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The frequency of precocious segregation of sister chromatids in mouse female meiosis I is affected by genetic background

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Abstract Mammalian female gametes frequently suffer from numerical chromosomal aberrations, the main cause of miscarriages and severe developmental defects. The underlying mechanisms responsible for the development of aneuploidy in oocytes are still not completely understood and remain a subject of extensive research. From studies focused on prevalence of aneuploidy in mouse oocytes, it has become obvious that reported rates of aneuploidy are strongly dependent on the method used for chromosome counting. In addition, it seems likely that differences between mouse strains could influence the frequency of aneuploidy as well; however, up till now, such a comparison has not been available. Therefore, in our study, we measured the levels of aneuploidy which has resulted from missegregation in meiosis I, in oocytes of three commonly used mouse strains—CD-1, C3H/HeJ, and C57BL/6. Our results revealed that, although the overall chromosomal numerical aberration rates were similar in all three strains, a different number of oocytes in each strain contained prematurely segregated sister chromatids (PSSC). This indicates that a predisposition for this type of chromosome segregation error in oocyte meiosis I is dependent on genetic background.

Keywords Meiosis · Oocyte · Aneuploidy · Numerical chromosomal aberrations · Precocious segregation of sister chromatids · Chromosomes · Univalents

Abbreviations

CGH	Comparative genomic hybridization
CSF	Cytostatic factor
FISH	Fluorescence in situ hybridization
GV	Germinal vesicle
GVBD	Germinal vesicle breakdown
PB	Polar body
PSSC	Prematurely segregated sister chromatids/ precociously separated sister chromatids
SAC	Spindle assembly checkpoint

Introduction

Meiosis is a unique type of cell division, during which the male and female haploid gametes are generated. Male germ cells are continuously entering meiosis during almost the entire lifespan of the individual. In contrast, the onset of meiotic division in oocytes, during the intrauterine development, is separated in time from the resumption of meiosis after reaching puberty. During this interval, oocytes are arrested in the prophase of the first meiotic division. In certain species, this might last for decades and is most likely a cause for high levels of chromosome segregation errors and subsequent

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aneuploidy. It has been reported that 5–10 % of the clinically recognized pregnancies in humans are afflicted by monosomy or trisomy, which originates in oocytes (Hassold et al. 2007; Nagaoka et al. 2012). Other mammalian species seem to share this predisposition with humans, with levels reaching up to 12 % in porcine oocytes (Hornak et al. 2011) and 7.1 % in cattle (Lechniak and Switonski 1998). In contrast, the rate of chromosomal segregation errors during meiosis in lower eukaryotes such as *Saccharomyces cerevisiae* is 1 to 10,000 (Sears et al. 1992). The vast majority of human aneuploid pregnancies terminate without ever being diagnosed, and thus, the actual level of aneuploidy in human oocytes and embryos is much higher. Detailed studies on human oocytes and embryos, which were meant for IVF, have demonstrated levels of aneuploidy reaching 20–40 % (Martin et al. 1991; Jacobs 1992; Jamieson et al. 1994; Eichenlaub-Ritter 1998; Hunt and Hassold 2010; Munne et al. 2007; Fragouli et al. 2011; Fragouli et al. 2013). It has also been shown that there is a strong correlation between maternal age and the occurrence of aneuploidy, with up to 50 % of the eggs of females over 40 years old containing an incorrect number of chromosomes (Hassold and Jacobs 1984; Hassold and Chiu 1985; Hassold and Hunt 2001; Kuliev et al. 2005; Hassold and Hunt 2009; Gianaroli et al. 2010; Hunt and Hassold 2010; Kuliev et al. 2011). In 60 % of cases, aneuploidy in female gametes results from predivision, the condition in which sister chromatids are already separated during the first meiotic division (Rosenbusch 2004; Rosenbusch 2006). Precociously separated sister chromatids are subsequently randomly segregated between the oocyte and the first polar body, creating an egg containing either one of the sister chromatids (and thus being aneuploid) or both separated sister chromatids (balanced predivision), predetermining the oocyte for aneuploidy after the second meiotic division in 50 % of cases (Angell 1997; Rosenbusch et al. 2001).

Although the causes of aneuploidy in oocytes have been studied for a relatively long time, the underlying mechanisms remain not completely understood (Eichenlaub-Ritter 2012; Howe and FitzHarris 2013; Jones and Lane 2013). Numerous studies have demonstrated that mouse oocytes do not only have a similar predisposition for aneuploidy as human oocytes (Golbus 1981; Zackowski and Martin-Deleon 1988; Zuccotti et al. 1998; Duncan et al. 2009; Sebestova et al. 2012), but also share patterns of increased aneuploidy levels relative to maternal age (Pan et al. 2008; Duncan et al. 2009; Merriman et al. 2011; Sebestova et al. 2012). This, together with the possibility to create animals with a disruption of a particular gene, makes mice an ideal model for research focused on the origins of aneuploidy in oocytes.

Based on previously published data, we can assume that the differences in reported rates of aneuploidy in mouse oocytes (Table 1) are predominantly dependent on the technique used for detection. The genetic background, however, should be taken into account as well, since, even within mice strains, differences can be observed (Aldinger et al. 2009). Moreover, recent studies have revealed that genetic background can influence the age-related aneuploidy rise in mice (Shomper et al. 2014; Yun et al. 2014b). The purpose of our study was to determine aneuploidy levels in in vitro matured oocytes of commonly used laboratory mouse strains. For this, we have selected the CD-1 outbred and the C57BL/6 and C3H/HeJ inbred mouse strains. The latter was chosen based on a comparison of previous studies, in which this strain was found to have the lowest aneuploidy rates (Hansmann 1974; Rohrborn and Hansmann 1974). To measure the levels of aneuploidy, we used a method which allowed us not only to score numbers of chromosomes but also to analyze the mutual positions of sister chromatids and the distance between their kinetochores in intact cells. Our results showed that assessing the configuration of sister chromatids in oocytes is at least as important as determining the overall number of chromosomes.

Materials and methods

Mice

The CD-1, C3H/HeJ, and C57BL/6 mouse strains were purchased from AnLab, Czech Republic, and the Animal Breeding and Experimental Facility, Faculty of Medicine, Masaryk University, Czech Republic. All animal work was conducted in accordance with Act No 246/1992 Coll., on the protection of animals against cruelty under the supervision of the Central Commission for Animal Welfare, approval ID 018/2010.

Table 1 Overview of previously published aneuploidy rates in mouse strains

Strain	Age of animals	Aneuploidy rate	Technique	Reference
CD-1	4–12 weeks	3–4 %	In vitro (hCG)/monastrol/CREST	Merriman et al. (2011)
	8–12 weeks	13.7 %	In vivo (PMSG)/C-banded	Mailhes et al. (2002)
	8–20 weeks	4.1 %	In vitro/monastrol/CREST	Sebestova et al. (2012)
C57BL/6	6–8 weeks	4.3 %	In vivo (PMSG)/spread	Cheng et al. (2011)
C3H/HeJ	10–12 weeks	3.6 %		Hansmann 1974

Oocyte harvesting and maturation

Adult (12–20 weeks) female mice were sacrificed and the ovaries were excised. The ovarian tissue was disaggregated in a drop of M2 medium (Sigma-Aldrich) with 100 μM 3-isobutyl-1-methylxanthine (IBMX, Sigma-Aldrich). Germinal vesicle (GV)-stage oocytes were subsequently incubated in a drop of M16 medium, (Sigma-Aldrich) containing 100 μM IBMX and covered with a mineral oil (Sigma-Aldrich), at 37 °C, 5 % CO_2, for at least 1 h prior to further procedures. Maturation was induced by the removal of the inhibitor from the media, and 1.5 h after the onset of maturation, the oocytes, which had not undergone germinal vesicle breakdown (GVBD), were discarded from further use.

Immunofluorescence and kinetochore counting assay

The immunofluorescence protocol and kinetochore counting assay were adopted from Duncan et al. (2009) and Sebestova et al. (2012). Twenty hours after the onset of maturation, MII-stage oocytes were selected, washed in M16 medium with 100 μM monastrol (Sigma-Aldrich) or 2 μM dimethylenastron (Sigma-Aldrich), and incubated at 37 °C, 5 % CO_2 for 2 h.

The zona pellucida and polar bodies (PBs) were subsequently removed by a short incubation in Pronase (Sigma-Aldrich). The oocytes were fixed with 2 % paraformaldehyde (Sigma-Aldrich) for 20 min and permeabilized with 0.1 % Triton for 15 min. The fixation was followed by immunostaining with a human anti-centromere antibody (HCT-0100, Immunovision, 1:500) and an Alexa Flour 555 goat anti-human secondary antibody (A21433, 1:500, Invitrogen, Life Technologies). Vectashield with DAPI (H-1200, Vector Laboratories) was used as a mounting medium. The cells were scanned using a Leica AF 6000 inverted fluorescence microscope, equipped with a HCX PL APO ×100/1.4–0.7 oil objective. Leica A filter cube (exCitation filter

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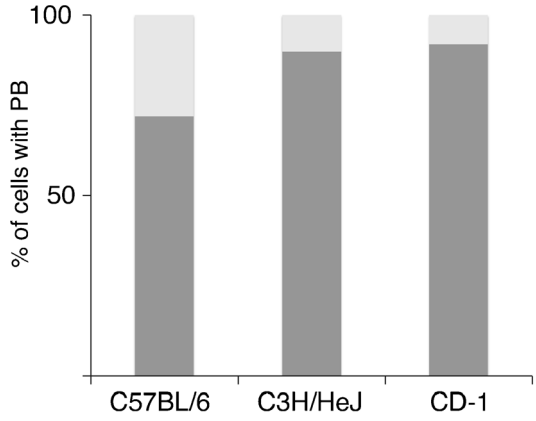


B

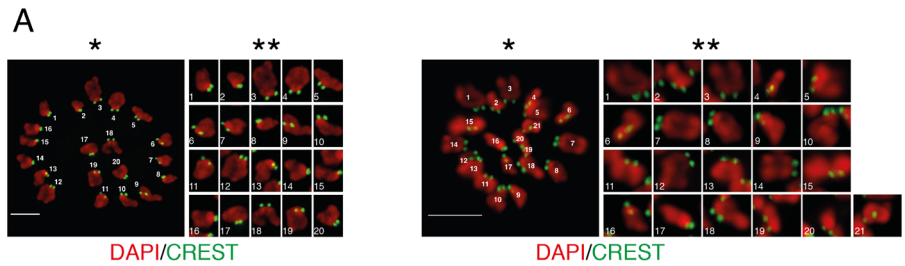
Mouse strain	Number of oocytes	Number of cells with PB after 20 hrs
C57BL/6	342	246
C3H/HeJ	241	217
CD-1	389	358

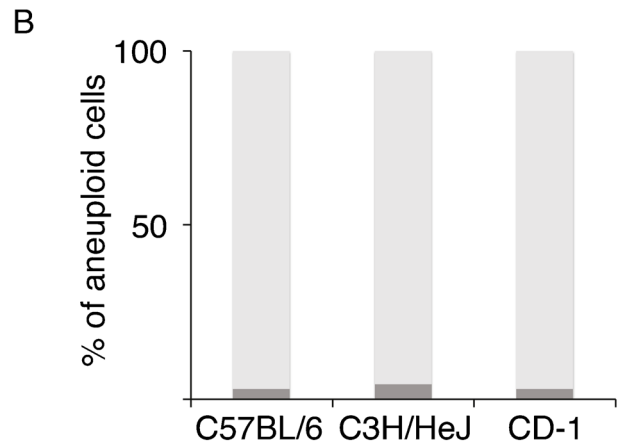
Fig. 1 Polar body extrusion during in vitro maturation of oocytes isolated from C57BL/6, C3H/HeJ, and CD-1 strains. **a** Oocytes from the C57BL/6, C3H/HeJ, and CD-1 mouse strains which have undergone GVBD within 1.5 h after the onset of maturation were scored for the presence of polar bodies after 20 h of maturation. Among the oocytes, 71.9 % from C57BL/6 (n=342), 90 % from C3H/HeJ (n=241), and 92 % from CD-1 (n=389) mice reached the MII-stage and extruded PB. The *light grey bars* indicate a portion of cells which have not reached the MII-stage. The *dark grey bars* indicate the percentage of oocytes with PB after 20 h of maturation. **b** The total numbers of oocytes from each strain used in the experiments are indicated in the *table*

BP 360/40) and Leica DsRed ET filter cube (exCitation filter BP 546/11) were used for the detection of DAPI and an Alexa Fluor 555, respectively. The Z-resolution was automatically optimized by LAS AF software. IMARIS software was used for 3D reconstruction.

Statistical analysis

Data were analyzed using Fisher's exact test. Statistical analysis was performed using Prism software, version 5.00 for Mac (GraphPad Software, San Diego, CA, USA, www.graphpad.com).





C

Mouse strain	Number of cells	Number of aneuploid cells
C57BL/6	236	7
C3H/HeJ	190	7
CD-1	327	10

Fig. 2 Aneuploidy rates are similar in C57BL/6, C3H/HeJ, and CD-1 mouse strains. **a** *left panel, single asterisk*: a euploid MII-stage oocyte fixed after monastrol treatment, with 20 pairs of closely positioned kinetochores; *left panel, double asterisks*: 20 individual univalents from the same cell reconstructed from selected z plains. *Right panel, single asterisk*: an aneuploid oocyte with an additional univalent; *right panel, double asterisks*: 21 individual pairs of attached sister chromatids. Chromosomes (in *red*) stained with DAPI, kinetochores (in *green*) labeled by CREST antiserum. *Scale bar* represents 5 μm. The chromosomes are numbered randomly. **b** The frequency of aneuploidy was scored in mice from inbred C57BL/6 (n=236) and C3H/HeJ (n=190) strains and the CD-1 outbred strain (n=327). Aneuploidy levels reached 2.97 % in C57BL/6, 3.68 % in C3H/HeJ, and 3.06 % in CD-1 mice. No significant difference was observed between the represented strains (p>0.05). The *light grey bars* represent the rate of euploid oocytes; the *dark grey bars* represent the rate of aneuploid cells. **c** The numbers of oocytes from each strain, which were analyzed for aneuploidy, are indicated in the *table*

Results

The ability to complete meiosis in vitro varies between selected mouse strains

We analyzed the ability of oocytes from adult mice (12–20 weeks) of all three strains to resume and complete meiosis in our culture conditions (see "Materials and methods"). Most of the oocytes resumed meiosis within 1.5 h after the onset of maturation, and only the oocytes which accomplished GVBD within this time were selected for further analysis. Twenty hours after the onset of maturation, oocytes from each strain were scored for polar body extrusion (PBE). The lowest maturation rate, 71.9 %, was observed in C57BL/6 oocytes, in contrast to 90 % in the C3H/HeJ and 92 % in the CD-1 strains (Fig. 1a, b). Moreover, the ovaries of C57BL/6 mice contained a lower number of fully grown GV oocytes compared to those of the other strains in our study. On average, we were able to obtain 22 fully grown GV oocytes per mice from the C57BL/6 strain and 35 and 45 in the C3H/HeJ and CD-1 strains, respectively (data not shown).

The frequency of aneuploidy in MII-stage oocytes is similar for CD-1, C57BL/6, and C3H/HeJ strains

After PBE and the formation of the second meiotic spindle, oocytes arrest at the metaphase II due to the activity of the cytostatic factor (CSF) (Madgwick and Jones 2007). At this time point, we scored the outcome of the first meiotic division. To establish the number of chromosomes in the MII-stage oocytes, we employed the kinetochore counting assay (Duncan et al. 2009; Sebestova et al. 2012). Oocytes which contained 40 kinetochores were scored as euploid (Fig. 2a, left panel). Cells with a different number of kinetochores were scored as aneuploid (Fig. 2a, right panel). Thanks to the optimization of cell coverage by z stacks and the subsequent 3D reconstruction of the entire cell by Imaris software, we were able to resolve the superimposed or closely associated kinetochores as well (Fig. S1). Our results revealed that the frequency of aneuploidy in oocytes of all three strains is similar, ranging from 2.97 % in C57BL/6 through 3.06 % in CD-1 and up to 3.68 % in C3H/HeJ (Fig. 2b, c). According to statistical analysis, the differences in aneuploidy levels between selected strains were statistically not significant. The aneuploidy rates obtained in our experiments were consistent with previously published results (Hansmann 1974; Duncan et al. 2009; Cheng et al. 2011; Merriman et al. 2011; Sebestova et al. 2012; Table 1).

The frequency of prematurely separated sister chromatids varies between selected mouse strains

While examining metaphase II oocytes for aneuploidy, we detected separated kinetochore signals of sister

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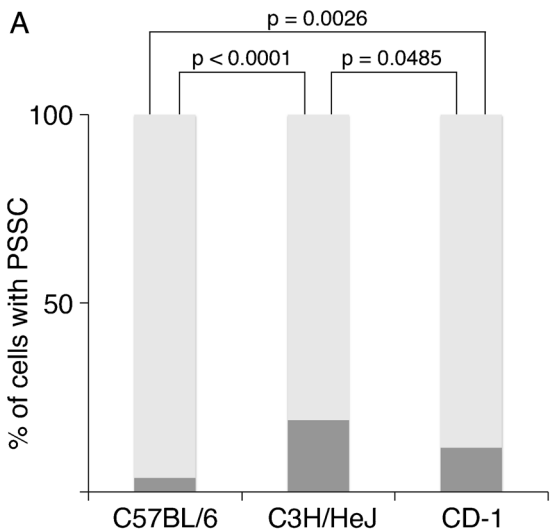

B

Mouse strain	Number of cells	Number of cells with PSSC
C57BL/6	215	8
C3H/HeJ	174	33
CD-1	242	28

Fig. 3 Levels of prematurely segregated sister chromatids in oocytes from C57BL/6, C3H/HeJ, and CD-1 mouse strains. **a** In 3.72 % of the C57BL/6 oocytes (n=215), 18.97 % of the C3H/HeJ (n=174), and 11.57 % of the CD-1 (n=242), PSSC were detected. There was a significant difference in the number of oocytes with prematurely segregated sister chromatids between all three strains (p<0.0001 for C57BL/6 vs. C3H/HeJ; p=0.0026 for C57BL/6 vs. CD-1 strains; p=0.0485 for C3H/HeJ vs. CD-1 strains). The *light grey bars* signify oocytes which did not contain PSSC; the *dark grey bars* indicate the rate of cells with PSSC. **b** The number of the oocytes from selected mouse strains containing PSSC is specified in the *table*

chromatids in some cells. The presence of single chromatids in MII-stage oocytes could lead to incorrect chromosome segregation in the following division and might impairs the subsequent development of an aneuploid embryo. Therefore, we decided to establish the number of cells containing prematurely segregated sister chromatids/precociously separated sister chromatids (PSSC), by scoring separated sister chromatids in the cells, which were previously analyzed for aneuploidy. Our results showed dramatic differences in the number of oocytes with PSSC between the selected strains (Fig. 3a, b). As shown in Fig. 4a, 11,57 % of CD-1 oocytes, 18,97 % of C3H/HeJ and 3,72 % of C57BL/6 oocytes contained at least one separated pair of kinetochores or a single kinetochore (Fig. 4a). However, we realized that cells with PSSC did not always contain a numerical chromosomal aberration. Therefore, the proportion of euploid versus aneuploid cells in the group of oocytes containing PSSC was established (Fig. 4b). Strikingly, the majority of the cells with prematurely segregated sister chromatids had a correct number of chromosomes, despite the fact that the actual proportion was different for each strain. More specifically, 37.5 % of oocytes from C57BL/6, 78.8 % from C3H/HeJ, and 78.6 % from CD-1 strains, which contained PSSC, were euploid.

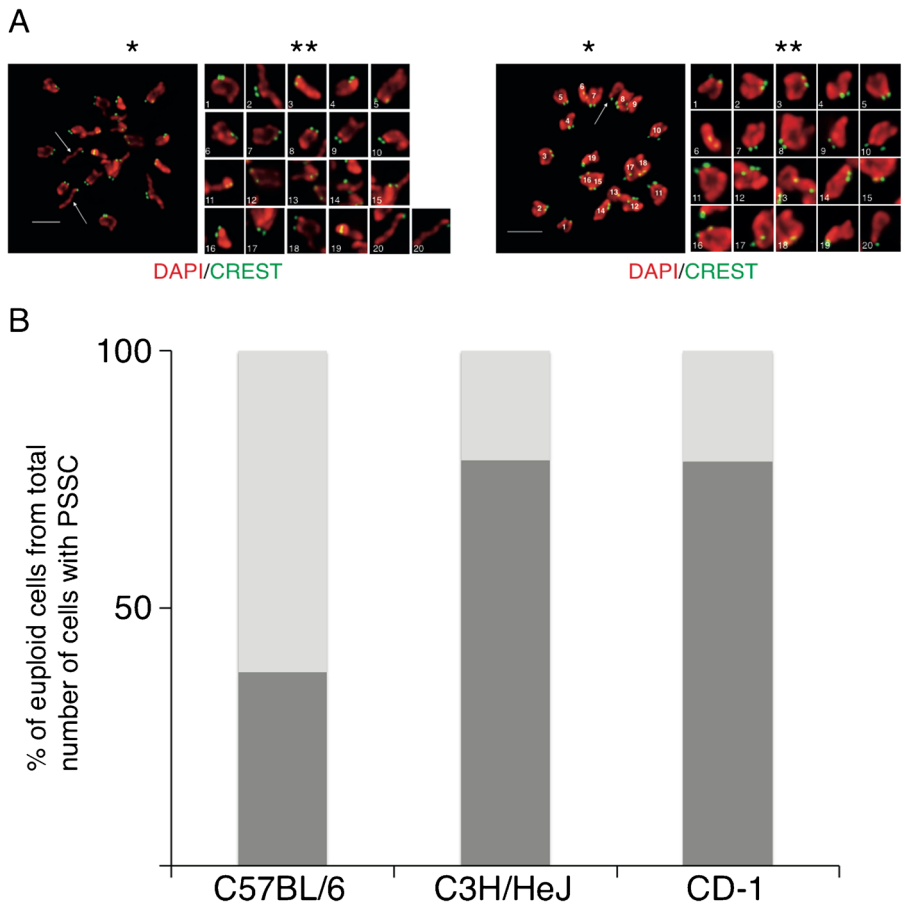

Fig. 4 Proportion of cells with balanced and unbalanced predivision in oocytes from C57BL/6, C3H/HeJ, and CD-1 mouse strains. **a** *Left panel, single asterisk*: predivision in the euploid oocyte; *left panel, double asterisks*: 19 univalents and 2 prematurely segregated sister chromatids. **a** *right panel, single asterisk*: oocyte with aneuploidy caused by predivision; *right panel*, *double asterisks*: 19 individual dyads and 1 single chromatid. Sister chromatids (marked by *arrows*) display one kinetochore signal each. Chromosome and kinetochore staining is like in Fig. 2a. *Scale bar* represents 5 μm. The chromosomes are numbered randomly. **b** The numbers of euploid oocytes from the total amount of oocytes with PSSC for each mouse strain were as follows: 37.5 % of the oocytes from the C57BL/6 strain (n=8), 78.8 % from the C3H/HeJ strain (n=33), and 78.6 % from the CD-1 (n=28). The *light grey bars* represent oocytes with unbalanced predivision: the *dark grey bars* represent cells with balanced predivision

Discussion

In our study, we analyzed the frequency of aneuploidy in the oocytes of three commonly used mouse strains. Thanks to the method we used, we were able to not only determine the number of chromosomes in each oocyte but also to evaluate the distance between all the sister chromatids and their relative positions. In comparison, conventional FISH is usually limited by the number of probes and routinely only three to six chromosomes per cell are detected (Nagaoka et al. 2012). Even when using the newest techniques, such as comparative genome hybridization (CGH) and array comparative genome hybridization (array-CGH), it is impossible to detect all the cells with PSSC since the cells with a balanced predivision are scored as euploid (Gutierrez-Mateo et al. 2011; Colls et al. 2012).

Our study revealed that the rates of numerical chromosomal aberrations in in vitro matured MII-stage oocytes were similar between the selected strains. However, more frequently than an incorrect number of chromosomes, oocytes harbored prematurely separated sister chromatids in metaphase II. Our results clearly show that the frequency of PSSC varies between the strains of our selection, and therefore, the predisposition for predivision depends on the genetic background. This finding is important because the precocious dissolution of the ties between sister chromatids is a major source of aneuploidy in oocytes and embryos, constituting more than half of the aneuploidy cases in humans (Rosenbusch 2004; Rosenbusch 2006). Moreover, PSSC is reported to be a main reason for age-related aneuploidy increase in both humans and mice (Vialard et al. 2006; Yun et al. 2014a). The precociously separated sister chromatids exploit a blind spot of the control mechanism called the spindle assembly checkpoint (SAC) by establishing a merotelic kinetochore-microtubule attachment, thus escaping detection by SAC (O'Connell et al. 2008; Gregan et al. 2011). Undetected by the surveillance mechanisms, sister chromatids are then distributed randomly between the polar body and the oocyte in anaphase II, causing a numerical abnormality in 50 % of cells (Angell 1997; Rosenbusch et al. 2001).

Our results are opening new avenues for studying the mechanisms responsible for predivision in oocytes. A comparison of mouse strains with different levels of PSSC might help our understanding of the mechanisms behind maternal age-related aneuploidy. There is, however, a possibility that the premature segregation of sister chromatids in in vitro cultured oocytes has a different underlying mechanism from PSSC in oocytes from animals of advanced age. Indeed, our preliminary results indicate that the amount of cohesin subunit Rec8 on chromosomes does not vary significantly between the strains used in this study (data not shown), although the deterioration of cohesion is most likely behind maternal age-related aneuploidy (Chiang et al. 2010; Lister et al. 2010; Revenkova et al. 2010; Tachibana-Konwalski et al. 2010) as well as aneuploidy in oocytes from young mice (Merriman et al. 2013).

The differences between mouse strains have been shown to interfere with the progression of female germ cells through meiosis (Polanski et al. 1998) or with the correlation of aneuploidy occurrence with the maternal age (Shomper et al. 2014; Yun et al. 2014a, b). Our results emphasize the importance of the careful selection of mouse strains for experiments, due to the influence, which the genetic background might have on the outcome of meiosis.

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Ethical standards The authors declare that all experiments performed in this study comply with the current laws of the Czech Republic. All institutional and national guidelines for the care and use of laboratory animals were followed.

Conflict of interest The authors (A.D., K.K., T.A., and M.A.) declare that they have no conflict of interest.

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