require a spindle assembly checkpoint response adapted to the developmental context. The importance of SAC control for the generation of healthy oocytes that can be fertilized, harboring the correct number of chromosomes has been clearly demonstrated. Future work will show how the SAC recognizes wrong attachments in the two meiotic divisions, and possible other roles of checkpoint proteins for chromosome orientation, segregation, and cell cycle progression in oocytes. These studies will help us get insights why chromosome segregation goes wrong so frequently in human oocytes.

Acknowledgments Work in the lab of K. Wassmann is supported by a grant from the Agence Nationale de la Recherche (ANR-12-BSV2-0005-01), the Centre National de la Recherche Scientifique (CNRS), and Université Paris 6. We thank E. Buffin, A. Vallot, and W. El Yakoubi for discussion and comments on the manuscript.

Conflict of interest The authors declare that they have no conflict of interest. For this review article, no studies with human participants or animals were performed by any of the authors.

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