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Department Title

Restaging the Spindle Assembly Checkpoint in Female Mammalian Meiosis I

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KEY WORDS

Mad2, mouse oocytes, spindle assembly checkpoint, aneuploidy, APC/C, cyclin B, securin

ABBREVIATIONS

abbreviations here

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ABSTRACT

In mammalian somatic cells, the spindle assembly checkpoint (SAC) is indispensable for ensuring the fidelity of chromosome segregation by delaying cell-cycle progression in the face of even a single misaligned chromosome. In contrast, the role of the SAC in unperturbed mammalian oocytes is less well defined as progression through meiosis I is unaltered in mouse oocytes in the presence of one or a few misaligned chromosomes. Furthermore, attempts to disable the function of the SAC protein, Mad2, in mouse oocytes have produced conflicting results. To gain further insight into SAC function during female mammalian meiosis I, we recently utilised a morpholino-based antisense approach to deplete the majority of Mad2 in mouse oocytes. Our results define a clear role for Mad2 in ensuring the proper timing of meiosis I events and ultimately, in ensuring the fidelity of homologue disjunction. We discuss the implications of these results for the regulation of meiosis I in mammalian oocytes and for the genesis of human aneuploidy.

INTRODUCTION: THE SAC IN MITOSIS

The spindle assembly checkpoint (SAC) is tasked with monitoring the process of chromosome segregation and is comprised primarily of the Mad (mitotic arrest-deficient) and Bub (budding uninhibited by benzimidazole) proteins.¹ The downstream target of the SAC is a multi-subunit ubiquitin ligase called the anaphase-promoting complex or cyclo-some (APC/C).² The SAC components Mad2 and BubR1 (the vertebrate homologue of Mad3) inhibit the APC/C by sequestering the APC/C substrate specificity factor Cdc20.² Once all chromosomes become properly aligned, the inhibitory SAC signal is extinguished allowing the APC/C^{Cdc20} to direct the destruction of key regulatory proteins such as securin and cyclin B required for anaphase-onset and mitotic exit. In somatic cells lacking Mad2, mitotic progression is accelerated and proteolysis of securin and cyclin B1 occur prematurely culminating in aneuploidy³ thus underpinning the indispensability of the SAC to mammalian mitosis.

THE SAC IN FEMALE MAMMALIAN MEIOSIS I

Meiosis converts diploid cells into haploid gametes via two rounds of nuclear division following a single DNA replication phase. Meiosis I is the first of these divisions and represents a highly specialised process during which homologous chromosomes segregate (or disjoin) whilst during meiosis II, sister chromatids separate akin to mitosis.⁴ As in mitosis, the available evidence strongly suggest that mammalian oocytes also require the APC/C^{Cdc20} for homologue disjunction and exit from meiosis I.^{5,6}

Evidence regarding the SAC in female mammalian meiosis I is conflicting. Spindle disruption by pharmacological agents in mouse oocytes engages a Mad2-mediated meiosis I arrest characterised by stabilisation of cyclin-dependent kinase 1 (Cdk1)⁷ and inhibition of securin and cyclin B1 destruction (Homer H, unpublished data). These data demonstrate that mouse oocytes possess an SAC machinery during meiosis I which can be activated by spindle disruption. Curiously however, mouse oocytes possessing a univalent X chromosome (XO oocytes) are incapable of delaying anaphase I in the presence of one or a few misaligned chromosomes.^{8,9} Moreover, agents aimed at impairing Mad2 function have produced inconsistent results: a constitutionally phosphorylated mutant form of Mad2 which has a dominant negative effect on mitotic SAC function had no effect in unperturbed mouse oocytes⁷ whilst a C-terminally truncated Mad2 mutant unable to bind Cdc20 accelerated progression through meiosis I.¹⁰ Thus, the role of the SAC in unperturbed oocytes remained unclear.

In order to explore this further, we employed a post-transcriptional gene silencing approach to examine the role of Mad2 in mouse oocytes during meiosis I.¹¹ We depleted the majority of Mad2 (~90%) in fully-grown oocytes using morpholino antisense technology. This approach was important as a complete absence of Mad2 is embryonic lethal¹² and deletion of one *Mad2* allele¹³ would be expected to produce chromosome segregation defects during mitotic proliferation in pre-meiotic germ cells that would be difficult to differentiate from errors arising purely during meiosis I.

We utilised mouse oocytes from the MF1 strain in which the duration of meiosis I as measured from the time of germinal vesicle breakdown (GVBD) to first polar body extrusion (PBE) is about 11 hours (see Fig. 1A). Following Mad2 knockdown, the duration of meiosis I was significantly reduced to ~9 hours and was accompanied by a ~2 hour earlier onset of destruction of securin and cyclin B1 (Fig. 1B).¹¹ Importantly, we found that this degree of Mad2 depletion produced a dramatic increase in aneuploidy rates from ~2% to ~32%.¹¹ Overall therefore, these data indicate that mammalian oocytes require Mad2 for averting aneuploidy likely by delaying APC/C^{Cdc20} activation.

IMPLICATIONS FOR APC/C REGULATION IN FEMALE MAMMALIAN MEIOSIS I

Timelapse analyses indicate that securin and cyclin B1 levels first begin to decline about 8–9 hours post-GVBD in wild-type MF1 mouse oocytes.^{5,11} In contrast, following Mad2 depletion, protein degradation commences about 6–7 hours post-GVBD.¹¹ In addition, there is no difference in either the duration of protein destruction (2–3 hours) or of protein expression for the first 6–7 hours between wild-type and Mad2-depleted oocytes (Fig. 1B).¹¹ Overall, this implies that Mad2 is important for regulating APC/C^{Cdc20} activity within a relatively narrow window during the latter phases of meiosis I (Fig. 1B).

In somatic cells, the APC/C^{Cdc20} is active and capable of degrading cyclin B1 and securin upon entry into mitosis but is normally prevented from doing so by the activity of the SAC.^{3,14,15} We speculate that the stability of securin and cyclin B1 during the first 6–7 hours in mouse oocytes could plausibly be due to a lack of active APC/C^{Cdc20} around the time of GVBD (Fig. 1B). Incomplete APC/C^{Cdc20} assembly in early meiosis I might be one reason for this, in keeping with which Cdc20 is absent prior to metaphase I during budding yeast meiosis I.¹⁶ Alternatively, factors other than Mad2 might negatively regulate the APC/C^{Cdc20} during the early phases of meiosis I. In this respect, it will be important to investigate the role of APC/C^{Cdc20} inhibitors such as Emi1,¹⁷ RASSF1A¹⁸ and Erp1¹⁹ during meiosis I in mouse oocytes. Although there appears to be some inconsistency regarding the expression of Emi1 in *Xenopus* oocytes,^{17,20} the emerging picture supports Emi1 as a potentially important regulator of the meiotic programme in vertebrate oocytes.^{21,22} SAC proteins other than Mad2 could also account for some of the residual delay of female meiosis I following Mad2 depletion. In keeping with this, disrupting the function of endogenous Bub1 and BubR1 accelerate meiosis I in mouse oocytes.¹⁰

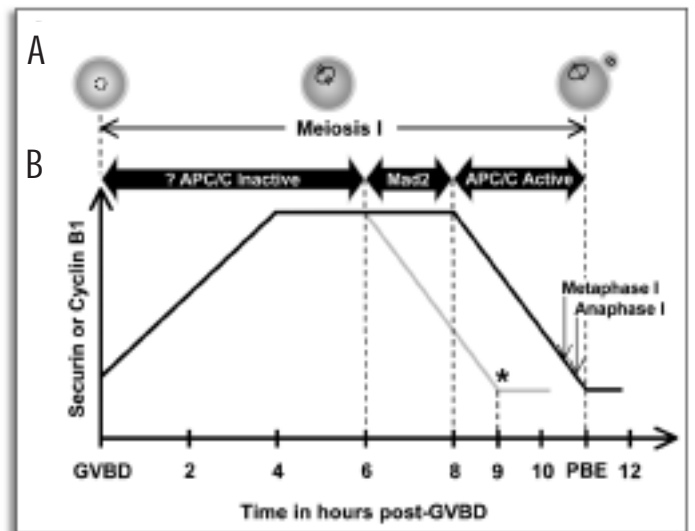


Figure 1. (A) Meiosis I timelines in MF1 mouse oocytes. (B) A proposed model for the temporal regulation of the APC/C^{Cdc20} during meiosis I in mouse oocytes. The approximate timings of metaphase I and anaphase I are extrapolated from Brunet et al.²⁴ The black plot is a schematic representation of a profile for either securin or cyclin B1 in wild-type mouse oocytes.^{5,11} The grey line depicts the protein degradation profile observed following Mad2 depletion whilst the asterisk denotes the average time at which PBE occurred in Mad2-depleted oocytes.¹¹ Mad2, proposed period during which Mad2 inhibits APC/C^{Cdc20} activity during meiosis I; GVBD, germinal vesicle breakdown; PBE, first polar body extrusion. See main text for further details.

NON-CONFORMITY IN THE FEMALE MAMMALIAN MEIOSIS I SAC

During mitosis, SAC-mediated inhibition of the APC/C^{Cdc20} is extinguished once kinetochores become stably attached to spindle microtubules.¹ As a result, cyclin B1 destruction commences upon attachment of the final chromosome to the spindle.²³ In mouse oocytes, although side-on kinetochore-microtubule interactions first occur at mid-meiosis I, it is some hours hence before stable end-on kinetochore fibres are formed in late prometaphase I, shortly before the metaphase I-to-anaphase I transition and PBE.²⁴ Given that protein degradation in mouse oocytes commences 2 to 3 hours prior to PBE,^{5,11} it is apparent that APC/C^{Cdc20} activation occurs well in advance of completion of stable kinetochore-microtubule attachments. It therefore appears that prior to the formation of stable kinetochore fibres, accumulating side-on kinetochore attachments are sufficient to cause the APC/C^{Cdc20}-inhibitory signal to fall below a threshold level. In keeping with this, immunofluorescence indicates that the Mad2-derived signal at kinetochores begins to decline some hours before anaphase I in mouse oocytes.⁷

The overall implication of these findings is that SAC signalling in mammalian oocytes does not conform to the prevailing model for SAC signalling during mitosis. During mitosis, the attachment status of kinetochores tightly couples the SAC and ubiquitination machineries^{1,23} whereas in mouse oocytes, the APC/C^{Cdc20} is activated well in advance of stable kinetochore fibres.^{5,11,24} This uncoupling in the oocyte may reflect a lack of sensitivity to individual unattached kinetochores which could account for the failure of XO oocytes to arrest in response to one or a few misaligned chromosomes whereas anaphase I and PBE are robustly inhibited when the majority of chromosomes fail to establish stable bipolar attachments

in oocytes with severely reduced recombination due to lack of the DNA mismatch repair gene *Mlh1*^{-/-}.²⁵ The prolonged phase of protein destruction towards the end of meiosis I (Fig. 1B) which is ~4–6 times as long as the equivalent phase in mitosis²³ might be an oocyte-intrinsic phenomenon which, coupled with an SAC-induced delay, partially compensates for a reduced sensitivity by furnishing sufficient time for stable end-on kinetochore fibres to be formed before anaphase I. Notably, the extensive protein-degradation phase is not sufficient on its own as loss of the Mad2-induced delay results in aneuploidy.¹¹

The ability to respond to a single misaligned chromosome might ultimately be less critical for mouse oocytes than for mammalian somatic cells due to differences in spindle assembly pathways between the two systems. During mitosis, centrosome-driven spindle assembly and chromosome congression predominantly follow the “search-and-capture” model in which microtubules nucleated by centrosomes randomly probe the cytoplasm until they encounter a kinetochore.²⁶ Due to the stochastic nature of this process in which attachment and congression occur independently for each chromosome, there is a higher chance occurrence of individual misaligned chromosomes necessitating a highly sensitive error-detection mechanism for preventing mal-segregation. In mouse oocytes which lack centrosomes, spindle assembly is based on a “self-organisation” model in which the spindle is polymerised in the vicinity of chromosomes from a number of microtubule-organising centres which aggregate to form the spindle poles.^{24,26} In contrast to mitosis, this process in mouse oocytes results in relatively early positioning of chromosomes at the equatorial spindle region. Thus, whilst not attached to microtubules via stable end-on kinetochore interactions, chromosomes are already corralled as early as mid-meiosis I²⁴ and the scenario of outlying chromosomes is less likely to arise.

It is important to note that non-exchange homologues (univalents) are almost never encountered in wild-type mouse oocytes.²⁷ It is perhaps not surprising therefore that their presence has a disruptive impact on spindle assembly and chromosome congression in female meiosis I.^{8,9,25} Furthermore, the defect is pervasive as the presence of a single univalent is sufficient to disrupt the alignment of other chromosomes which have themselves undergone recombination.^{8,9} Thus, while XO oocytes^{8,9} and *Mlh1*^{-/-} oocytes²⁵ frequently possess misaligned chromosomes, wild-type oocytes do not.⁸ Rather than indicating a lack of SAC activity in mammalian oocytes therefore, the XO oocyte highlights the susceptibility of mammalian oocytes to univalents which perturb normal spindle/chromosome dynamics. This has implications for the origins of human aneuploidy as we discuss next.

PERSPECTIVES AND IMPLICATIONS FOR HUMAN ANEUPLOIDY

The adage *omne vivum ex ovo* or “all living things come from eggs” attributable to William Harvey aptly encapsulates the pivotal role of the oocyte in reproduction. One of the overwhelming priorities of the oocyte is to provide the developing embryo with all of the molecular factors it requires until the embryonic genetic programme is activated. Its large volume is well suited to this stock-piling role but at a cost: sensitivity to truant chromosomes is reduced. Evolutionary adaptations go some way in compensating however. Thus, spindle assembly in and about chromosomes help to shackle them within a manageable radius. In concert with this, restricting the time that stable microtubule-kinetochore interactions can be made to a narrow window prevents wayward chromosomes from

straying far from the fold until spindle assembly is virtually complete. Time is an essential ingredient to the recipe for chromosome alignment and attachment in oocytes and to this end, it is apparent that a number of regulators work in concert to prolong meiosis I. It is perhaps not surprising therefore that the duration of meiosis I ranges from 6 to 12 hours in mouse oocytes and from 24 to 36 hours in human oocytes versus mere minutes in mitosis. Curtailing this timing, even by a relatively modest amount, can be catastrophic.¹¹ Interestingly, the same proteins may have become adapted to fulfilling differing roles in mitosis and meiosis. Thus, after NEBD, Mad2 determines the majority of mitotic duration whilst Emi1 has relatively little role.^{3,28} In contrast, it appears that Emi1 might be crucial for the entire meiotic program²¹ with Mad2 orchestrating events at the end of meiosis I.¹¹

In humans, the process of female meiosis I is notoriously error-prone and susceptible to the aging process with the vast majority of human aneuploidies resulting from maternal meiosis I errors.²⁹ Due to a lack of a sensitive error-detection system, immense burden is brought to bear on the mammalian oocyte to get it right the first time; there are no second chances. Prolonging meiosis I to allow as much time as possible for chromosome alignment is one way of achieving this objective. An efficient waste-disposal system for sequestering errors could provide some back-up, consistent with which, the majority of aneuploid human conceptuses perish in utero.²⁹ Any “stressor” which perturbs the exquisite balance within the meiosis I engine is therefore likely to produce defects which could have disastrous consequences if they also elude any potential waste-disposal system. As alluded to previously, achiasmate chromosomes act as such a stressor in mouse oocytes.^{8,9,25} In human oocytes, in addition to achiasmate chromosomes, certain susceptible exchange-patterns evidently also pose problems as they account for a disproportionate amount of human aneuploidies.^{29,30} Furthermore, although the overall incidence of aneuploidy amongst younger women is relatively low, the preponderance of susceptible chiasmata among trisomy 21 cases from younger women suggests that even their oocytes have difficulties processing these recombinants.³¹

The two-hit hypothesis posits that susceptible chiasmate configurations are established in the fetal ovary (hit-1; age-independent) and that oocyte factors which deteriorate with age increase the risk of non-disjunction for these exchange patterns (hit-2).³⁰ Attention has previously been drawn to one important prediction of this model: recombination should be similarly altered in non-disjunctional meioses from young and older women.²⁹ Recent evidence does not support this prediction however as susceptible patterns account for a much lower proportion of all exchanges in trisomy 21 cases from older women (10%) than they do in cases from younger women (34%).³¹ Moreover the exchange patterns amongst the oldest age group approximated that observed for normally disjoining chromosomes 21.³¹ From this it can be inferred that in aged oocytes, there is global deregulation of the chromosome segregation process which does not distinguish between different exchange patterns but instead impairs the ability to accurately disjoin even stable chiasmata. Reduced levels of Mad2 would be expected to produce such a pervasive defect as a result of premature APC/C^{Cdc20} activation,¹¹ leaving insufficient time for the establishment of stable kinetochore fibres prior to anaphase I. Reduced levels of oocyte SAC proteins such as Mad2 could therefore account for the elusive second hit (even though the first one is now dispensable for the age affect) responsible for the observed rise in aneuploidy with advancing female age.³⁰ In support of this notion, oocytes from older women

exhibit a trend towards reduced levels of Mad2 transcripts when compared with oocytes from younger women³² and levels of ovarian BubR1 decline with age in mice.³³ Furthermore, oocytes from aged mice demonstrate accelerated progression through meiosis I and suffer increased rates of aneuploidy³⁴ similar to the phenotype observed following Mad2 depletion.¹¹

Although the basic machinery comprising the SAC appears to be conserved, findings in mouse oocytes question the applicability of prevailing models of mitotic SAC regulation to female mammalian meiosis I. It will be important to further define the role of other SAC proteins such as BubR1 as well as that of other APC/C^{Cdc20} regulators including Emi1 in mouse oocytes during meiosis I. Ultimately, theories regarding female age-related aneuploidies will have to be put to the test by extending investigations to human oocytes.

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