PORTLAND PRESS

Review Article

Regulation of the meiotic divisions of mammalian oocytes and eggs

Jessica R. Sanders and Keith T. Jones

School of Biological Sciences, Faculty of Natural and Environmental Sciences, University of Southampton, Southampton SO17 1BJ, U.K.

Correspondence: Jessica R. Sanders (j.r.sanders@soton.ac.uk)

OPEN ⬡ ACCESS

Initiated by luteinizing hormone and finalized by the fertilizing sperm, the mammalian oocyte completes its two meiotic divisions. The first division occurs in the mature Graafian follicle during the hours preceding ovulation and culminates in an extreme asymmetric cell division and the segregation of the two pairs of homologous chromosomes. The newly created mature egg rearrests at metaphase of the second meiotic division prior to ovulation and only completes meiosis following a Ca^{2+} signal initiated by the sperm at gamete fusion. Here, we review the cellular events that govern the passage of the oocyte through meiosis I with a focus on the role of the spindle assembly checkpoint in regulating its timing. In meiosis II, we examine how the egg achieves its arrest and how the fertilization Ca^{2+} signal allows the initiation of embryo development.

Introduction

In mammals, under hormonal cues, oocytes mature into eggs that are then fertilized [1–3]. Oocytes spend the vast majority of their life having entered meiosis but arresting before its completion. In the fetal ovary, oocytes are formed from primordial germ cells. These cells commit in a one-way journey to enter meiosis, which at its earliest stage, involves a whole genome replication (S-phase) followed immediately by a specialized pairing of all homologous chromosomes. In this way, a newly replicated pair of maternal origin chromosome 1 joins up with a newly replicated paternal origin chromosome 1, and so on for all autosomes as well as the sex chromosomes that pair through their PAR regions. In what appears to be the biological pinnacle of self-harm, these paired homologous chromosomes are then fragmented by deliberate double-strand DNA breakage [4–6]. The subsequent repair of such breaks results in a physical tethering of the two pairs of homologous chromosomes and generates chromosomes made from both maternal and paternal components that will eventually separate. Therefore, the self-harm is indeed essential given it provides a shuffling of the genes that is so advantageous and which, from an evolutionary perspective, gives meaning to sexual reproduction.

The physically tethered pair of homologous chromosomes (homolog pairs) forms a structure known as a bivalent. In the two meiotic divisions that follow, the bivalent divides reductionally in meiosis I (MI) to form two sister chromatid pairs. Cell division is very asymmetric in oocytes during MI, such that the products are a mature egg and a much smaller first polar body (PB1), which later degenerates and plays no part in embryo development. In mammals, it is a hormonal cue, luteinizing hormone (LH), which is responsible for this process. Prior to this signal, the oocyte is essentially in an arrested dictyate state, and also said to be in the germinal vesicle (GV) stage which is similar to G2 of a somatic cell. As such, as the oocyte resumes MI, it undergoes a process of nuclear envelope breakdown (NEB) caused by activation of Cdk1 — this is a G2/M transition [7,8]. In mammals, the time from a rise in LH to PB1 extension is several hours but varies between species [9]. Luckily for research purposes such a process, known as oocyte (or meiotic) maturation, can be replicated simply by removing the oocyte from the ovary and culturing it in media. This is because the ovary provides an oocyte maturation inhibitory environment [10].

Having completed MI, the mature egg rearrests at metaphase of meiosis II (MII). Such an event happens a short while before ovulation. This means that a metaphase II (metII)-arrested egg is ovulated into the female reproductive tract. If sperm are present, the egg is fertilized and it is this event that triggers the egg to complete MII. This second division, which is also asymmetric, resulting in a one-cell embryo and a second polar body (PB2) is described as an equational division. It involves the segregation of a sister chromatid pair and, in this respect, it resembles chromosome division in mitosis.

This review focuses on how the two meiotic divisions of the mammalian oocyte, specifically mouse oocytes, are controlled. It begins with an examination of how bivalents congress on the meiotic spindle in MI during oocyte maturation followed NEB; and it explores the factors responsible for faithful segregation. It then examines how metII is achieved and how sperm break this arrest from the perspective of cell division. We make analogy and give contrast where needed between these two divisions that temporally are separated by only a few hours.

Meiosis I completion

In mitosis, the kinetochores of sister chromatids bi-orientate towards opposite poles of the spindle but during MI the sister kinetochores align side-by-side, and in so doing 'mono-orient' towards the same pole. For mammalian oocytes, MI prometaphase is prolonged, lasting several hours, which may be due to this unique co-alignment of sister kinetochore pairs. Such an arrangement may well be inefficient in binding microtubules and achieving correct orientation with respect to the meiotic spindle. As with all other mammalian cell divisions, the segregation of chromosomes in MI is a result of anaphase-promoting complex (APC) activity which must be tightly controlled [11–15]. One component that regulates APC activity is the spindle assembly checkpoint (SAC). This brake acts as a block to anaphase until bivalents are captured on the spindle correctly and become aligned [16–20] (see Figure 1). The SAC is therefore thought to function in decreasing the risk of chromosome segregation errors. In oocytes, this is important given the high incidence of aneuploidies reported to occur that are derived from segregation errors in MI [21–25].

The meiotic SAC does not operate as an on/off binary switch [26] (in fact in mitosis, this is likely also to be the case [27]). As such, in maturing oocytes, the SAC is never truly off, such that even at the height of its activity the APC is only 50% of its possible maximal rate. 100% full APC is uncovered only in the presence of SAC inhibitors. Additionally, the switch from 'off' to '50% on' is not entirely achieved through bi-orientation of bivalents, as oocytes can and do show considerable APC activity when bivalents are highly scattered in the cytoplasm [28]. The lack of ability of the SAC to act as a brake for completion of MI when bivalents are not properly bi-oriented has given it the moniker of being weak in oocytes. Indeed, it is now a well-established observation that oocytes can proceed through MI with a degree of bivalents not being bi-oriented [28–32]. However, their ability to respond well to DNA damage (see later) makes this observation surprising. The SAC can act as a strong brake in oocytes, so its strength appears dependent on what is the underlying trigger for its activation.

When the SAC is active, unattached kinetochores act as a docking site for proteins which bind in a hierarchal manner (see Figure 1). This is the case for both mitosis and oocytes in MI. During mitosis, Mps1 binds to free kinetochores and acts as a platform for binding other SAC proteins including Bub1, BubR1 and Bub3 [33]. Mps1 also binds kinetochores in oocytes and is essential for ensuring the correct timing of cell cycle progression [34]. Mps1 activity can be inhibited by the small molecule Reversine by ATP competition [35]. Bub1, BubR1 and Bub3 have all been found to play a role in regulating the SAC in mouse oocytes [36–38]. Mad1 and Mad2 are also expressed in mouse oocytes and are recruited directly to the kinetochores [39–41]. In mitosis, it is known that Mad2 undergoes a conformational change, resulting in the formation of a cytoplasmic mitotic checkpoint complex (MCC) that acts as a potent APC inhibitor [42]. Closed Mad2 (C-Mad2) with Mad1 binds directly to the kinetochore and recruits open Mad2 (O-Mad2), converting O-Mad2 to an intermediate form I-Mad2. This I-Mad2 binds to the APC activator cdc20 and closes thus inhibiting APC activity [43]. The activity of MCC during meiosis is not yet clear; however, it is very likely that there is a similar mechanism in oocytes because of the existence of its component parts (see Figure 1). Bisected oocytes that are free of bivalents rapidly lose this MCC brake to the APC, and so similar to somatic cells, it must be that the MCC is short-lived and requires the kinetochores for its continued existence [44]. It is unclear how far the MCC is able to diffuse in the cytoplasm of oocytes. As oocytes have a large volume, it is possible that the diffusible signal of the SAC response is not able to diffuse sufficiently which could lead to the weak SAC in oocytes [45]. However, even
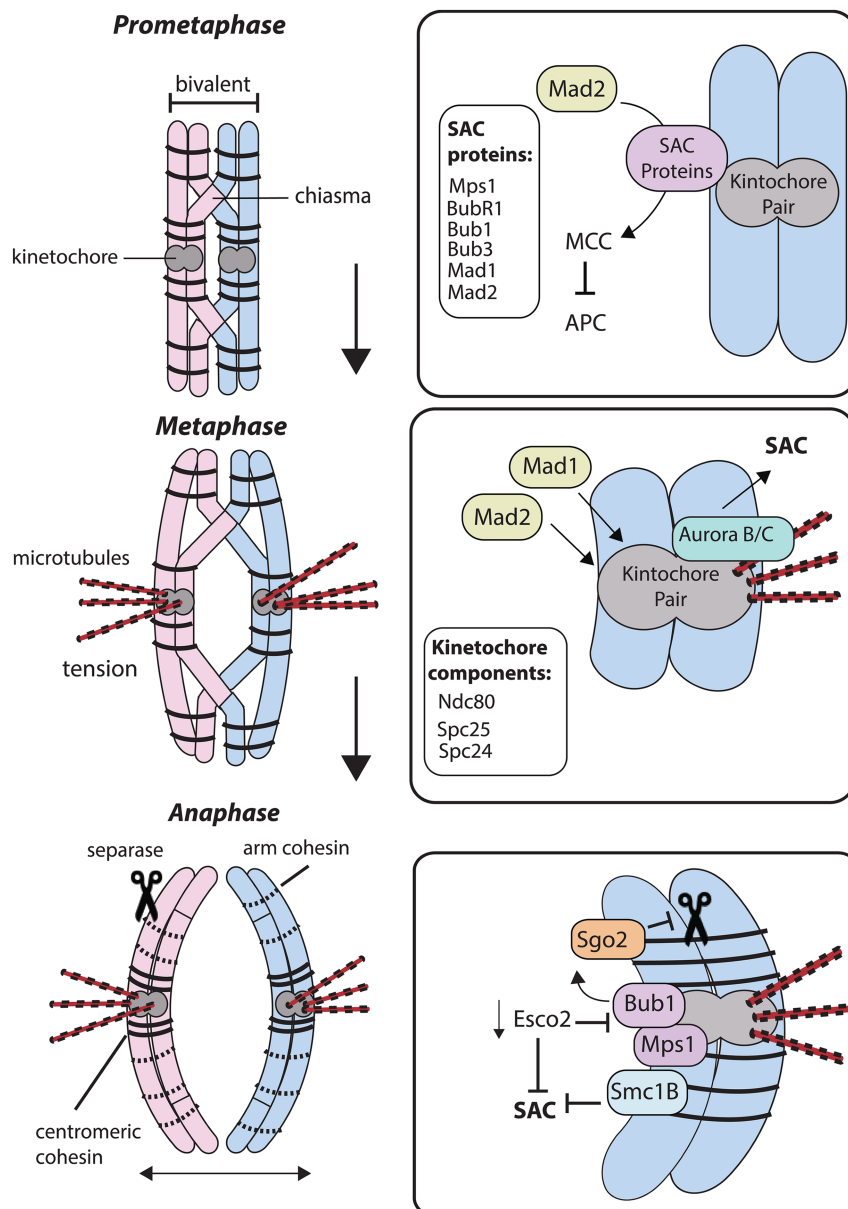
Figure 1. Cell cycle proteins mediating progression during MI.

Homologous chromosome pairs are bound together through recombination-derived cross-over events, forming a bivalent. During prometaphase and metaphase, the SAC is active due to a lack of microtubule–kinetochore attachment and/or tension between the bivalent and microtubules. During SAC activation, Mps1 is recruited to unattached kinetochores leading to further recruitment of Bub1, Bub3 and BubR1. Mad1 and Mad2 are also directly recruited to the kinetochore. Mad2 undergoes a conformational change, which promotes the formation of the potent APC inhibitor MCC in the cytoplasm. The kinetochore protein Ndc80 (Hec1) binds directly to microtubules to promote microtubule–kinetochore attachment and also the recruitment of Mad1 to kinetochores. Spc24 and Spc25 are other kinetochore proteins which regulate SAC activation through the recruitment of Mad2. As microtubules attach to kinetochores correctly, tension across the bivalent increases. Insufficient tension can also activate the SAC via Aurora B/C activation and the error correction pathway. At anaphase, the bivalents are separated by the cleavage of cohesin by separase, but centromeric cohesin holding the chromatids together is protected. Sgo2 inhibits separase activity at the centromeric region. Mps1 and Bub1 ensure the correct localization of Sgo2. Esco2 is a cohesin-producing enzyme which is also essential for SAC activation. If Esco2 activity is not sufficient, SAC is not activated when required therefore proteins such as Bub1 are mislocalized. The cohesin subunit Smc1B is also necessary for SAC activation.

oocytes with over 80% reduced volume are still prone to chromosome segregation errors [46], so volume *per se* is unlikely to be an explanation of mis-segregation errors.

The loss of SAC components in oocytes leads to an acceleration through MI, principally because the brake is removed from APC activity anaphase happens sooner [21,25]. A high rate of bivalent mis-segregation leading to aneuploid eggs follows the loss of individual SAC components, which suggests that this checkpoint serves a necessary component in maintaining a high rate of faithful chromosome division in MI [34,36,37,40,47]. The SAC is sensitive to many different chromosome and spindle abnormalities in oocytes. One important factor in ensuring correct chromosome segregation is sufficient kinetochore–microtubule attachment. During mitosis, the KNL-1/Mis12 complex Ndc80 complex (KMN) network is responsible for promoting kinetochore–microtubule attachment and is composed of many protein complexes [48]. For example, Ndc80 (HEC1) binds directly to microtubules and anchors these to other protein complexes at the kinetochore [49,50]. Ndc80 is also responsible for recruiting SAC-related proteins such as Mad1 [51]. It is unclear whether the KMN network plays a role in monitoring kinetochore–microtubule attachments during meiosis; however, Ndc80 levels at microtubules increase during oocyte maturation and overexpression of Ndc80 causes cell cycle arrest in oocytes [52] (see Figure 1). Other components of the Ndc80 complex, Spc25 and Spc24, have also been found to play a role in regulating the SAC in oocytes including the recruitment of Mad2 [53,54] (see Figure 1). Other proteins associated with SAC activation such as Aurora B kinase may also play a role in stabilizing kinetochore–microtubule attachments [49,55,56]. During oocyte maturation, Aurora C kinase is also expressed and its activity appears to compensate for loss of Aurora B kinase [57]. Inhibiting Aurora kinase has been found to accelerate oocyte maturation and reverse an SAC-induced arrest [47]. A recent study has also suggested that Aurora B/C could play a role in detecting tension between bivalents and the spindle poles during MI. In this instance, Aurora B/C induces an error correction pathway that in turn activates SAC [58] (see Figure 1). This is a mechanism similar to that present for detecting insufficient chromatid tension during mitosis [59].

At chromosome segregation, the cohesin-binding homologous chromosomes together must be cleaved. This occurs as a result of separase activity following the activation of the APC [11]. However, because chromosome segregation in oocytes occurs in two phases, during MI and MII, it is key that the sister chromatids remain bound by centromeric cohesin and only the two homologous chromosome pairs that constitute the bivalent are separated during MI. Therefore, cohesin has to be removed in a stepwise manner. One protein involved in regulating this is Shugoshin 2 (Sgo2), which acts to protect centromeric cohesin from separase activity during MI through the recruitment of the PP2A phosphatase PP2A-C [60,61] (see Figure 1). It is thought that the correct localization of PP2A-C prevents separase cleavage of cohesin by dephosphorylating cohesin components such as Rec8 [61]. Interestingly, the correct localization of Sgo2 to the centromeric and pericentromeric region is dependent on the SAC components Mps1 and Bub1 [62] (see Figure 1). Insufficient sister chromatid cohesion could be an activator of the SAC in oocytes. Esco1 and Esco2 both play a role in regulating cohesin through the acetylation of the cohesin subunit Smc3. However, unlike Esco1, which is mainly responsible for maintaining the non-cohesive properties of cohesin, Esco2 plays a key role in establishing the cohesin complex and also in activating SAC [63]. Depletion of Esco2 leads to an inactivated SAC, loss of Bub1 from kinetochores and escape from MI arrest induced by the spindle poison nocodazole [64] (see Figure 1). The meiosis-specific cohesin subunit Smc1B is essential for maintaining sister chromatid cohesion through MI [65]. The presence of Smc1B is required for SAC activation and without it the chromosomes fail to align correctly [66] (see Figure 1). Securin, which binds and in so doing inhibits separase activity, is destroyed by APC during MI exit and can be modulated by the activity of SAC kinases [67]. When this centromeric cohesion is lost during MI, the SAC is not correctly activated and SAC-related proteins, such as Bub1, do not become correctly localized to the kinetochores [68] (see Figure 1).

Once the checkpoint has been satisfied, SAC proteins detach from the kinetochores and APC activity rises, albeit in oocytes to a submaximal peak [69]. During MI in oocytes, the SAC appears to be weak and ineffectual at detecting chromosomal alignment abnormalities compared with its activity during mitosis. As such, the SAC often allows the completion of meiosis even if not all the bivalents are correctly aligned or attached [70]. This leads to high rates of aneuploidy in oocytes by incorrect segregation of bivalents, raising the question of whether the SAC is activated/inactivated in response to any other factors during MI.

It appears that the SAC may play an additional role in responding to DNA damage accumulated during MI. For example, if DNA damage is induced in oocytes, the SAC is activated and the cell cycle is arrested at metaphase I (metI) [71,72]. This metI arrest can be triggered in response to DNA damage induced in a chemical or physical way but not by all types of DNA damage [73]. Double-strand breaks (DSBs) induced by

neocarzinostatin, etoposide or laser beam dissection all increase the rate of MI arrest [73–75]. However, in contrast, interstrand cross-links induced by mitomycin C do not affect meiotic progression [75]. Interestingly, even though metI arrest occurs in oocytes exposed to DNA-damaging agents at any stage of MI, NEB still occurs in GV oocytes that have been exposed [73]. This suggests that there is no DNA damage checkpoint in operation in GV stage oocytes that prevents NEB. This is in contrast with somatic cells, where there is often a block in the G2/M transition following exposure to DSB-inducing agents [76]. The mechanism by which DSBs activate the SAC in oocytes is not yet fully known. It appears that DNA damage has no effect on kinetochore–microtubule interaction, the number of k-fibres, bi-orientation of the chromosomes or the tension across these chromosomes [73,77]. However, there is an assembly of SAC-associated proteins at the kinetochores [77]. Furthermore, this response appears to be reliant on the activity of Mps1, Aurora kinase and haspin [77]. Crucially, this DNA damage response does not involve Ataxia telangiectasia-mutated (ATM) or ATM and RAD3-related (ATR) signaling, which are normally integral to signaling in DNA damage responses [77]. Also, this arrest appears to be a unique feature of MI oocytes, as DNA damage in metII eggs does not activate the SAC [77].

Meiosis II completion

MI is completed with the extrusion of the first PB and MII entry immediately follows. As the chromosomes remaining in the mature oocyte (hereafter referred to as an egg) are already co-located, it is probably unsurprising that metII is achieved within an hour. The egg becomes arrested at this point until fertilization, and its cell cycle release is a crucial component of fertilization. It is therefore vital that metII arrest and release are tightly controlled (see Figure 2).

During metII arrest, Cdk1 activity is kept high [78]. This is a combination of high levels of cyclin B1 synthesis and an increase in Cdk1 activation through dephosphorylation by the phosphatase Cdc25A [79].
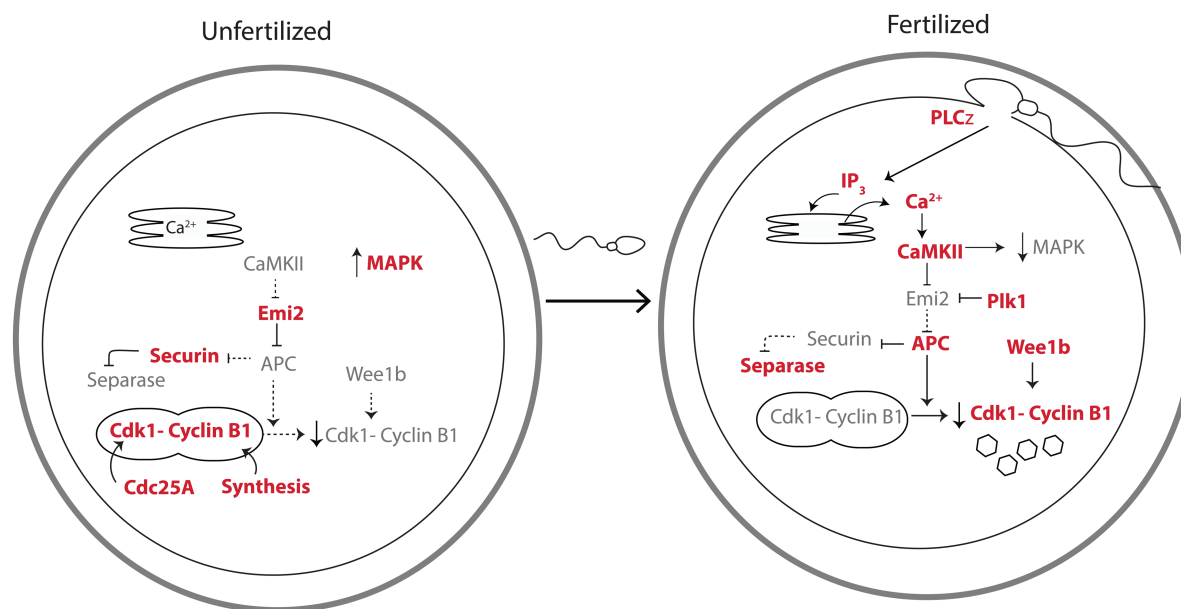
Figure 2. Cell cycle proteins involved in arrest and release from metII during egg activation.
During metII arrest, Emi2 is kept high. It inhibits the APC, thus preventing loss Cdk1 activity through cyclin B1 proteolysis. Cdk1 activity is further maintained by continual cyclin B1 synthesis and stimulation of Cdc25. MAPK levels are also high in unfertilized eggs. At fertilization, following sperm-egg fusion, PLCζ diffuses into the egg and hydrolyses PIP_2 to produce IP_3 which releases Ca^{2+} from the endoplasmic reticulum and so activates CamKII. Emi2 is a CamKII and Plk1 substrate, with its phosphorylation leading to degradation. Loss of Emi2 frees the APC to be active, causing cyclin B1 degradation and consequently lowering Cdk1 activity, a process enhanced by Cdk1 phosphorylation by Wee1b. APC activation also degrades securin leading to the activation of separase, promoting chromosome segregation by cohesin cleavage. The increase in cystosolic Ca^{2+} also decreases MAPK activity, which promotes the formation of the nuclear envelope.

Furthermore, the degradation of cyclin B1 and securin is prevented through the inhibition of APC by Emi2, which appears to be made only at the completion of MI [80]. MetII arrest can last tens of hours, during which time the spindle remains intact, although postovulatory ageing of the egg is observed over extended periods with an associated loss in some spindle integrity [81]. It is not until fertilization that MII is completed and the second polar body is extruded.

At fertilization, the metII egg undergoes a series of physiological and biochemical changes known as activation. When the sperm and egg fuse, phospholipase C zeta (PLCζ) is released from the sperm into the egg cytoplasm [82,83]. This triggers Ca^{2+} release from the endoplasmic reticulum through the hydrolysis of phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$) and the production of inositol trisphosphate (IP_3) [82,83]. The Ca^{2+} release that occurs follows a pattern of oscillations, a series of repetitive, transient increases in cytosolic Ca^{2+} concentrations that last for many hours [82,84,85]. PLCζ activity appears to be sufficient to induce these Ca^{2+} oscillations, which go on to trigger many of the subsequent events of egg activation including resumption of MII. However, there also exists a cryptic secondary factor in the sperm capable of causing some Ca^{2+} release, but is 'cryptic' because it is only observable when PLCζ is absent [86,87]. Its presence may be indicative of a backup mechanism, ensuring that fertilization will take place, but its exact identity remains currently unknown.

There is a clear link between the Ca^{2+} oscillations and cell cycle resumption through the Ca^{2+} sensing enzyme calmodulin-dependent protein kinase II (CamKII) [88,89]. CamKII activates protein tyrosine kinase Wee1b, which inhibits Cdk1 through phosphorylation [90]. The APC inhibitor Emi2 is also a CamKII substrate, which leads to further phosphorylation of Emi2 by Polo-like kinase 1 (Plk1) [91]. As Emi2 is degraded, the APC is activated [80], enabling the targeted destruction of cyclin B1 and securin thus promoting cell cycle progression [92]. The centromeric cohesin is no longer protected as Sgo2 is removed and the PP2A phosphatase inhibitor 12PP2A is activated [60,93]. The decrease in securin directly activates separase, which allows the sister chromatids to be separated at anaphase [94]. For the full completion of MII however, the nuclear envelope must reform and chromosomes decondense. This process requires the destruction of another signaling component, MAPK [95]. Like Cdk1, MAPK levels are kept high during metII arrest [96]. However, MAPK requires many Ca^{2+} oscillations before it is destroyed effectively at egg activation [97]. This means that though the destruction of cyclin B1 is sufficient to resume MII, in order to complete MII it is essential that MAPK is destroyed.

Like MI oocytes, metII-arrested eggs are able to respond to DNA damage. However, these eggs respond differently to MI oocytes and the SAC is not activated in response to DNA damage. If metII eggs are exposed to etoposide and nocodazole treatment, only a small amount of Mad1 becomes localized to the kinetochores, far less than that seen in MI oocytes [77]. Furthermore, these damaged eggs are still able to activate at high rates [77]. This shows that similar to somatic cells during mitosis, metII eggs do not display arrest in response to DNA damage. However, very high levels of damage do have a negative effect on metII eggs. Exposing unfertilized metII eggs to the anti-tumor drug doxorubicin (DXRS) triggers apoptosis by the canonical caspase cascade [98]. Crucially, DNA damage can be detected very early in response to DXRS [99]. It is now believed that apoptosis in metII eggs is triggered as a result of two different checkpoints: one is DNA integrity and the other is mitochondrial integrity [100]. Cytochrome c leakage from the mitochondria can facilitate the formation of a protein complex known as the apoptosome which then activates caspases [101]. It is important to note that this response to DNA damage only occurs in unfertilized egg. When fertilized, one-cell embryo do not undergo apoptosis in response to drugs such as DXR, instead these cells arrest in their cell cycle much like MI oocytes [98]. The reason for these cell cycle-dependent difference in DNA damage responses remains unknown.

Conclusions

Despite much of the cell cycle machinery being conserved between mitosis and meiosis, there still appears to be some unique features of control in maturing oocytes and mature eggs. This is likely due to the unique nature of the two meiotic divisions, relating to their prolonged duration punctuated by stops and starts, which likely necessitates for a nunaced level of control not observed in somatic cells. The SAC is active in oocytes yet displays different levels of effectiveness against microtubules attachment errors (weak) and DNA damage (strong arrest). Why this apparent difference in the strength of the SAC exists is unclear, but if resolved may shed some insight into a fundamental aspect of meiotic cell cycle regulation. Similarly, in eggs, the identity of

PORTLAND
PRESS

the second sperm-activating factor that is not PLCζ may shed light on a novel signaling pathway employed in eggs to activate the cell cycle machinery required for completion of MII.

Abbreviations

APC, anaphase-promoting complex; ATM, Ataxia telangiectasia-mutated; CamKII, calmodulin-dependent protein kinase II; DSBs, double-strand breaks; DXRS, doxorubicin; GV, germinal vesicle; I-Mad2, intermediate form of Mad2; IP$_3$, inositol trisphosphate; KMN, KNL-1/Mis12 complex Ndc80 complex; LH, luteinizing hormone; MCC, mitotic checkpoint complex; metI, metaphase I; metII, metaphase II; MI, meiosis I; MII, meiosis II; NEB, nuclear envelope breakdown; O-Mad2, open Mad2; PAR, pseudoautosomal region; PB1, first polar body; PI(4,5)P$_2$, phosphatidylinositol 4,5-bisphosphate; PLCζ, phospholipase C zeta; Plk1, Polo-like kinase 1; SAC, spindle assembly checkpoint; Sgo2, Shugoshin 2.

Funding

Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

References

1   Jones, K.T. (2008) Meiosis in oocytes: predisposition to aneuploidy and its increased incidence with age. *Hum. Reprod. Update* **14**, 143–158 https://doi.org/10.1093/humupd/dmm043

2   Jaffe, L.A. and Egbert, J.R. (2017) Regulation of mammalian oocyte meiosis by intercellular communication within the ovarian follicle. *Annu. Rev. Physiol.* **79**, 237–260 https://doi.org/10.1146/annurev-physiol-022516-034102

3   Conti, M., Hsieh, M., Zamah, A.M. and Oh, J.S. (2012) Novel signaling mechanisms in the ovary during oocyte maturation and ovulation. *Mol. Cell. Endocrinol.* **356**, 65–73 https://doi.org/10.1016/j.mce.2011.11.002

4   MacLennan, M., Crichton, J.H., Playfoot, C.J. and Adams, I.R. (2015) Oocyte development, meiosis and aneuploidy. *Semin. Cell Dev. Biol.* **45**, 68–76 https://doi.org/10.1016/j.semcdb.2015.10.005

5   de Boer, E., Jasin, M. and Keeney, S. (2015) Local and sex-specific biases in crossover vs. noncrossover outcomes at meiotic recombination hot spots in mice. *Genes Dev.* **29**, 1721–1733 https://doi.org/10.1101/gad.265561.115

6   Wojtasz, L., Cloutier, J.M., Baumann, M., Daniel, K., Varga, J., Fu, J. et al. (2012) Meiotic DNA double-strand breaks and chromosome asynapsis in mice are monitored by distinct HORMAD2-independent and -dependent mechanisms. *Genes Dev.* **26**, 958–973 https://doi.org/10.1101/gad.187559.112

7   Adhikari, D., Zheng, W., Shen, Y., Gorre, N., Ning, Y., Halet, G. et al. (2012) Cdk1, but not Cdk2, is the sole Cdk that is essential and sufficient to drive resumption of meiosis in mouse oocytes. *Hum. Mol. Genet.* **21**, 2476–2484 https://doi.org/10.1093/hmg/dds061

8   Han, S.J., Martins, J.P.S., Yang, Y., Kang, M.K., Daldello, E.M. and Conti, M. (2017) The translation of cyclin B1 and B2 is differentially regulated during mouse oocyte reentry into the meiotic cell cycle. *Sci. Rep.* **7**, 14077 https://doi.org/10.1038/s41598-017-13688-3

9   Shen, Y., Betzendahl, I., Tinneberg, H.R. and Eichenlaub-Ritter, U. (2008) Enhanced polarizing microscopy as a new tool in aneuploidy research in oocytes. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **651**, 131–140 https://doi.org/10.1016/j.mrgentox.2007.10.013

10 Eppig, J.J., Freter, R.R., Ward-Bailey, P.F. and Schultz, R.M. (1983) Inhibition of oocyte maturation in the mouse: participation of cAMP, steroid hormones, and a putative maturation-inhibitory factor. *Dev. Biol.* **100**, 39–49 PMID:6194027

11 Terret, M.E., Wassmann, K., Waizenegger, I., Maro, B., Peters, J.-M. and Verlhac, M.-H. (2003) The meiosis I-to-meiosis II transition in mouse oocytes requires separase activity. *Curr. Biol.* **13**, 1797–1802 https://doi.org/10.1016/j.cub.2003.09.032

12 Holt, J.E., Tran, S.M.-T., Stewart, J.L., Minahan, K., Garcia-Higuera, I., Moreno, S. et al. (2011) The APC/C activator FZR1 coordinates the timing of meiotic resumption during prophase I arrest in mammalian oocytes. *Development* **138**, 905–913 https://doi.org/10.1242/dev.059022

13 Reis, A., Madgwick, S., Chang, H.-Y., Nabti, I., Levasseur, M. and Jones, K.T. (2007) Prometaphase APCcdh1 activity prevents non-disjunction in mammalian oocytes. *Nat. Cell Biol.* **9**, 1192–1198 https://doi.org/10.1038/ncb1640

14 Nabti, I., Marangos, P., Bormann, J., Kudo, N.R. and Carroll, J. (2014) Dual-mode regulation of the APC/C by CDK1 and MAPK controls meiosis I progression and fidelity. *J. Cell Biol.* **204**, 891–900 https://doi.org/10.1083/jcb.201305049

15 Marangos, P., Verschuren, E.W., Chen, R., Jackson, P.K. and Carroll, J. (2007) Prophase I arrest and progression to metaphase I in mouse oocytes are controlled by Emi1-dependent regulation of APC^Cdh1. *J. Cell Biol.* **176**, 65–75 https://doi.org/10.1083/jcb.200607070

16 Musacchio, A. (2015) The molecular biology of spindle assembly checkpoint signaling dynamics. *Curr. Biol.* **25**, R1002–R1018 https://doi.org/10.1016/j.cub.2015.08.051

17 Stukenberg, P.T. and Burke, D.J. (2015) Connecting the microtubule attachment status of each kinetochore to cell cycle arrest through the spindle assembly checkpoint. *Chromosoma* **124**, 463–480 https://doi.org/10.1007/s00412-015-0515-z

18 Wang, Y., Jin, F., Higgins, R. and McKnight, K. (2014) The current view for the silencing of the spindle assembly checkpoint. *Cell Cycle* **13**, 1694–1701 https://doi.org/10.4161/cc.29027

19 Foley, E.A. and Kapoor, T.M. (2013) Microtubule attachment and spindle assembly checkpoint signalling at the kinetochore. *Nat. Rev. Mol. Cell Biol.* **14**, 25–37 https://doi.org/10.1038/nrm3494

20 Lara-Gonzalez, P., Westhorpe, F.G. and Taylor, S.S. (2012) The spindle assembly checkpoint. *Curr. Biol.* **22**, R966–R980 https://doi.org/10.1016/j.cub.2012.10.006

21   Touati, S.A. and Wassmann, K. (2016) How oocytes try to get it right: spindle checkpoint control in meiosis. *Chromosoma* **125**, 321–335 https://doi.org/10.1007/s00412-015-0536-7

22   Herbert, M., Kalleas, D., Cooney, D., Lamb, M. and Lister, L. (2015) Meiosis and maternal aging: insights from aneuploid oocytes and trisomy births. *Cold Spring Harb. Perspect. Biol.* **7**, a017970 https://doi.org/10.1101/cshperspect.a017970

23   Webster, A. and Schuh, M. (2017) Mechanisms of aneuploidy in human eggs. *Trends Cell Biol.* **27**, 55–68 https://doi.org/10.1016/j.tcb.2016.09.002

24   Kitajima, T.S. (2018) Mechanisms of kinetochore–microtubule attachment errors in mammalian oocytes. *Dev. Growth Differ.* **60**, 33–43 https://doi.org/10.1111/dgd.12410

25   Jones, K.T. and Lane, S.I.R. (2013) Molecular causes of aneuploidy in mammalian eggs. *Development* **140**, 3719–3730 https://doi.org/10.1242/dev.090589

26   Lane, S.I.R. and Jones, K.T. (2014) Non-canonical function of spindle assembly checkpoint proteins after APC activation reduces aneuploidy in mouse oocytes. *Nat. Commun.* **5**, 3444. https://doi.org/10.1038/ncomms4444

27   Collin, P., Nashchekina, O., Walker, R. and Pines, J. (2013) The spindle assembly checkpoint works like a rheostat rather than a toggle switch. *Nat. Cell Biol.* **15**, 1378–1385 https://doi.org/10.1038/ncb2855

28   Lane, S.I.R., Yun, Y. and Jones, K.T. (2012) Timing of anaphase-promoting complex activation in mouse oocytes is predicted by microtubule-kinetochore attachment but not by bivalent alignment or tension. *Development* **139**, 1947–1955 https://doi.org/10.1242/dev.077040

29   Kitajima, T.S., Ohsugi, M. and Ellenberg, J. (2011) Complete kinetochore tracking reveals error-prone homologous chromosome biorientation in mammalian oocytes. *Cell* **146**, 568–581 https://doi.org/10.1016/j.cell.2011.07.031

30   Kolano, A., Brunet, S., Silk, A.D., Cleveland, D.W. and Verlhac, M.-H. (2012) Error-prone mammalian female meiosis from silencing the spindle assembly checkpoint without normal interkinetochore tension. *Proc. Natl Acad. Sci. U.S.A.* **109**, E1858–E1867 https://doi.org/10.1073/pnas.1204686109

31   Sebestova, J., Danylevska, A., Novakova, L., Kubelka, M. and Anger, M. (2012) Lack of response to unaligned chromosomes in mammalian female gametes. *Cell Cycle* **11**, 3011–3018 https://doi.org/10.4161/cc.21398

32   Gui, L. and Homer, H. (2012) Spindle assembly checkpoint signalling is uncoupled from chromosomal position in mouse oocytes. *Development* **139**, 1941–1946 https://doi.org/10.1242/dev.078352

33   von Schubert, C., Cubizolles, F., Bracher, J.M., Sliedrecht, T., Kops, G.J.P.L. and Nigg, E.A. (2015) Plk1 and Mps1 cooperatively regulate the spindle assembly checkpoint in human cells. *Cell Rep.* **12**, 66–78 https://doi.org/10.1016/j.celrep.2015.06.007

34   Hached, K., Xie, S.Z., Buffin, E., Cladière, D., Rachez, C., Sacras, M. et al. (2011) Mps1 at kinetochores is essential for female mouse meiosis I. *Development* **138**, 2261–2271 https://doi.org/10.1242/dev.061317

35   Santaguida, S., Tighe, A., D'Alise, A.M., Taylor, S.S. and Musacchio, A. (2010) Dissecting the role of MPS1 in chromosome biorientation and the spindle checkpoint through the small molecule inhibitor reversine. *J. Cell Biol.* **190**, 73 https://doi.org/10.1083/jcb.201001036

36   McGuinness, B.E., Anger, M., Kouznetsova, A., Gil-Bernabé, A.M., Helmhart, W., Kudo, N.R. et al. (2009) Regulation of APC/C activity in oocytes by a Bub1-dependent spindle assembly checkpoint. *Curr. Biol.* **19**, 369–380 https://doi.org/10.1016/j.cub.2009.01.064

37   Li, M., Li, S., Yuan, J., Wang, Z.-B., Sun, S.-C., Schatten, H. et al. (2009) Bub3 is a spindle assembly checkpoint protein regulating chromosome segregation during mouse oocyte meiosis. *PLoS ONE* **4**, e7701 https://doi.org/10.1371/journal.pone.0007701

38   Wei, L., Liang, X.-W., Zhang, Q.-H., Li, M., Yuan, J., Li, S. et al. (2010) Bubr1 is a spindle assembly checkpoint protein regulating meiotic cell cycle progression of mouse oocyte. *Cell Cycle* **9**, 1112–1121 https://doi.org/10.4161/cc.9.6.10957

39   Niault, T., Hached, K., Sotillo, R., Sorger, P.K., Maro, B., Benezra, R. et al. (2007) Changing Mad2 levels affects chromosome segregation and spindle assembly checkpoint control in female mouse meiosis I. *PLoS ONE* **2**, e1165 https://doi.org/10.1371/journal.pone.0001165

40   Homer, H.A., McDougall, A., Levasseur, M., Yallop, K., Murdoch, A.P. and Herbert, M. (2005) Mad2 prevents aneuploidy and premature proteolysis of cyclin B and securin during meiosis I in mouse oocytes. *Genes Dev.* **19**, 202–207 https://doi.org/10.1101/gad.328105

41   Zhang, D., Li, M., Ma, W., Hou, Y., Li, Y.-H., Li, S.-W. et al. (2005) Localization of mitotic arrest deficient 1 (MAD1) in mouse oocytes during the first meiosis and its functions as a spindle checkpoint protein. *Biol. Reprod.* **72**, 58–68 https://doi.org/10.1095/biolreprod.104.032987

42   De Antoni, A., Pearson, C.G., Cimini, D., Canman, J.C., Sala, V., Nezi, L. et al. (2005) The Mad1/Mad2 complex as a template for Mad2 activation in the spindle assembly checkpoint. *Curr. Biol.* **15**, 214–225 https://doi.org/10.1016/j.cub.2005.01.038

43   Hara, M., Özkan, E., Sun, H., Yu, H. and Luo, X. (2015) Structure of an intermediate conformer of the spindle checkpoint protein Mad2. *Proc. Natl Acad. Sci. U.S.A.* **112**, 11252–11257 https://doi.org/10.1073/pnas.1512197112

44   Holt, J.E., Lane, S.I.R., Jennings, P., García-Higuera, I., Moreno, S. and Jones, K.T. (2012) APC^{FZR1} prevents nondisjunction in mouse oocytes by controlling meiotic spindle assembly timing. *Mol. Biol. Cell* **23**, 3970–3981 https://doi.org/10.1091/mbc.e12-05-0352

45   Kyogoku, H. and Kitajima, T.S. (2017) Large cytoplasm is linked to the error-prone nature of oocytes. *Dev. Cell* **41**, 287–298.e4 https://doi.org/10.1016/j.devcel.2017.04.009

46   Lane, S.I.R. and Jones, K.T. (2017) Chromosome biorientation and APC activity remain uncoupled in oocytes with reduced volume. *J. Cell Biol.* **216**, 3949–3957 https://doi.org/10.1083/jcb.201606134

47   Lane, S.I.R., Chang, H.-Y., Jennings, P.C. and Jones, K.T. (2010) The aurora kinase inhibitor ZM447439 accelerates first meiosis in mouse oocytes by overriding the spindle assembly checkpoint. *Reproduction* **140**, 521–530 https://doi.org/10.1530/REP-10-0223

48   Varma, D. and Salmon, E.D. (2012) The KMN protein network — chief conductors of the kinetochore orchestra. *J. Cell Sci.* **125**, 5927–5936 https://doi.org/10.1242/jcs.093724

49   Ciferri, C., Pasqualato, S., Screpanti, E., Varetti, G., Santaguida, S., Dos Reis, G. et al. (2008) Implications for kinetochore-microtubule attachment from the structure of an engineered Ndc80 complex. *Cell* **133**, 427–439 https://doi.org/10.1016/j.cell.2008.03.020

50   Kudalkar, E.M., Scarborough, E.A., Umbreit, N.T., Zelter, A., Gestaut, D.R., Riffle, M. et al. (2015) Regulation of outer kinetochore Ndc80 complex-based microtubule attachments by the central kinetochore Mis12/MIND complex. *Proc. Natl Acad. Sci. U.S.A.* **112**, E5583–E5589 https://doi.org/10.1073/pnas.1513882112

51   DeLuca, J.G., Howell, B.J., Canman, J.C., Hickey, J.M., Fang, G. and Salmon, E.D. (2003) Nuf2 and Hec1 are required for retention of the checkpoint proteins Mad1 and Mad2 to kinetochores. *Curr. Biol.* **13**, 2103–2109 https://doi.org/10.1016/j.cub.2003.10.056

52 Sun, S.-C., Zhang, D.-X., Lee, S.-E., Xu, Y.-N. and Kim, N.-H. (2011) Ndc80 regulates meiotic spindle organization, chromosome alignment, and cell cycle progression in mouse oocytes. *Microsc. Microanal.* **17**, 431–439 https://doi.org/10.1017/S1431927611000274

53 Sun, S.-C., Lee, S.-E., Xu, Y.-N. and Kim, N.-H. (2010) Perturbation of Spc25 expression affects meiotic spindle organization, chromosome alignment and spindle assembly checkpoint in mouse oocytes. *Cell Cycle* **9**, 4552–4559 https://doi.org/10.4161/cc.9.22.13815

54 Zhang, T., Zhou, Y., Wang, H.-H., Meng, T.-G., Guo, L., Ma, X.-S. et al. (2016) Spc24 is required for meiotic kinetochore-microtubule attachment and production of euploid eggs. *Oncotarget* **7**, 71987–71997 https://doi.org/10.18632/oncotarget

55 Liu, D. and Lampson, M.A. (2009) Regulation of kinetochore–microtubule attachments by Aurora B kinase. *Biochem. Soc. Trans.* **37**, 976–980 https://doi.org/10.1042/BST0370976

56 Cimini, D., Wan, X., Hirel, C.B. and Salmon, E.D. (2006) Aurora kinase promotes turnover of kinetochore microtubules to reduce chromosome segregation errors. *Curr. Biol.* **16**, 1711–1718 https://doi.org/10.1016/j.cub.2006.07.022

57 Schindler, K., Davydenko, O., Fram, B., Lampson, M.A. and Schultz, R.M. (2012) Maternally recruited Aurora C kinase is more stable than Aurora B to support mouse oocyte maturation and early development. *Proc. Natl Acad. Sci. U.S.A.* **109**, E2215–E2222 https://doi.org/10.1073/pnas.1120517109

58 Vallot, A., Leontiou, I., Cladière, D., El Yakoubi, W., Bolte, S., Buffin, E. et al. (2018) Tension-induced error correction and not kinetochore attachment status activates the SAC in an aurora-B/C-dependent manner in oocytes. *Curr. Biol.* **28**, 130–139.e3 https://doi.org/10.1016/j.cub.2017.11.049

59 Lampson, M.A. and Cheeseman, I.M. (2011) Sensing centromere tension: Aurora B and the regulation of kinetochore function. *Trends Cell Biol.* **21**, 133–140 https://doi.org/10.1016/j.tcb.2010.10.007

60 Lee, J., Kitajima, T.S., Tanno, Y., Yoshida, K., Morita, T., Miyano, T. et al. (2008) Unified mode of centromeric protection by shugoshin in mammalian oocytes and somatic cells. *Nat. Cell Biol.* **10**, 42–52 https://doi.org/10.1038/ncb1667

61 Xu, Z., Cetin, B., Anger, M., Cho, U.S., Helmhart, W., Nasmyth, K. et al. (2009) Structure and function of the PP2A-shugoshin interaction. *Mol. Cell* **35**, 426–441 https://doi.org/10.1016/j.molcel.2009.06.031

62 El Yakoubi, W., Buffin, E., Cladière, D., Gryaznova, Y., Berenguer, I., Touati, S.A. et al. (2017) Mps1 kinase-dependent Sgo2 centromere localisation mediates cohesin protection in mouse oocyte meiosis I. *Nat. Commun.* **8**, 694 https://doi.org/10.1038/s41467-017-00774-3

63 Alomer, R.M., da Silva, E.M.L., Chen, J., Piekarz, K.M., McDonald, K., Sansam, C.G. et al. (2017) Esco1 and Esco2 regulate distinct cohesin functions during cell cycle progression. *Proc. Natl Acad. Sci. U.S.A.* **114**, 9906–9911 https://doi.org/10.1073/pnas.1708291114

64 Lu, Y., Dai, X., Zhang, M., Miao, Y., Zhou, C., Cui, Z. et al. (2017) Cohesin acetyltransferase Esco2 regulates SAC and kinetochore functions via maintaining H4K16 acetylation during mouse oocyte meiosis. *Nucleic Acids Res.* **45**, 9388–9397 https://doi.org/10.1093/nar/gkx563

65 Revenkova, E., Eijpe, M., Heyting, C., Hodges, C.A., Hunt, P.A., Liebe, B. et al. (2004) Cohesin SMC1β is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. *Nat. Cell Biol.* **6**, 555–562 https://doi.org/10.1038/ncb1135

66 Miao, Y., Zhou, C., Cui, Z., Dai, X., Zhang, M., Lu, Y. et al. (2017) Smc1β is required for activation of SAC during mouse oocyte meiosis. *Cell Cycle* **16**, 536–544 https://doi.org/10.1080/15384101.2017.1282583

67 Nabti, I., Grimes, R., Sarna, H., Marangos, P. and Carroll, J. (2017) Maternal age-dependent APC/C-mediated decrease in securin causes premature sister chromatid separation in meiosis II. *Nat. Commun.* **8**, 15346 https://doi.org/10.1038/ncomms15346

68 Lagirand-Cantaloube, J., Ciabrini, C., Charrasse, S., Ferrieres, A., Castro, A., Anahory, T. et al. (2017) Loss of centromere cohesion in aneuploid human oocytes correlates with decreased kinetochore localization of the Sac proteins Bub1 and Bubr1. *Sci. Rep.* **7**, 44001 https://doi.org/10.1038/srep44001

69 Kops, G.J.P.L. and Shah, J.V. (2012) Connecting up and clearing out: how kinetochore attachment silences the spindle assembly checkpoint. *Chromosoma* **121**, 509–525 https://doi.org/10.1007/s00412-012-0378-5

70 Nagaoka, S.I., Hodges, C.A., Albertini, D.F. and Hunt, P.A. (2011) Oocyte-specific differences in cell-cycle control create an innate susceptibility to meiotic errors. *Curr. Biol.* **21**, 651–657 https://doi.org/10.1016/j.cub.2011.03.003

71 Marangos, P., Stevense, M., Niaka, K., Lagoudaki, M., Nabti, I., Jessberger, R. et al. (2015) DNA damage-induced metaphase I arrest is mediated by the spindle assembly checkpoint and maternal age. *Nat. Commun.* **6**, 8706. https://doi.org/10.1038/ncomms9706

72 Collins, J.K. and Jones, K.T. (2016) DNA damage responses in mammalian oocytes. *Reproduction* **152**, R15–R22 https://doi.org/10.1530/REP-16-0069

73 Collins, J.K., Lane, S.I.R., Merriman, J.A. and Jones, K.T. (2015) DNA damage induces a meiotic arrest in mouse oocytes mediated by the spindle assembly checkpoint. *Nat. Commun.* **6**, 8553 https://doi.org/10.1038/ncomms9553

74 Ma, J.-Y., Ou Yang, Y.-C., Wang, Z.-W., Wang, Z.-B., Jiang, Z.-Z., Luo, S.-M. et al. (2013) The effects of DNA double-strand breaks on mouse oocyte meiotic maturation. *Cell Cycle* **12**, 1233–1241 https://doi.org/10.4161/cc.24311

75 Yuen, W.S., Merriman, J.A., O'Bryan, M.K. and Jones, K.T. (2012) DNA double strand breaks but not interstrand crosslinks prevent progress through meiosis in fully grown mouse oocytes. *PLoS ONE* **7**, e43875 https://doi.org/10.1371/journal.pone.0043875

76 König, K. and Baisch, H. (1980) DNA synthesis and cell cycle progression of synchronized L-cells after irradiation in various phases of the cell cycle. *Radiat. Environ. Biophys.* **18**, 257–266 https://doi.org/10.1007/BF01324268

77 Lane, S.I.R., Morgan, S.L., Wu, T., Collins, J.K., Merriman, J.A., Ellnati, E. et al. (2017) DNA damage induces a kinetochore-based ATM/ATR-independent SAC arrest unique to the first meiotic division in mouse oocytes. *Development* **144**, 3475–3486 https://doi.org/10.1242/dev.153965

78 Hashimoto, N. and Kishimoto, T. (1988) Regulation of meiotic metaphase by a cytoplasmic maturation-promoting factor during mouse oocyte maturation. *Dev. Biol.* **126**, 242–252 https://doi.org/10.1016/0012-1606(88)90135-2

79 Oh, J.S., Susor, A., Schindler, K., Schultz, R.M. and Conti, M. (2013) Cdc25a activity is required for the metaphase II arrest in mouse oocytes. *J. Cell Sci.* **126**, 1081–1085 https://doi.org/10.1242/jcs.115592

80 Madgwick, S., Hansen, D.V., Levasseur, M., Jackson, P.K. and Jones, K.T. (2006) Mouse Emi2 is required to enter meiosis II by reestablishing cyclin B1 during interkinesis. *J. Cell Biol.* **174**, 791–801 https://doi.org/10.1083/jcb.200604140

81 Wakayama, S., Van Thuan, N. and Kishigami, S. (2004) Production of offspring from one-day-old oocytes stored at room temperature. *J. Reprod. Dev.* **50**, 627–637 PMID:15647614

82 Saunders, C.M., Larman, M.G., Parrington, J., Cox, L.J., Royse, J., Blayney, L.M. et al. (2002) PLC zeta: a sperm-specific trigger of Ca(2+) oscillations in eggs and embryo development. *Development* **129**, 3533–3544 PMID:12117804

83 Fujimoto, S., Yoshida, N., Fukui, T., Amanai, M., Isobe, T., Itagaki, C. et al. (2004) Mammalian phospholipase Cζ induces oocyte activation from the sperm perinuclear matrix. *Dev. Biol.* **274**, 370–383 https://doi.org/10.1016/j.ydbio.2004.07.025

84   Swann, K. and Lai, F.A. (2016) Egg activation at fertilization by a soluble sperm protein. *Physiol. Rev.* **96**, 127–149 https://doi.org/10.1152/physrev.00012.2015

85   Yeste, M., Jones, C., Amdani, S.N., Patel, S. and Coward, K. (2016) Oocyte activation deficiency: a role for an oocyte contribution? *Hum. Reprod. Update* **22**, 23–47 https://doi.org/10.1093/humupd/dmv040

86   Nozawa, K., Satouh, Y., Fujimoto, T., Oji, A. and Ikawa, M. (2018) Sperm-borne phospholipase C zeta-1 ensures monospermic fertilization in mice. *Sci. Rep.* **8**, 1315 https://doi.org/10.1038/s41598-018-19497-6

87   Hachem, A., Godwin, J., Ruas, M., Lee, H.C., Ferrer Buitrago, M., Ardestani, G. et al. (2017) PLCζ is the physiological trigger of the Ca^{2+} oscillations that induce embryogenesis in mammals but conception can occur in its absence. *Development* **144**, 2914–2924 https://doi.org/10.1242/dev.150227

88   Madgwick, S. (2005) Calmodulin-dependent protein kinase II, and not protein kinase C, is sufficient for triggering cell-cycle resumption in mammalian eggs. *J. Cell Sci.* **118**, 3849–3859 https://doi.org/10.1242/jcs.02506

89   Zhu, D.-M., Tekle, E., Chock, P.B. and Huang, C.Y. (1996) Reversible phosphorylation as a controlling factor for sustaining calcium oscillations in HeLa cells: involvement of calmodulin-dependent kinase II and a calyculin A-inhibitable phosphatase. *Biochemistry* **35**, 7214–7223 https://doi.org/10.1021/bi952471h

90   Oh, J.S., Susor, A. and Conti, M. (2011) Protein tyrosine kinase Wee1B is essential for metaphase II exit in mouse oocytes. *Science* **332**, 462–465 https://doi.org/10.1126/science.1199211

91   Solc, P., Kitajima, T.S., Yoshida, S., Brzakova, A., Kaido, M., Baran, V. et al. (2015) Multiple requirements of PLK1 during mouse oocyte maturation. *PLoS ONE* **10**, e0116783 https://doi.org/10.1371/journal.pone.0116783

92   Madgwick, S. and Jones, K.T. (2007) How eggs arrest at metaphase II: MPF stabilisation plus APC/C inhibition equals cytostatic factor. *Cell Div.* **2**, 4 https://doi.org/10.1186/1747-1028-2-4

93   Chambon, J.-P., Touati, S.A., Berneau, S., Cladière, D., Hebras, C., Groeme, R. et al. (2013) The PP2A inhibitor I2PP2A is essential for sister chromatid segregation in oocyte meiosis II. *Curr. Biol.* **23**, 485–490 https://doi.org/10.1016/j.cub.2013.02.004

94   Fulka, J., Moor, R.M. and Fulka, J. (1994) Sister chromatid separation and the metaphase-anaphase transition in mouse oocytes. *Dev. Biol.* **165**, 410–417 https://doi.org/10.1006/dbio.1994.1263

95   Verlhac, M.H., Kubiak, J.Z., Clarke, H.J. and Maro, B. (1994) Microtubule and chromatin behavior follow MAP kinase activity but not MPF activity during meiosis in mouse oocytes. *Development* **120**, 1017–1025 PMID:7600950

96   Dupré, A., Haccard, O. and Jessus, C. (2011) Mos in the oocyte: how to use MAPK independently of growth factors and transcription to control meiotic divisions. *J. Signal Transduct.* **2011**, 1–15 https://doi.org/10.1155/2011/350412

97   Gonzalez-Garcia, J.R., Bradley, J., Nomikos, M., Paul, L., Machaty, Z., Lai, F.A. et al. (2014) The dynamics of MAPK inactivation at fertilization in mouse eggs. *J. Cell Sci.* **127**, 2749–2760 https://doi.org/10.1242/jcs.145045

98   Perez, G.I., Knudson, C.M., Leykin, L., Korsmeyer, S.J. and Tilly, J.L. (1997) Apoptosis-associated signaling pathways are required for chemotherapy-mediated female germ cell destruction. *Nat. Med.* **3**, 1228–1232 https://doi.org/10.1038/nm1197-1228

99   Jurisicova, A., Lee, H.-J., D'Estaing, S.G., Tilly, J. and Perez, G.I. (2006) Molecular requirements for doxorubicin-mediated death in murine oocytes. *Cell Death Differ.* **13**, 1466–1474 https://doi.org/10.1038/sj.cdd.4401819

100   Perez, G.I., Acton, B.M., Jurisicova, A., Perkins, G.A., White, A., Brown, J. et al. (2007) Genetic variance modifies apoptosis susceptibility in mature oocytes via alterations in DNA repair capacity and mitochondrial ultrastructure. *Cell Death Differ.* **14**, 524–533 https://doi.org/10.1038/sj.cdd.4402050

101   Zou, H., Li, Y., Liu, X. and Wang, X. (1999) An APAf-1 · cytochrome *C* multimeric complex is a functional apoptosome that activates procaspase-9. *J. Biol. Chem.* **274**, 11549–11556 https://doi.org/10.1074/jbc.274.17.11549