

Possible role of Aurora-C in meiosis

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The meiotic generation of haploid gametes with equal contents of genetic material is important for sexual reproduction in mammals. Errors in the transmission of chromosomes during meiosis may lead to aneuploidy, which is the leading cause of miscarriage and congenital birth defects in humans. The Aurora kinases, which include Aurora-A, Aurora-B, and Aurora-C, are highly conserved serine-threonine kinases that play essential roles in centrosome function, chromosome segregation, and cytokinesis during mitosis and meiosis. While Aurora-A and Aurora-B have been extensively studied in mitosis, the role of Aurora-C in meiosis is only now starting to be revealed. For example, the perturbation of Aurora-C kinase activity by microinjection of Aurora-C-kinase-dead mutant mRNAs into mouse oocytes induced multiple defects, including chromosome misalignment, abnormal kinetochore-microtubule attachment, premature chromosome segregation, and failure of cytokinesis during meiotic division. However, the analysis of such defects is complicated by the possibility that Aurora-B may be present in mammalian germ cells. Interestingly, a homozygous mutation of Aurora-C in humans leads to the production of large-headed polyploid spermatozoa and causes male infertility, but homozygous females are fertile. Mouse studies regarding the roles of Aurora-B and Aurora-C in female meiotic divisions have yielded inconsistent results, and it has proven difficult to explain why homozygous human females have no significant clinical phenotype. In this review, we will discuss the controversial status of Aurora-B in oocytes and the possible role of Aurora-C during meiotic division.

Keywords: meiosis, oocyte, spermatocyte, aurora kinase, mitosis, polyploidy, male infertility, aneuploidy

Introduction

An essential process during the sexual reproduction of mammals is the production of haploid gametes from diploid precursors. This is done via meiosis, which consists of a single round of DNA duplication and two rounds of cell division that are called meiosis I (MI) and meiosis II (MII). Homologous chromosomes are segregated in MI, while sister chromatids are separated in MII via a process similar to that seen during mitosis (1, 2). Failures in chromosome segregation at meiosis result in aneuploidy, which is a major cause of miscarriages and birth defects in humans. However, the mechanisms underlying such failures are not completely understood (3). The Aurora kinases belong to a family of serine/threonine kinases that are pivotal in the regulation of cell division processes, including mitosis (4, 5) and meiosis (6–8). There are three Aurora kinases in mammals: Aurora-A and Aurora-B are ubiquitously expressed, and their functional roles in mitosis have been extensively studied (9–11); whereas Aurora-C is mainly restricted to germ cells (12), and is beginning to be functionally studied in meiosis. It is interesting to note that these three kinases share sequence homology in their central catalytic kinase domains, but differ widely in their N- and C-terminal

sequences (12). Mouse Aurora-B and Aurora-C share 77.6% amino acid sequence identity in their catalytic domains, while Aurora-A and Aurora-C share only 66.3% sequence identity in this region, suggesting that there may be a close functional link between Aurora-B and -C (12).

Aurora-C (also called AIE1/AIE2/STK13) was first identified in the Tang lab, in a screening for kinases expressed in sperm and eggs (12), and also independently by Bernard et al. in a homologous kinase screening in a human placental cDNA library (13). Aurora-A and -B are ubiquitously expressed in many tissues, particularly in actively dividing cells. In contrast, Aurora-C is predominantly expressed in the testis (12, 13) and is mainly restricted to meiotically active germ cells, including spermatocytes (14) and oocytes (6). Aurora-C was reported to be overexpressed in a variety of human cancer cell lines (15, 16) and ectopic overexpression of Aurora-C can also induce cell transformation and tumor formation (17). However, its expression in tumor cells and normal somatic tissues is still the matter of some debate (14, 18). Aurora-B is a member of the chromosomal passenger complex (CPC), which localizes to the centromeres/kinetochores from prophase to metaphase and to the central spindle and midbody during cytokinesis (19, 20). In contrast, endogenous Aurora-C protein has never been detected in normal somatic cells by immunofluorescence or Western blot analyses using fully validated antibodies (6, 14). Instead, ectopically expressed tagged Aurora-C has been detected in transfected cells, where it showed a localization pattern similar to that of Aurora-B (21–23). The role of Aurora-B in meiotic chromosome orientation during meiosis has recently been reviewed by Watanabe (1). In this review, we will focus on the possible role of Aurora-C during male and female meiotic divisions.

Aurora-C in Mouse Spermatocytes: Subcellular Localization, Transcriptional Regulation, and Functional Implications

The subcellular localization of endogenous Aurora-C during male meiotic division had been carefully examined by confocal immunofluorescence microscopy in mouse spermatocytes (14). In germ cells, the meiotic prophase consists of five sequential stages: leptotene, zygotene, pachytene, diplotene, and diakinesis. Aurora-C was first detected at the centromeric regions in early diplotene spermatocytes, after which it was found to spread along the chromosomal arms of sister chromatids during diakinesis. Upon the transition from diakinesis to MI, Aurora-C gradually dissociates from the chromosome arms and becomes concentrated at the centromeres near the kinetochores. Thereafter, it relocalizes to the spindle midzone and midbody during the anaphase I/telophase I and anaphase II/telophase II transitions, respectively (Figure 1) (14). A similar localization pattern was reported for Aurora-B in mouse spermatocytes (14, 24). However, while Aurora-B was detected in mitotic spermatogonia, Aurora-C was not, suggesting that Aurora-C may play a unique role in male meiotic division (14).

The finding that Aurora-C and -B co-localize during male meiotic divisions raised several interesting questions: (i) how are Aurora-C/-B recruited to the appropriate positions to

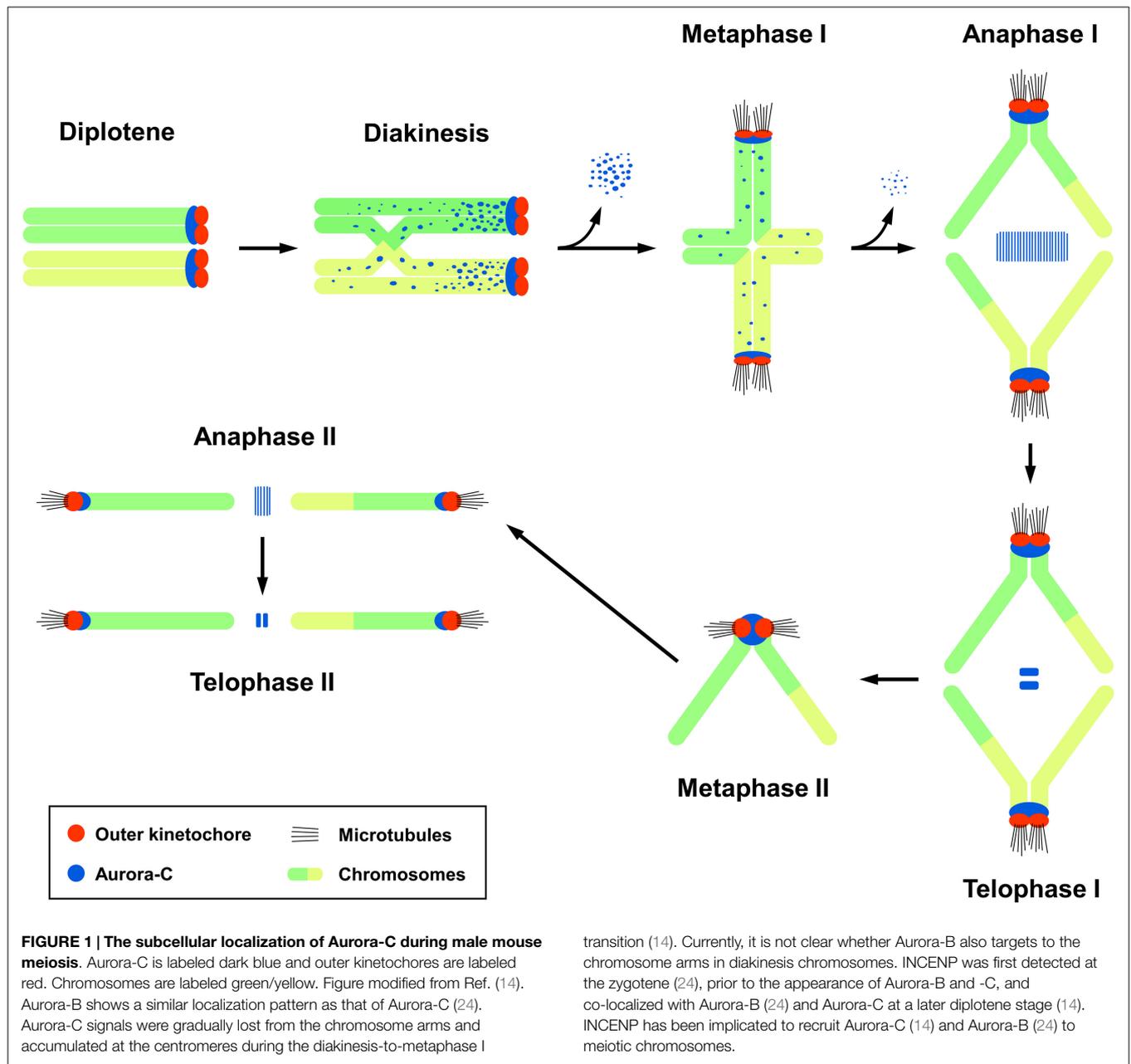
execute their meiotic functions during spermatogenesis? (ii) Do Aurora-C/-B play similar or different roles during male meiotic divisions? (iii) Since Aurora-C is mainly restricted in germ cells, how is Aurora-C regulated during spermatogenesis?

In somatic cells, Aurora-B is a member of the CPC along with several non-enzymatic subunits, including INCENP, survivin, and Borealin; together, the members of this complex contribute to regulation of chromosome segregation, microtubule-kinetochore attachments, and cytokinesis (19, 25). INCENP contains a conserved C-terminal IN-box that binds Aurora-B (26) and an N-terminal region that targets to centromeres (27).

Interestingly, INCENP can be detected in meiotic cells prior to the appearances of Aurora-B and -C (14, 24). It is first found at the central element (CE) of the synaptonemal complex (SC), from the zygotene to late pachytene stages (24). It then moves to heterochromatic chromocenters (14, 24) and co-localizes with Aurora-B and -C at the diplotene stage (14). Immunoprecipitation analyses showed that INCENP can form distinct complexes with either Aurora-C (INCENP/Aurora-C) or Aurora-B (INCENP/Aurora-B) in the testis (14). Together, these findings strongly support a model, in which INCENP recruits Aurora-C and -B to their appropriate locations and activates them to execute their meiotic functions in spermatocytes (14). Consistent with this notion, INCENP was reported to bind (21, 22) and activate Aurora-C (21) in somatic cells, and ectopically expressed Aurora-C was found to associate with survivin (28) and borealin (29). However, the functional linkage of these proteins during meiotic divisions has not yet been fully resolved. Recent studies have shown that BUB1, shugoshin proteins, and haspin kinase are also required for targeting Aurora-B to the centromeres of meiotic chromosomes (30–34). It will be interesting to test whether these proteins are also required for Aurora-C targeting to the centromeres in the future.

What is the role of Aurora-B and -C during male meiotic divisions? In somatic cell mitosis, Aurora-B and Polo-like kinase 1 (Plk1) phosphorylate the cohesion complexes to promote their dissociation from the chromosome arms (35–37). Interestingly, during meiosis, some SC components (e.g., SCP2 and SCP3) and cohesion subunits (e.g., SMC1b and SMC3, but not REC8) are gradually released from the chromosome arms and accumulate at the centromeres during the prophase I to metaphase I transition (38, 39). In accordance with this finding, Aurora-C was reported to be dissociated from the chromosome arms and concentrated at the centromeres during the diakinesis–metaphase I transition (14). Together, this seems to suggest that Aurora-C might regulate the release of cohesion subunits and SC components from the chromosome arms during MI. Future work is needed to test this possibility.

To investigate the role of Aurora-B/-C in spermatogenesis, Kimmins et al. (40) generated transgenic mice in which a pachytene-specific promoter drove the expression of an inactive Aurora-B mutant, and produced *Aurora-C* knockout mice by homologous recombination. Expression of the inactive Aurora-B dominant-negative (DN) mutant severely impaired spermatogenesis, resulting in abnormal spermatocytes, increased apoptosis, and spermatogenic arrest. The *Aurora-C* null mice were viable and had normal testis weights, sperm counts, and meiotic



progression, but some of the mutant males were sterile and had sperm abnormalities, including heterogeneous chromatin condensation, loose acrosomes, and blunted heads (40). As Aurora-B (24) and Aurora-C (14) co-localize and associate with INCENP, it has proven difficult to differentiate their roles in spermatogenesis. Furthermore, it is unclear why *Aurora-C* null mice show only minor sperm-related alterations. Previous reports have shown that ectopic expression of an Aurora-C kinase-dead mutant disrupts the association of INCENP with Aurora-B (22) and that Aurora-C can complement the function of Aurora-B Kinase in somatic cells (21, 23, 41). Thus, it is possible that endogenous Aurora-B could compensate for the function of Aurora-C in the *Aurora-C* null mice and that ectopic expression of the Aurora-B DN mutant could non-specifically block the function of endogenous

Aurora-C in *Aurora-B* mutant mice. Alternatively, studies have suggested that multiple tandem copies of the *Aurora-C* gene (42) or a potential “functional pseudogene” in the mouse genome may alleviate the spermatogenic effects in the *Aurora-C* null mice. Thus, why do mammals require both Aurora-C and -B kinases in spermatocytes? Do they play overlapping or differential roles during male meiotic divisions? These questions remain open in the context of mammalian spermatocytes.

Finally, the transcriptional regulation of Aurora-C during spermatogenesis is poorly understood. Our group isolated the cDNA clones encoding human TZFP (testis zinc finger protein) and mouse *Tzfp*, which are predominantly expressed in testis (43, 44). Human TZFP and mouse *Tzfp* contain a conserved N-terminal BTB (bric-a-brac, tramtrack, broad complex)/POZ (poxvirus,

zinc finger) domain and three C-terminal C2H2 zinc fingers (43, 44). Interestingly, the zinc finger domain of TZFP/Tzfp is closely related to the promyelocytic leukemia zinc finger (PLZF) protein, a known DNA-binding transcriptional repressor (45). Biochemical studies demonstrated that the C-terminal zinc finger domain of Tzfp directly binds to the TGTACAGTGT motif (designated as the Tzfp binding site, or tbs), located in the upstream flanking sequence of the *Aurora-C/Aie1* gene (44). These studies also showed that the N-terminal BTB/POZ domain has repressor activity, suggesting that Tzfp may negatively regulate *Aurora-C* gene expression in spermatocytes (44). Consistent with this notion, Tzfp is highly expressed in spermatocytes at the pachytene stage in MI, and *Tzfp*-knockout mice show downregulation of *Aurora-C/Aie1* expression (46).

Aurora-C/-B in Mouse Oocytes: Subcellular Localization and Potential Functions during Female Meiotic Divisions

The localization of endogenous Aurora-C has been examined in detail during the various stages of meiotic division in mouse oocytes (6). Aurora-C was detected at the chromosome axes and centromeres in prometaphase I–metaphase I, in which Aurora-C was also phosphorylated at Thr171 (**Figure 2**) (6). During the anaphase I–telophase I transition, Aurora-C was dephosphorylated and relocated to the midzone and midbody (**Figure 2**) (6), and thus shows a pattern similar to that reported in spermatocytes (14). Interestingly, protein kinase A (PKA) can phosphorylate recombinant Aurora-C/Aie1 protein *in vitro* at Thr171 (47), yet its physiological meaning is not clear. Unexpectedly, no endogenous Aurora-B protein was detected on the meiotic chromosomes of mouse oocytes when assessed by immunofluorescence staining with the same antibody that had successfully detected Aurora-B in spermatocytes (6) nor was it detected in experiments using other antibodies and fixation conditions (48). In contrast, Balboula and Schindler (7) detected endogenous Aurora-B at the nuclei of prophase-arrested oocytes and the meiotic spindle at metaphase I and metaphase II. This apparent discrepancy may reflect the specificities of the utilized different antibodies or other, yet unknown factors.

In experiments using exogenous proteins, GFP-Aurora-B expressed in injected oocytes was clearly detected at the centromeres/kinetochores at metaphase I (6, 48, 49, 51) and at the spindle midzone and midbody during the anaphase I–telophase I transition (6, 48, 51), thereby showing a pattern similar to that of endogenous Aurora-C (6). Furthermore, it was reported that *Aurora-C* mRNA is recruited for translation more efficiently than the *Aurora-B* mRNA, and that exogenously expressed Aurora-B protein is not stable during meiosis (49). Thus, despite the abundance of the mRNAs for Aurora-B and Aurora-C in mouse oocytes (6, 49) and the high-level expression of the Aurora-C protein in both male and female mouse germ cells (6, 14), little or no Aurora-B protein appears to be expressed in mouse oocytes. This interesting observation suggests that the translation of Aurora-B protein level is differentially regulated in female germ cells.

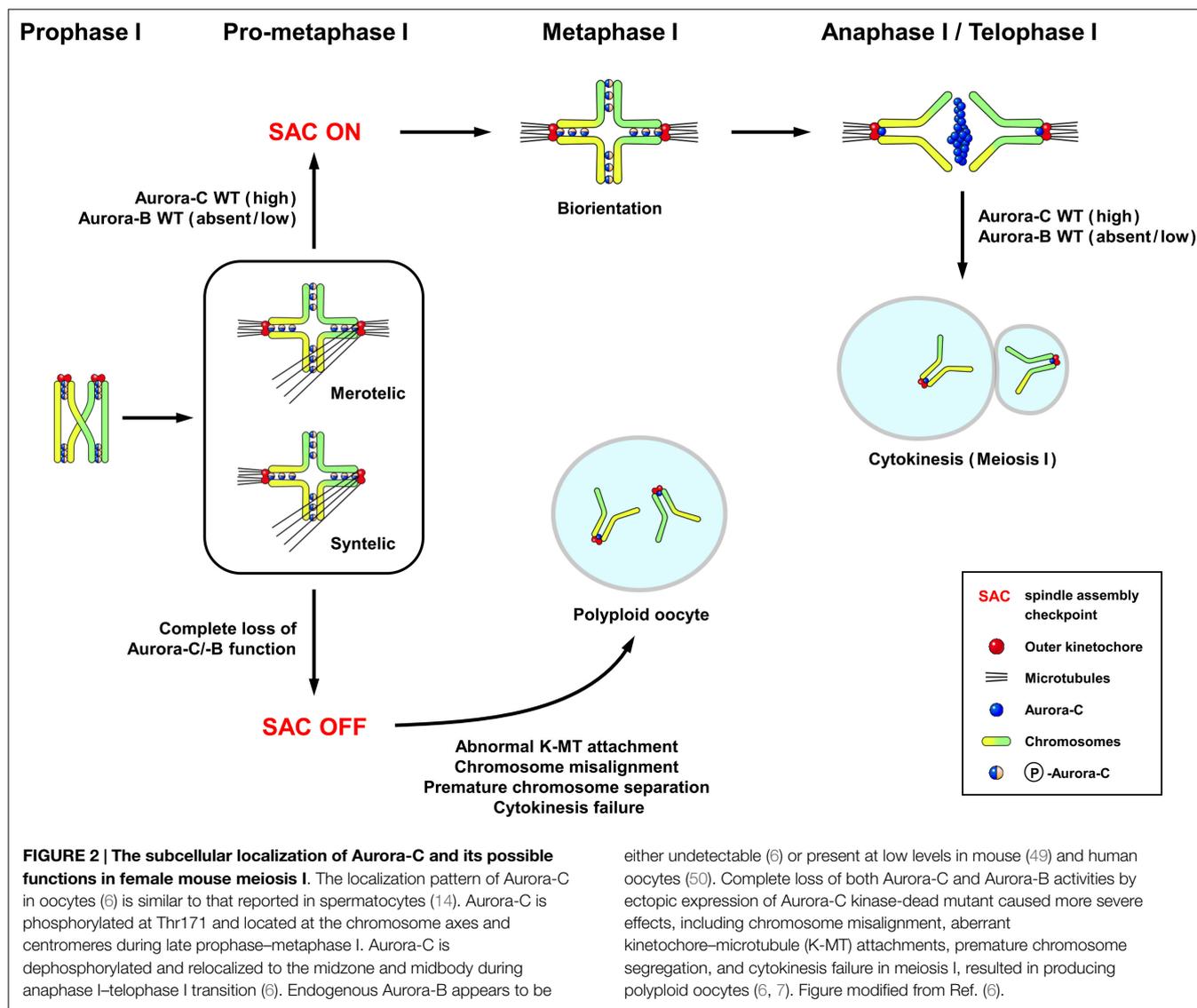
The role of Aurora-C in oocytes has recently been investigated using a number of approaches, including exogenously expressed

Aurora-C kinase-dead or gatekeeper mutants (6, 7), treatment with small molecule inhibitors (ZM447439 and AZD1152) of Aurora kinases (6, 48, 51, 52), siRNA-mediated knockdown (51), and the generation of *Aurora-C* knockout (*Aurkc*^{-/-}) mice (7, 49, 53). Yang et al. (6) first reported that exogenous expression of kinase-dead Aurora-C mutant (T171A, T175A, designated Aurora-C-KD) in mouse oocytes significantly inhibited endogenous Aurora-C activity and produced multiple defects, including chromosome misalignment, abnormal kinetochore–microtubule (K-MT) attachment, premature chromosome segregation, and failure of cytokinesis in MI. This phenotype was partially recapitulated in oocytes injected with an INCENP-targeting siRNA (51), in an INCENP-delIN deletion mutant that lacked the Aurora-C-binding motif (6), and in oocytes treated with high doses of small molecule inhibitors of Aurora-B (ZM447439 and AZD1152), that are also likely to inhibit Aurora-C (6, 51, 52). Unexpectedly, *Aurkc*^{-/-} knockout mice were found to be subfertile (49). The overall percentage of chromosome misalignment in MI oocytes of *Aurkc*^{-/-} mice was not strikingly different from that of wild-type controls, but a portion of the oocytes in knockout mice arrested in MI and displayed abnormally aligned chromosomes (49). Recently, Balboula and Schindler (7) developed an ATP-binding-pocket-Aurora-C mutant (L93A, gatekeeper mutant) that appears to selectively disrupt the function of Aurora-C, but not Aurora-B, during female meiotic divisions, and microinjected this mutant into mouse oocytes. Their observations suggested that the specific loss of Aurora-C function caused chromosome misalignment and failure to correct erroneous K–MT attachments (7), which is similar to the deficits observed in oocytes expressing the Aurora-C kinase-dead mutant (T171A/T175A) (6). Meanwhile, the process of cytokinesis in oocytes appears to be regulated by either the Aurora-B–CPC complex or by the activities of both Aurora-B and Aurora-C (7).

In sum, there is currently no suitable model that encompasses all of the reported roles of Aurora-C during female meiotic divisions. The efforts to generate such a consensus have been complicated by the possible functional compensation of Aurora-B in oocytes (7, 48, 49, 51, 54), the lack of selectivity and specificity among the known small molecule inhibitors (6, 51, 52), problems with the efficiency of siRNA knockdown (51), and the possible presences of multiple tandem copies of the *Aurora-C* gene (42) and/or a potential “functional pseudogene” in the mouse genome. Given these limitations, however, the speculated roles of Aurora-C and -B during female meiotic divisions are summarized in **Figure 2**.

Aurora-C/-B in Human Germ Cells and Preimplantation Embryos: Subcellular Localization and Aurora-C-Deficient Human Patients

Recently, Santos et al. (50) reported the localizations and mRNA expression levels of endogenous Aurora-B and Aurora-C in human germ cells and preimplantation embryos developed from tri-pronuclear (3PN) zygotes. They observed the signal corresponding to Aurora-C in the region surrounding the centromeres



either undetectable (6) or present at low levels in mouse (49) and human oocytes (50). Complete loss of both Aurora-C and Aurora-B activities by ectopic expression of Aurora-C kinase-dead mutant caused more severe effects, including chromosome misalignment, aberrant kinetochore–microtubule (K-MT) attachments, premature chromosome segregation, and cytokinesis failure in meiosis I, resulted in producing polyploid oocytes (6, 7). Figure modified from Ref. (6).

in human MI and MII oocytes. This was consistent with the localization pattern described in mouse oocytes (6). Human Aurora-C first appeared at the pericentric heterochromatin in pachytene spermatocytes (50), whereas mouse Aurora-C was first detected at the diplotene stage (6). In contrast, endogenous Aurora-B was hardly detected in human oocytes at MI (50).

In preimplantation embryos, Aurora-C appears to be the major Aurora kinase expressed during the first three embryonic cell cycles, where it can be visualized on prometaphase chromosomes in zygotes and two- and four-cell-stage human embryos. The endogenous Aurora-B protein was expressed at low-to-undetectable levels during these embryonic stages, but increased significantly after the eight-cell stage. It is interesting to note that the expression of Aurora-C occurs earlier, and is completely replaced by Aurora-B at the blastocyst stage of human embryonic development. These findings prompted the authors to hypothesize that Aurora-C could be the main enzymatic component of the CPC, and thus plays a specific role during human female meiosis and preimplantation embryo development (50). However, it is not

yet clear whether its deficiency is linked to a high aneuploidy rate in human preimplantation embryos.

Recently, three naturally occurring mutations in the human *Aurora-C* kinase gene were reported to be associated with male infertility: c.144delC, which deletes a cytosine in exon 3 (8); c.686G > A, which is a missense mutation in exon 6 (p.Cys229Tyr) (55); and c.436-2A.G, which is a splicing site mutation that leads to the skipping of exon 5 (56). Individual males carrying homo- or hetero-allelic combinations of null or strong loss-of-function *Aurora-C* mutations frequently produce polyploidy and multi-flagellar spermatozoa that are unsuitable for fertilization. Males homozygous for c.144delC had no obvious physiological or anatomical defects beyond sperm abnormalities, suggesting that *Aurora-C* is not essential for somatic cell division (55). Moreover, females carrying the same homozygous mutation (c.144delC) were fertile, suggesting that *Aurora-C* may be dispensable for meiotic divisions in the human female (55).

The question of how the large-headed multi-flagellar polyploid spermatozoa are generated in humans cannot be answered using

the *Aurkc*^{-/-} knockout mice. However, speculations can be made. One possible explanation is that Aurora-C plays a critical role in cytokinesis during spermatogenesis. Indeed, mouse oocytes injected with Aurora-C-kinase-dead mRNAs showed failure in the cytokinesis of MI (6). This resulted in the production of large polyploid mouse oocytes, which could be compared to the polyploid spermatocytes found in Aurora-C-deficient humans. However, we cannot yet explain why Aurora-C-deficient human females are fertile and do not have polyploid oocytes.

Conclusion

In mouse spermatocytes, both Aurora-B (24) and Aurora-C (14) proteins are present at relatively high levels and show a similar localization pattern (Figure 1). Both are also likely to be recruited to meiotic chromosomes by INCENP (14, 24). The functional differences in these proteins during male meiotic divisions remain largely unknown. In females, endogenous Aurora-B is either undetectable (6) or present at low levels in mouse (49) and human oocytes (50). Here, Aurora-C appears to be the major

enzymatic component of the CPC, and thus may play a specific role during female meiotic divisions (6, 49–51). The differential roles of Aurora-B and Aurora-C during female meiosis have been addressed by a number of different approaches, but no conclusive answer has yet been obtained. Furthermore, it is difficult to use the results obtained from mouse studies to interpret the clinical phenotypes in human Aurora-C-deficient subjects. For example, microinjection of Aurora-C-kinase-dead mRNAs into mouse oocytes caused failure of cytokinesis in MI and the production of large polyploid oocytes (6), whereas a homozygous Aurora-C mutation in human affects male (but not female) germ cells. This discrepancy could reflect species-specific differences, and further studies are needed to resolve the differential roles of Aurora-B and Aurora-C during meiotic divisions in mouse and human germ cells.

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