Role of the X and Y Chromosomes in the Female Germ Cell Line Development in the Mouse (*Mus musculus*)

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Abstract

Background: In eutherian mammals, the sex chromosome complement, XX and XY, determines sexual differentiation of gonadal primordia into testes and ovaries, which in turn direct differentiation of germ cells into haploid sperm and oocytes, respectively. When gonadal sex is reversed, however, the germ cell sex becomes discordant with the chromosomal sex. XY females in humans are infertile, while XY females in the mouse (*Mus musculus*) are subfertile or infertile dependent on the cause of sex reversal and the genetic background. This article reviews publications to understand how the sex chromosome complement affects the fertility of XY oocytes by comparing with XX and monosomy X (XO) oocytes. **Summary:** The results highlight 2 folds disadvantage of XY oocytes over XX oocytes: (1) the X and Y chromosomes fail to pair during the meiotic prophase I, resulting in sex chromosome aneuploidy at the first meiotic division and (2) expression of the Y-linked genes during oocyte growth affects the transcriptome landscape and renders the ooplasmic compo-

nent incompetent for embryonic development. **Key Message:** The XX chromosome complement gives the oocyte the highest competence for embryonic development.

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Introduction

The X and Y chromosomes have evolved from a pair of autosomes to acquire the male-determining function on the Y chromosome in eutherian mammals [Nagai, 2001; Wallis et al., 2008]. Thus, the sex chromosome complement, XX and XY, dictates sexual differentiation of the gonadal primordium into a testis and an ovary, which in turn direct differentiation of germ cells into haploid sperm and oocytes, respectively [Cotinot et al., 2002; Kashimada and Koopman, 2010; Eggers et al., 2014]. Sexual differentiation of reproductive organs other than gonads is largely determined by circulating gonadal hormones and not directly affected by the sex chromosome complement. By contrast, functional differentiation of germ cells requires proper combination of sex chromosomes. In particular, the meiotic prophase I (MPI) involves pairing and recombination between the sex chro-

mosomes, and a failure in this process results in loss of gametes or sex chromosome aneuploidy at the first meiotic cell division. In the XY spermatocyte, the X and Y chromosomes have retained limited homologous regions, named pseudoautosomal region (PAR), and evolved unique mechanisms for securing their pairing and segregation [Smith and Benavente, 1992; Blackmon and Demuth, 2015; Papanikos et al., 2019]. In the XX oocyte, the 2 X chromosomes are expected to behave like an autosomal pair. However, when monosomy X (XO) or XY sex reversal occurs, a single X chromosome is missing its pairing partner in the XO oocyte or the X and Y chromosomes fail to pair in the XY oocyte. While the X chromosome has evolved to adjust its gene transcript levels in XY and XX somatic cells, how the X chromosome adjusts its gene dosage in the oocyte is not fully understood. Furthermore, how the Y chromosome affects gene transcript levels in the oocyte remains largely unknown. The influence of the sex chromosome complement on the fertility of XO and XY oocytes is the subject of this review.

Monosomy X (XO) Females

In humans, monosomy 45,X (XO) embryos rarely survive in utero, and those who have reached term suffer from congenital abnormalities and infertility, termed Turner's syndrome [Turner, 1938; Singh and Carr, 1966; Ogata and Matsuo, 1995; Hook and Warburton, 2014]. The Turner mosaic (XO/XX) usually shows milder phenotypes and occasional fertility. In mice, by contrast, most XO embryos survive to term and show no gross anomalies except for lower body weights than their XX littermates [Cattanach, 1962; Burgoyne et al., 1983]. These striking somatic differences between the 2 species can be attributed to the greater number of genes that escape from X chromosome inactivation in humans compared to mice [Fisher et al., 1990; Carrel and Willard, 2005; Berletch et al., 2010, 2015; Lopes et al., 2010; Yang et al., 2010; Tukiainen et al., 2017]. Moreover, XO female mice are fertile, suggesting that one X chromosome is sufficient for rendering the oocyte to become competent for embryonic development in the mouse. Nonetheless, XX and XO oocytes do not share the quality. For example, when a Y-linked *Eif2s3y* transgene is expressed in embryonic stem cells (ESCs), the number of oocytes derived from the ESCs in culture is severely reduced in the cells carrying single X chromosomes compared to those carrying XX chromosomes [Hamada et al., 2020]. When a *Zfy2* transgene is expressed in vivo, XO oocytes become infertile,

while XX oocytes remain fertile [Vernet et al., 2014]. Furthermore, XO female mice have a smaller ovarian reserve and shorter reproductive life than XX female mice [Burgoyne and Baker, 1981; Vaz et al., 2020].

Several genetic mouse models are available for generating XO females. The initial XO female was identified during mouse crosses [Cattanach, 1962]. It was later found that a mutation or chromosomal rearrangement on the X chromosome causes XY non-disjunction during spermatogenesis, and the sperm lacking sex chromosome sires XO daughters carrying maternal X chromosomes [Burgoyne et al., 1983; Lane and Davisson, 1990; Ashworth et al., 1991; Burgoyne and Evans, 2000]. Once generated, the XO female produces oocytes lacking X chromosomes and, consequently, XO daughters carrying paternal X chromosomes. The XO embryo carrying the paternal X chromosome displays developmental retardation at gastrulation and early organogenesis or even early death, whereas the XO embryo carrying the maternal X chromosome does not [Jamieson et al., 1998; Vaz et al., 2020]. This difference can be attributed to epigenetic modifications of the X chromosome through spermatogenesis versus oogenesis [Hunt, 1991; Thornhill and Burgoyne, 1993; Latham and Rambhatla, 1995]. Since epigenetic modifications are erased in the germ cell line prior to sexual differentiation [Kato et al., 1999; Lee et al., 2002; Hackett et al., 2013; Kim et al., 2014], the parental origin of the X chromosome should play little role in oogenesis.

XY Sex-Reversed Females

Molecular mechanisms of gonadal sex determination and differentiation have been thoroughly reviewed by other authors [Kashimada and Koopman, 2010; Eggers et al., 2014; She and Yang, 2014; Greenfield, 2021]. In brief, the primary male-determining *Sry* gene is expressed from the Y chromosome in the XY gonadal primordium and upregulates its target *Sox9* on the mouse chromosome 11. SOX9 in turn initiates sequential expression of multiple genes such as *Fgf9* and *Pgd2*, leading to morphological testis differentiation, while suppressing the genes required for ovarian differentiation such as *Wnt4* and *Foxl2*. Reciprocally, the absence of SRY in the XX gonadal primordium allows for upregulation of the genes required for ovary differentiation while suppressing the genes required for testis differentiation. Therefore, in theory, a loss of any gene function essential for testis differentiation or the overexpression of genes supporting ovary dif-

ferentiation would lead to XY sex reversal [Colvin et al., 2001; Barrionuevo et al., 2006; Bouma et al., 2007; Garcia-Moreno et al., 2019]. Furthermore, *Sry* transcription is coordinately regulated by multiple autosomal genes, and ablation of such genes would lead to XY sex reversal [Kato-Fukui et al., 1998; Larney et al., 2014; She and Yang, 2014; Carré et al., 2018]. In reality, however, complete XY sex reversal is rare by manipulating a couple of genes. Furthermore, alterations of autosomal genes affect the development of other organs and often result in early lethality. Therefore, deleting the *Sry* gene function remains the best strategy to generate XY females to study the role of sex chromosomes in the oocyte. A caveat here is that deletion or modification of a Y-linked gene may affect the higher-order Y chromatin structure that influences the behavior of the Y chromosome [Capel et al., 1993]. It is ideal to have an intact Y chromosome in the XY oocyte.

The B6.Y^{TIR} mouse was established by placing the Y chromosome from a variant of *Mus musculus domesticus* caught in Tirano, Italy (TIR) onto the C57BL/6 J (B6) genetic background by repeating backcross [Eicher et al., 1982; Nagamine et al., 1987; Albrecht et al., 2003]. The gonadal sex is reversed because the SRY protein encoded on the Y^{TIR} chromosome has polymorphic differences from that encoded on the Y^{B6} chromosome and fails to properly upregulate its target *Sox9* on the B6 autosome [Coward et al., 1994; Taketo et al., 2005; Park et al., 2011]. Similar sex reversal has been reported using the Y chromosome from other variants of *M. musculus domesticus*, such as Y^{POS} and Y^{AKR} [Eicher et al., 1982; Nagamine et al., 1987]. Whether the origins of B6.Y^{TIR} and B6.Y^{POS} mice are distinct remains controversial [Eva Eicher, pers. commun.]. However, the B6.Y^{TIR} strain has been maintained in our mouse colony over the 80th backcross generation and stands as the most consistent producer of XY sex reversal in the mouse.

Greater Loss of Oocytes with Monosomy X

In fetal ovaries, the germ cells enter meiosis to become oocytes and go through MPI, during which homologous chromosomes pair and recombine. In the XX germ cell, 1 of the 2 X chromosomes is initially inactivated like in somatic cells, but it becomes reactivated prior to the entry into meiosis, and the 2 transcriptionally active X chromosomes efficiently pair and recombine during the MPI progression [de Napoles et al., 2007; Sugimoto, 2007; Chuva De Sousa Lopes et al., 2008]. When the oocytes reach the end of MPI, they become individually surrounded by

granulosa cells to form primordial follicles in neonatal ovaries. This pool of oocytes in primordial follicles, named ovarian reserve, dictates the success and length of the female reproductive life.

The XO female mouse has a smaller ovarian reserve. In the XO oocyte, the single X chromosome is missing its pairing partner and fails in homologous synapsis, which provokes the meiotic silencing of unsynapsed chromosomes (MSUC) [Baarends et al., 2005; Turner et al., 2005; Cloutier et al. 2015, 2016]. Since silencing of X-linked genes is variable, the XO oocyte may survive or die depending on the repertoire of silenced genes [Cloutier et al., 2016]. An alternative explanation for the XO oocyte loss is the haplodeficiency of X-linked gene products. The ratio of X-linked versus autosomal gene transcript levels is lower in XO oocytes than in XX oocytes from the onset of meiosis [Sangrithi et al., 2017; Hamada et al., 2020]. However, our study has shown comparable numbers of oocytes between XO and XX ovaries on the B6 genetic background until birth [Alton et al., 2008; Vaz and Taketo, unpubl. data]. Therefore, the haplodeficiency of X-linked gene products appears to exert little effect on the oocyte survival in fetal life. After birth, the oocyte population declines in the XO ovary to half or as low as 15% of that in the XX ovary, dependent on the genetic background [Burgoyne and Baker 1981; Vaz et al., 2020]. This postnatal XO oocyte loss can be prevented by ablation of H2AFX phosphorylation, which is essential for exerting MSUC [Fernandez-Capetillo et al., 2003; Cloutier et al., 2015]. Therefore, MSUC rather than the haplodeficiency of X-linked gene products appears to contribute to the greater neonatal XO oocyte loss. It remains an open question whether the genetic background affects the MSUC efficiency or the survival of oocytes with a deficiency in X-linked gene products. The XO oocytes that have survived in neonatal ovaries can produce offspring, but the smaller ovarian reserve reflects in a shorter reproductive life span [Burgoyne and Baker 1981; Vaz et al., 2020].

The fate of XY germ cells in the ovary is more complex and controversial. Sakashita et al. [2019] have generated XY^{Sry}-sex-reversed mice on the B6 genetic background by deleting a part of the *Sry* gene using the CRISPR/Cas9 system. They reported fewer germ cells at embryonic day 13.5, prior to the onset of meiosis, and a subsequent delay in the onset of meiosis in the XY^{Sry}-ovary compared to the XX ovary. Furthermore, the XY^{Sry}-oocytes exhibit various abnormalities with the meiotic chromosomal configuration during the MPI progression, and their population diminishes rapidly by 8 days after birth. The authors speculated that expression of some Y-linked genes

contributes to the meiotic defects, resulting in oocyte demise. We reported a different sequence of events in the B6.Y^{TIR} female mouse carrying an intact Y chromosome. Neither the onset of meiosis nor the initial oocyte population differs between the B6.Y^{TIR} and XX ovaries [Park and Taketo, 2003]. However, in the B6.Y^{TIR} ovary, there is a total loss of oocytes in the medullary region, where the oogonia first enter meiosis. Consequently, this region remains lacking oocytes until folliculogenesis begins postnatally [Villalpando et al., 1993]. The total number of oocytes is initially not affected because more oogonia are recruited into meiosis [Park and Taketo, 2003]. Thus, the most advanced MPI stage in the B6.Y^{TIR} ovary is delayed by one day compared to the XX ovary. After birth, another wave of major oocyte loss occurs, as reported for the XY^{Sry} ovary. Recent study in our laboratory showed that the neonatal oocyte loss in the B6.Y^{TIR} ovary is comparable to that in the XO ovary on the B6 genetic background, suggesting that the greater XY oocyte loss can be largely attributed to the monosomy X, not the presence of the Y chromosome [Vaz and Taketo, unpubl. data]. In agreement with this conclusion, similar selective oocyte loss in the medullary region has been reported in the XO ovary on the B6 genetic background [Miura et al., 2017]. To our knowledge, no other XY female model has been examined as to the fate of oocytes in detail during fetal and neonatal development.

Gene Transcription in XX, XO, and XY Oocytes during Follicular Growth

When oocytes reach the end of MPI, they form primordial follicles with neighboring granulosa cells and enter the resting stage until they are recruited into follicular growth. Despite the similar sizes of the ovarian reserve in neonatal XO and B6.Y^{TIR} (simply XY, herein) females on the B6 genetic background, the XY female loses the primordial follicles in the ovarian reserve faster than the XO female during postnatal development and retains very few follicles at puberty [Taketo-Hosotani et al., 1989]. The cause of the faster follicular loss in the XY female remains an enigma.

In the XX adult ovary, a cohort of primordial follicles enter the growth phase, during which oocytes increase in their diameter from 20 to 80 μm , while granulosa cells actively proliferate to form multilayers and the antrum filled with follicular fluid [Liu et al., 2006]. The oocyte robustly synthesizes and accumulates RNAs and proteins during follicular growth [Bachvarova, 1974; Sternlicht and Schul-

tz, 1981; Kaplan et al., 1982]. While the majority of newly synthesized RNAs are ribosomal, a constant percentage is allocated to polyA-containing mRNAs up to the mid-growth phase [Brower et al., 1981; Sternlicht and Schultz, 1981]. The oocyte ceases transcription before reaching the maximum growth; therefore, the subsequent events are carried out by the RNAs and proteins accumulated during the growth phase until zygotic genes are activated. Shortening of polyA-tails at the end of oocyte growth is essential for stabilizing mRNAs and for regulating translation or degradation of the mRNAs at specific stages of oocyte development [Stutz et al., 1998; Su et al., 2007; Morgan et al., 2017; Sha et al., 2020]. During the growth phase, the oocyte also undergoes unique epigenetic modifications including histone modifications and DNA methylation, which are critical for success in embryonic development [Hiura et al., 2006; Smallwood et al., 2011; Ma et al., 2012].

While the transcriptome of XX oocytes during the growth phase has been reported, particularly in association with the chromatin accessibility and de novo DNA methylation [Veselovska et al., 2015; Gu et al., 2019], how the sex chromosome complement affects the transcriptome during this period was not known. Our recent study [Yamazaki et al. 2021] compared the transcriptomes among XX, XO, and XY oocytes of 50–60 μm in diameter by deep RNA-sequencing. We chose this size because the XY oocytes of larger sizes become morphologically and transcriptionally abnormal (see below). The results revealed that when X-linked genes are transcribed at low levels, they are equalized among XX, XO, and XY oocytes and match the global transcript levels of autosomal genes. However, when X-linked genes are transcribed at high levels, their levels correspond to the X chromosome dosage, i.e., higher in XX oocytes than in XO or XY oocytes, while no difference is seen between XO and XY oocytes. Interestingly, of the autosomal genes which are differentially expressed among the oocytes of the 3 genotypes, near 30% are comparable between XX and XY oocytes and significantly lower in XO oocytes, suggesting that the haplodeficiency of X-linked genes reflects in lower transcript levels of many autosomal genes, while the presence of the Y chromosome compensates the absence of one X chromosome. Indeed, many Y-linked genes are highly expressed in XY oocytes. Whether X- and Y-linked homologs share biological activities in oocytes remains to be investigated. The number of genes that are differentially expressed in XY oocytes compared to XX or XO oocytes is surprisingly small. These results suggest that the sex chromosome dosage plays a major role in defining the transcriptome landscape during the oocyte growth.

To determine when the sex chromosome complement affects gene transcription during follicular growth, we compared the transcript levels of selected genes in XX, XO, and XY oocytes during the entire growth phase as well as at the end of growth phase (FG-oocytes) using quantitative RT-PCR [Yamazaki et al., 2021]. The results revealed that transcript levels of all examined genes increase with oocyte growth while the X chromosome dosage dependence is maintained. However, near the end of the growth phase, XY oocytes fail to increase the transcript levels of some X-linked genes as fast as XO oocytes. The presence of the Y chromosome appears to render the transcriptome of XY oocytes divergent from XX oocytes at the end of the growth phase.

Abnormality in XY Fully-Grown Oocytes

Transcriptional silencing in fully-grown oocytes (also named GV-oocytes) accompanies drastic changes in the chromatin and cytoplasmic organization. Interphase chromatin is initially distributed over the nucleus, named non-surrounded nucleolus (NSN); however, at the end of the growth phase, chromatin becomes condensed around the nucleolus, named surrounded nucleolus (SN) [Debey et al., 1993; Zuccotti et al., 1995; de la Fuente and Eppig, 2001]. The transition from NSN to SN coincides with transcriptional silencing. The nucleus is initially located off the center during the growth phase, but it moves to the center in the fully grown GV-oocyte. In the cytoplasm, the GV-oocyte shows morphological changes in the organelles such as ribosomes, endoplasmic reticulum, mitochondria, and Golgi apparatus, in agreement with their high metabolic activities [Szollosi et al., 1972; Wassarman and Josefowicz, 1978; van Blerkom and Runner, 1984].

In the XY oocyte, morphological abnormality becomes apparent near the end of the growth phase (Fig. 1) [Yamazaki et al., 2021]. Chromatin is condensed along the nuclear envelope in addition to along the nucleolus in the XY GV-oocyte; such chromatin condensation has never been reported in the XX oocyte. Mitochondria distribution is also abnormal. By contrast, no obvious morphological abnormality is recognized in the XO oocyte despite the low transcript levels of many genes during the growth phase.

We have previously compared gene transcript levels among XX, XO, and XY GV-oocytes by cDNA microarray [Xu et al., 2012]. While many genes show different transcript levels between XY and XX oocytes, little differ-

ence is found between XO and XX oocytes. We suggested that accumulation of mRNAs is adjusted in the XO oocyte while Y-linked gene products alter the transcriptome landscape that persists until the end of the growth phase. It remains unknown if the morphological abnormalities observed in the XY GV-oocyte are associated with the altered transcriptome, premature termination of *de novo* transcription, or involving bi-directional communication with the surrounding granulosa (now named cumulus) cells [Xu et al., 2014; Yamazaki et al., 2021].

Meiotic Resumption and Maturation of Oocytes

Once the oocyte reaches the end of the growth phase in an antral follicle, LH surge from the pituitary stimulates the resumption of the meiotic cell cycle in the oocyte *in vivo* [Fu et al., 2007; Conti et al., 2012]. Isolation of the oocyte surrounded by cumulus granulosa cells, named cumulus-oocyte-complex (COC), from an antral follicle also renders the oocyte to resume meiosis *in vitro* [Erickson and Sorensen, 1974]. Once meiosis is resumed, the nuclear membrane breaks down and the first metaphase (MI)-spindle is formed in the center of the oocyte. Then, the MI-spindle migrates towards the oolemma, and homologous chromosomes segregate into the oocyte and the first polar body at the first meiotic division. In the oocyte, the remaining chromosomes form the second metaphase (MII)-spindle, which is positioned parallel to the oolemma in the mouse, and the MII-oocyte is transiently arrested at this stage. This transition from the GV- to MII-stage is named oocyte maturation. Both XO and XY oocytes undergo oocyte maturation *in vivo* and *in vitro* similarly to XX oocytes [Hunt et al., 1995; Amleh et al., 1996; LeMaire-Adkins et al., 1997; Hodges and Hunt, 2002; Villemure et al., 2007].

Correct segregation of homologous chromosomes at the first meiotic division is critical for production of euploid embryos. Both XO and XY oocytes encounter a challenge at this stage because of a lack of crossover between the sex chromosome(s). It has been shown that the univalent X chromosome in the XO oocyte is subject to either non-disjunction or premature separation of sister chromatids (PSSC), the 2 forms of aneuploidy [Hunt et al., 1995; LeMaire-Adkins et al., 1997; LeMaire-Adkins and Hunt, 2000]. Interestingly, segregation of the single X chromosome is not random; 60% of oocytes retain the X chromosome, named meiotic drive. Furthermore, the frequency of PSSC is affected by the genetic background of XO females; much higher in the C3H/HeJ strain than

Fig. 1. Abnormal aspects in the XY oocyte during the growth phase and subsequent meiotic progression and zygotic development.

in the B6 strain [Hodges et al., 2001]. For comparison, Hodges and Hunt [2002] examined the XY oocytes from B6.Y^{POS} females and found major defects such as abnormal chromosome congression in both MI and MII-spindles and high rates of aneuploidy involving autosomes, compared to XX oocytes. We reported much more suc-

cessful meiotic progression in the XY oocytes from B6.Y^{TIR} females [Villemure et al., 2007]. Although whether B6.Y^{POS} and B6.Y^{TIR} mice share the genetic constitution remains unsolved, we suggested that the experimental design, particularly the maintenance of cumulus cells (COCs) during oocyte maturation, can be attributed to

the proper meiotic progression in the XY oocytes from B6.Y^{TIR} females. Nonetheless, we also recognized meiotic drive in the XY oocyte; 70% of oocytes retain 19 autosomal chromosomes and univalent X or Y chromosome (35% each) [Villemure et al., 2007]. In addition, 25–40% of the euploid oocytes from XY females show PSSC [Zhu et al., 2017], consistent with the report for the XO oocyte [LeMaire-Adkins et al., 1997]. At the end, certain percentages of oocytes from XO and XY females retain single X chromosomes as expected in the oocytes of XX females. Therefore, sex chromosome aneuploidy in oocytes may contribute to the subfertility of XO females but not fully explain the infertility of XY females.

The Second Meiotic Division and Embryonic Development

Upon fertilization or parthenogenetic activation in the MII-oocytes from XX females, the MII-spindle rotates into the perpendicular orientation and the sister chromatids segregate into the oocyte and the second polar body at the second meiotic division [Mihajlović and FitzHarris, 2018; Wang et al., 2020]. The chance for the XY female mouse to produce offspring is abolished at this stage since very few MII-oocytes complete the second meiotic division or initiate zygotic development [Taketo-Hosotani et al., 1989; Amleh et al., 1996; Villemure et al., 2007; Zhu et al., 2017]. We initially reported that the MII-spindle is bulky and orientated perpendicular, instead of parallel, to the ooplasm [Villemure et al., 2007; Obata et al., 2008]. However, we later found largely normal MII-spindle orientation in the oocytes from XY females in a constructed 3D-model using confocal microscopy [Zhu et al., 2017]. We cannot explain this discrepancy, but our recent study again confirmed the perpendicular orientation by confocal microscopy [Yamazaki and Taketo, unpubl. data]. Although sister chromatids are separated at the second anaphase in the oocytes from XY females, more than half of the oocytes fail to extrude the second polar body, and when the second polar body is extruded, all chromatids are often retained in the oocyte while the polar body is empty [Villemure et al., 2007; Zhu et al., 2017]. Regardless, the remaining chromatids undergo precocious chromatin decondensation and form 2 or more pronuclei. We have suggested that the oocytes from XY females lack coordination between chromatin segregation and the second meiotic cytokinesis. Subsequently, the fertilized oocytes from XY females rarely complete the first cleavage [Amleh et al., 1996; Zhu et al., 2017]. Similar failure in the

second meiotic cytokinesis and precocious chromatin decondensation has been reported in the oocytes from the XO female expressing a Y-linked *Zfy2* transgene on a mixed genetic background [Vernet et al., 2014]. Most of such oocytes undergo the first cleavage but arrest at the 2-cell stage. The molecular mechanisms responsible for the failure in the second meiotic cytokinesis in the oocytes from XY females remain unknown.

Defects in the Nucleus versus Cytoplasm in the XY Oocyte

The failure in the zygotic development in the oocytes from XY females can be attributed to cytoplasmic defects; when the XY oocyte nucleus has been transferred into an enucleated XX oocyte, the reconstructed oocyte develops into a healthy pup after in vitro fertilization and embryo transfer [Obata et al., 2008]. The aneuploidy of the sex chromosomes at the first meiotic division is inherited by the offspring except for the early loss of YO embryos. Since transcription ceases at the end of oocyte growth, the cytoplasm of XY oocytes must become defective prior to the meiotic resumption. The *Zfy2* gene transcripts have been proposed for causing the XY oocyte to fail in zygotic development [Vernet et al., 2014]. However, the *Zfy2* gene has polymorphic differences among mouse strains [Nagamine et al., 1989], and whether the *Zfy2* gene is responsible for the failure in the second meiotic cytokinesis in the oocytes from B6.Y^{TIR} females remains to be investigated.

Conclusion

XY sex-reversed females are not always infertile in rodents. For example, in the south American field mouse *Akodon azarae*, XY sex-reversed females are not only fertile but also produce more progeny than XX females [Bianchi et al., 1993; Espinosa and Vitullo, 1996]. By contrast, human XY and XO females (without mosaicism) are invariably infertile. Clarifying the cause of infertility in *M. musculus* XY females would promote our understanding of the evolutionary role of sex chromosomes in the differentiation of germ cells. In addition to the sex chromosome pairing failure in the fetal oocyte, the X-linked gene dosage and expression of Y-linked genes in the oocyte during follicular growth appears to determine the competence of oocytes for embryonic development.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.Y., S.L.T., and T.T. contributed to the conception of this review, drafting and editing the article, and approved the final version.

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