Genetic background of the differences in timing of meiotic maturation in mouse oocytes: a study using recombinant inbred strains

Z. Polański

Department of Genetics and Evolution, Jagiellonian University, Kraków, Poland

Recombinant inbred strains of mice derived from CBA and KE strains were used for studying the genetic background of the duration of the first meiotic cycle which differs in oocytes from progenitor strains. Oocytes were screened *in vitro* for the timing of germinal vesicle breakdown as well as for the timing of first polar body extrusion, and the approximate duration of the first meiotic M-phase was calculated. Although oocytes from progenitor strains did not differ in the duration of germinal vesicle breakdown, this characteristic segregated in recombinant strains showing involvement of at least two genes. Because of the similar duration of germinal vesicle breakdown in CBA and KE oocytes, the difference in timing of first polar body extrusion (9 h and 12 h for CBA and KE, respectively) reflects the difference in the duration of the first meiotic M-phase. The timing of germinal vesicle breakdown and the duration of M-phase in recombinant strains were negatively correlated ($P < 0.01$); in general, the more time needed for breakdown of the germinal vesicle, the shorter the M-phase. The timing of first polar body extrusion varied among strains: in some it was similar to one of the parental strains; in others it was intermediate between the two, which again shows the involvement of at least two genes in the control of this character. The linkage analysis suggests that one of the putative genes influencing the timing of first polar body extrusion may be situated near the *Gpi-1* locus on chromosome 7, that is, in the region containing the locus for cyclin E. The possible involvement of cyclin E in the control of the timing of first meiosis in mouse oocytes is discussed.

Introduction

Mouse oocytes enter prophase of meiosis at the end of fetal life and become arrested in late prophase of the first meiotic division at the germinal vesicle (GV) stage. After a long arrest, fully grown oocytes start meiotic maturation (in response to gonadotrophins *in vivo*, and when released from antral follicles *in vitro*) which begins with the breakdown of the nuclear envelope (germinal vesicle breakdown, GVBD). The oocytes then progress through first metaphase, anaphase and telophase with the extrusion of the first polar body to the second metaphase, which is the final stage of meiotic maturation (Donahue, 1968). The oocytes remain at this stage until fertilization or parthenogenetic activation stimulate completion of meiosis and transition to the first mitotic cycle.

Mouse oocytes from the inbred strains CBA and KE differ greatly in the rate of meiotic maturation; *in vivo* the CBA oocytes extrude their first polar bodies at about 9 h of maturation, whereas the KE oocytes do so approximately 3–4 h later (Polański, 1986). Thus, oocytes from these two strains provide a good model for studying factors involved in the control of the first meiotic cycle.

In this study, mice from CBA, KE and recombinant inbred (RI) strains developed from these progenitor strains were used.

Recombinant inbred strains, first developed and described by Bailey (1971), are especially useful for gene mapping, for analysis of pleiotropism, and for studying genetic and physiological correlations between characters, because each RI strain provides a repeatable, homozygous sample of a particular recombination (haplotype) of alleles that is different in the progenitor strains. In this study RI strains were used to investigate the genetic factors affecting the duration of first meiosis in mouse oocytes.

Materials and Methods

Mice

Adult female mice from two inbred strains, CBA/Kw (referred to hereafter as CBA) and KE as well as from RI strains were used in this study. Five RI strains (EXCB 2, 3, 5, 6 and 10) were obtained from the original cross of KE females with CBA males, and five (CBXE 12, 13, 15, 17 and 20) from the reciprocal cross. The strain distribution pattern of the following genetic markers segregating in the RI strains is known: coat colour markers for the loci *a*, *b* and *c*; histocompatibility locus *H-2*, and electrophoretic markers *Idh-1*, *Upg-2*, *Svp-1*, *Car-2*, *Ce-2*, *Es-9*, *Gpi-1*, *Hbb*, *Ldr-1*, *Mod-1*, *Trf* and *Upg-1* (Rafinski *et al.*, 1991; Krzanowska *et al.*, 1994). Additional testing was also performed

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on nine incipient RI lines (CBXE 21-34) that had passed through only 13–15 generations of inbreeding but were already homozygous for the loci that have been tested (*a*, *Sop-1*, *b*, *Gpi-1*, *c*, *Hbb*, *Trf*; Krzanowska *et al.*, 1994; *Idh-1*, *Car-2*, *Ce-2*; J. Styrna, personal communication).

The rate of oocyte maturation in vitro

The oocytes at the GV stage were obtained by puncturing the antral follicles of dissected ovaries. The cumulus cells, if present, were removed by passing the oocytes through a narrow pipette. These operations were performed in Hepes-buffered M2 culture medium (Fulton and Whittingham, 1978) supplemented with 150 µg dibutyryl cAMP (dbcAMP) ml⁻¹ to prevent the oocytes from resuming maturation before being placed in the culture (Cho *et al.*, 1974). After collection the oocytes were rinsed three times in M2 without dbcAMP and cultured in this medium (4–10 oocytes per drop of about 10 µl) at 37°C under paraffin oil for 16 h in air. The start of the culture was considered as the start of meiotic maturation. From the eighth hour of the culture, the oocytes were inspected every hour under the inverted microscope for the presence of the first polar body.

In separate experiments the timing of GVBD was tested. The oocytes, after isolation and being placed in the culture, were inspected for the disappearance of the germinal vesicle at 1, 1.5, 2, 2.5, 3, 4 and 5 h of incubation.

During inspection the Petri dishes were placed on a warm (37°C) transparent plate (Kitazato Supply Co., Ltd., Fujinomiya City, Japan) to prevent cooling of the culture.

Statistical analyses

Differences among groups were analysed by the ANOVA or Bonferroni test (Statistix Version 4.0, Analytical Software). A unit of measure within the group was the mean value obtained from all oocytes of an individual. $P < 0.05$ was considered as statistically significant.

Results

During this study oocytes were cultured *in vitro* for 5 or 16 h to estimate the timing of GVBD and first polar body extrusion, respectively. The 16 h culture also allowed evaluation of the efficiency of *in vitro* maturation of oocytes in different strains (Table 1). The frequency of GVBD and first polar body extrusion was similar in the two parental strains. Therefore, the data from CBA and KE females were pooled to evaluate the difference in efficiency of GVBD and first polar body extrusion between the parental and RI strains. Only one RI strain differed from the parental strains with respect to GVBD frequency (Table 1). More variance was observed regarding the efficiency of first polar body extrusion, where four phenotypes could be distinguished: efficient (frequency significantly higher than in progenitor strains; three RI strains), moderate (not differing from progenitors; most RI strains), low (significantly lower than in progenitors; one RI strain), and very low (significantly lower than in RI strain with low phenotype; one RI strain).

Table 1. The efficiency in progression of meiotic maturation of mouse oocytes from inbred strains, CBA and KE, and recombinant inbred strains during 16 h of culture *in vitro*

Strain	Number of females	Oocytes undergoing GVBD (%)	Oocytes extruding first polar body ^a (%)
CBA	6	93.1 ± 3.2	81.9 ± 3.5
KE	6	96.1 ± 1.3	78.8 ± 6.1
EXCB2	6	95.5 ± 1.6	82.2 ± 3.7
EXCB3	2	89.1 ± 0.9	65.3 ± 5.3
EXCB5	6	87.5 ± 1.8*	26.8 ± 3.1**
EXCB6	6	94.8 ± 3.0	83.6 ± 4.2
EXCB10	6	97.0 ± 3.0	78.4 ± 5.9
CBXE12	6	92.6 ± 3.2	65.5 ± 8.4
CBXE13	6	93.0 ± 2.8	92.0 ± 2.7**
CBXE15	6	98.2 ± 1.2	86.5 ± 4.7
CBXE17	6	91.7 ± 4.2	51.3 ± 5.4**
CBXE20	6	89.3 ± 5.7	66.8 ± 7.6
CBXE21	6	97.0 ± 3.0	75.6 ± 8.3
CBXE24	6	93.7 ± 3.1	88.4 ± 4.0
CBXE26	6	90.4 ± 2.2	86.1 ± 4.9
CBXE27	3	100	96.7 ± 3.3**
CBXE28	5	95.3 ± 2.9	72.5 ± 4.1
CBXE29	6	98.1 ± 1.8	81.0 ± 6.7
CBXE32	5	91.2 ± 4.1	87.4 ± 2.3
CBXE33	3	100	71.2 ± 10.8
CBXE34	6	96.6	94.8 ± 2.5**

Values expressed as means ± SEM.

^aCalculated in relation to oocytes that had undergone germinal vesicle breakdown (GVBD).

***Significantly different from pooled data from CBA and KE females (in relation to GVBD and extrusion of first polar body, respectively).

In some cases the cytokinesis resulted in the formation of two daughter cells of equal size rather than in that of the large MII oocyte and the first polar body. This phenomenon occurs very rarely at first meiotic division (Braden, 1957, cf. Tarkowski, 1971) and resembles the 'immediate cleavage' that occurs frequently in parthenogenetically activated eggs (Tarkowski, 1971; Kaufman, 1973). The frequency of equal division was low: in only five of 21 tested strains (CBA and KE included) did it exceed 10% of oocytes that had undergone first meiotic division, reaching the maximum (13.6%) in the RI strain CBXE21. Within a given strain the timing of cytokinesis did not differ between oocytes cleaving equally and those extruding first polar bodies.

The mean time of GVBD did not differ significantly between progenitor strains CBA and KE ($P > 0.6$), although it varied considerably among RI strains, ranging from 1.7 h to 2.8 h (Table 2). Analysis of the differences between progenitor strains (pooled data for CBA and KE) and RI strains revealed three phenotypes with respect to timing of GVBD: slow (one RI strain significantly slower than parental strains), moderate (RI strains not differing significantly from parental strains), and fast (four RI strains significantly faster than parental strains; Table 2).

The mean time of first polar body extrusion differed greatly between progenitor strains ($P < 0.0001$): 9 h for CBA and 12 h

Table 2. The timing of germinal vesicle breakdown (GVBD) and first polar body (PB1) extrusion in mouse oocytes from inbred strains, CBA and KE, and recombinant inbred strains

Strain	GVBD		PB1 extrusion				<i>Gpi-1</i> form
	Number of females	Time of GVBD (h)	Number of females	Time of PB1 extrusion (h)	Phenotypes classified by		
					ANOVA	Bonferroni	
CBA	6	2.3 ± 0.06	6	9.0 ± 0.34	CBA	CBA	CBA
KE	4	2.2 ± 0.16	6	12.0 ± 0.24	KE	KE	KE
CBXE12	4	2.2 ± 0.20	6	12.2 ± 0.24	KE	KE	KE
CBXE17	5	1.9 ± 0.17*	6	11.7 ± 0.32	KE	KE	KE
EXCB10	3	1.7 ± 0.10*	6	11.5 ± 0.23	KE	KE	KE
EXCB3	not determined ^a		2	11.4 ± 0.04	KE	KE	KE
CBXE32	6	2.2 ± 0.12	5	11.0 ± 0.25	I	KE	KE
CBXE33	3	2.0 ± 0.15	3	10.9 ± 0.24	I	I	CBA
CBXE34	6	2.0 ± 0.40	6	10.8 ± 0.39	I	KE	KE
CBXE21	6	2.1 ± 0.08	6	10.7 ± 0.25	I	KE	KE
CBXE29	6	2.4 ± 0.40	6	10.7 ± 0.53	I	KE	KE
CBXE26	6	2.0 ± 0.14	6	10.6 ± 0.38	I	I	KE
CBXE24	5	2.2 ± 0.27	6	10.6 ± 0.20	I	I	CBA
EXCB2	4	2.2 ± 0.08	6	10.4 ± 0.24	I	I	KE
EXCB6	4	2.1 ± 0.12	6	10.4 ± 0.28	I	I	KE
CBXE28	5	1.9 ± 0.12*	5	10.3 ± 0.45	I	CBA	CBA
EXCB5	3	2.5 ± 0.08	6	10.2 ± 0.25	I	CBA ^b	KE
CBXE20	4	2.1 ± 0.14	6	10.2 ± 0.07	I	CBA	CBA
CBXE15	4	2.1 ± 0.09	6	10.2 ± 0.23	I	CBA	CBA
CBXE27	3	1.9 ± 0.14*	3	10.1 ± 0.34	CBA ^b	I	KE
CBXE13	3	2.8 ± 0.17*	6	9.6 ± 0.29	CBA	CBA	CBA

Values expressed as means ± SEM.

^aThis strain died out in the course of experiments, before examination of the timing of GVBD.

^bPhenotype nonmatching to *Gpi-1* form.

*Significantly different from pooled females from CBA and KE strains.

'I' denotes a phenotype intermediate between parental phenotypes (CBA or KE). Using ANOVA these strains differed significantly from both progenitor strains. Using the Bonferroni test these strains did not differ significantly from either progenitor strain.

for KE mice (Table 2). These values fit well to the rate of meiotic maturation that had been previously estimated *in vivo*: in females stimulated with exogenous gonadotrophins most oocytes extruded first polar body at about 9 h in CBA strain and 12–13 h in KE strain (Polański, 1986). This finding shows that removal of cumulus cells has little (if any) effect on the kinetics of oocyte maturation in culture. Each RI strain was individually compared with each of progenitor strains using ANOVA to evaluate the differences. In two RI strains (EXCB13, CBXE27) the timing of first polar body extrusion was similar to that of the CBA strain (difference statistically not significant), whereas in four lines (EXCB3, EXCB10, CBXE12, CBXE17) it was similar to the KE strain. In the remaining lines the mean time of first polar body extrusion was intermediate and differed significantly from both parental strains (Table 2).

To find possible linkages between the timing of first polar body extrusion and genetic markers determined earlier in our RI strains, their strain distribution patterns (SDPs) were compared. However, only six RI strains showed the phenotype of first polar body extrusion as KE or CBA when classified by ANOVA (Table 2); this is the minimum number of strains that allows testing of the significance of linkage (Silver, 1985). Therefore, the Bonferroni test of all comparisons among means,

less sensitive in these conditions, was also used. When this test was used, 13 RI strains were classified as similar to one of the parental strains, thus revealing their phenotypes (Table 2).

In both cases of phenotype identification (ANOVA and Bonferroni) the SDP for timing of first polar body extrusion was most similar to the SDP of locus *Gpi-1* (chromosome 7). In the first case (Table 2) in one of six RI strains these SDPs did not match (linkage not significant); in the second case the discordance was 1/13 and gave statistically significant linkage ($P < 0.01$; according to Silver, 1985). This linkage would still be significant even when considering the RI strains CBXE27 and CBXE33 (with a small number of females tested; Table 2) as displaying parental phenotypes CBA and KE, respectively (3/15, $P < 0.05$; Silver, 1985). The value of linkage was calculated according to the formula

$$r = R/(4-6R)$$

where r is the map distance (multiplied by 100 this gives the value in centiMorgans; cM) and R is the proportion of nonmatching RI strains (Taylor, 1981). This gives (considering the data obtained by using the Bonferroni test) a distance of 2.2 cM between *Gpi-1* and a putative gene affecting the timing

Fig. 1. Simplified map of chromosome 7. Asterisks mark two possible locations of a putative gene affecting the timing of first polar body extrusion calculated from the linkage value to *Gpi-1* = 0.022. The range covering its localization, assuming a 95% confidence limit, is indicated. The region of cyclin E locus is marked in black. CE: centromere.

Fig. 2. Relationship between timing of germinal vesicle breakdown (GVBD) and the duration of the first meiotic M-phase. The duration of M-phase was calculated from data shown in Table 2. The regression coefficient (b) is statistically significant ($P < 0.01$).

of first polar body extrusion. Correcting for the 95% confidence limit it should lie not closer than 0.05 cM and not further than 19.6 cM (Silver, 1985) from *Gpi-1* (up and down). This delimits the segment of chromosome 7 of length 31.6 cM beginning with the centromere, for the location of this gene (Fig. 1).

Two other loci on chromosome 7, *c* and *Hbb*, were also available for analysis. The increasing number of RI strains that did not match with these loci (*Gpi-1*: 1/13; *c*: 6/13; *Hbb*: 7/13) reflects their order and distance on the chromosome: *Gpi-1*, *c* and *Hbb* are mapped 12 Cm, 42 Cm and 50 Cm from the centromere, respectively (Lyon and Kirby, 1996). The minimal linkage to *c* and its lack to *Hbb* are in agreement with the proposed position of a putative gene close to *Gpi-1*.

For all other loci, except *Gpi-1*, the linkage, even when detected, was not significant.

The similar timing of GVBD in CBA and KE strains shows that the difference in the timing of first polar body extrusion between these strains refers to the period of maturation between GVBD and first polar body extrusion. Since upon GVBD the oocyte enters M-phase (Maro *et al.*, 1994; Kishimoto, 1994), the difference between CBA and KE oocytes reflects the difference in the length of the first meiotic M-phase. The approximate length of first M-phase among the tested strains was calculated by subtracting the mean time of GVBD from the mean time of first polar body extrusion. A negative correlation ($P < 0.01$) was found between the duration of these two steps of oocyte maturation. Generally, the more time is needed for GVBD the shorter is the duration of the M-phase and *vice versa* (Fig. 2).

Discussion

The rate of meiotic maturation was analysed in the present study by measuring the timing of GVBD and first polar body extrusion in maturing oocytes. It was found that, although the timing of GVBD did not differ between CBA and KE oocytes, it segregated between RI strains. This suggests that the timing of GVBD is polygenically determined and parental strains have different allele forms of genes involved. The number of loci responsible for this difference may be evaluated using the formula (Bailey, 1981):

$$\text{minimum number of effective loci} = \log(F + 2)/\log 2$$

where F = number of recombinant strain phenotypes different from progenitor phenotypes (in this case $F = 2$). According to such a calculation the parental strains differ for at least two loci the alleles of which probably act contrarily, hence CBA and KE mice are similar in timing of GVBD. The same conclusions may be drawn with respect to the observed variations in the efficiency of first polar body extrusion: for $F = 3$ the minimum number of effective loci is also two, and CBA and KE strains are similar in efficiency of first polar body extrusion.

Considering the timing of the first meiotic division, it is concluded that the difference between parental strains also relates to at least two loci because some of the RI strains have an intermediate phenotype. However, it seems that these are different genes from those affecting the timing of GVBD in RI strains, because (1) the parental strains do not differ in the timing of GVBD (as in the case of first polar body extrusion) and (2) there is no positive correlation between the time needed for GVBD and the duration of the first meiotic M-phase among the lines tested. Involvement of different genes at these two steps of maturation accords with the present knowledge on the changes in activity of the maturation promoting factor (MPF), a universal factor controlling cell cycle progression (Murray, 1992). In maturing mouse oocytes this activity first appears around GVBD, increases as the oocyte enters first meiotic metaphase and then rapidly drops concomitant with first polar body extrusion (Hashimoto and Kishimoto, 1988; Choi *et al.*, 1991; Kubiak *et al.*, 1992). Moreover, initial growth of MPF activity, sufficient for GVBD, does not depend on protein synthesis, whereas its further increase requires synthesis of new protein(s) (Hashimoto and Kishimoto, 1988), most probably cyclin B (Hampl and Eppig, 1995). This finding suggests a different mechanism of control of MPF activity at transition from GV to GVBD and during M-phase.

The data presented in this study show a negative correlation between duration of GVBD and M-phase. A possible interpretation of this may be based on reports on the cooperation between nuclear and cytoplasmic factors of the cell cycle controlling mechanism. For example, CAK, a kinase responsible for MPF activation, has constant activity throughout the somatic cell cycle and its catalytic subunit p40^{MO15} is localized in the nucleus at all stages except mitosis, when it redistributes throughout the cell (Tassan *et al.*, 1994). The predominant localization of CAK in the GV as well as a similar lack of changes in activity have been demonstrated in *Xenopus* oocytes (Brown *et al.*, 1995). Reciprocal fusion of nucleate and anucleate halves of oocytes from CBA and KE strains shows that the

nucleus affects the timing of first polar body extrusion. Hybrids resulting from such fusions have the same cytoplasmic composition (50% KE/50% CBA) but differ in the type of GV (CBA or KE) and first polar body is extruded significantly earlier in those containing a CBA nucleus (Z. Polański, N. J. Winston, M. H. Verlac, M. Weber, J. Z. Kubiak and B. Maro, unpublished). However, cytoplasm also contains an important factor(s): fusion of GV-containing fragment from KE oocytes with a cytoplasmic fragment obtained from CBA oocytes either equal in size or three times larger increased significantly and in a dose-dependent manner the rate at which the first polar body was extruded, compared with pure KE combination (Z. Polański, N. J. Winston, M. H. Verlac, M. Weber, J. Z. Kubiak and B. Maro, unpublished). These data suggest that a possible mechanism of regulation of M-phase progression is a spatial separation of given factors into nuclear and cytoplasmic compartments during interphase and their interaction during M-phase, after breakdown of the nuclear envelope. It is possible that these factors accumulate in the GV or cytoplasm (or in both compartments) just after resumption of meiotic maturation, and after GVBD cooperate in driving the M-phase. A good candidate would be, for example, cyclin B. It is intensively synthesized during the first meiotic M-phase of the mouse oocyte but an increase in both its quantity and its synthesis can be seen as early as during the first 2 h of maturation (Hampl and Eppig, 1995), whereas, in the same study, GVBD was observed after approximately 2 h of maturation. This raises the possibility that the triggering of cyclin B synthesis may precede the GVBD. Okumura *et al.* (1996) suggested that triggering the M-phase in starfish oocytes needs the participation of a process(es) independent of cdc2 kinase activation. Therefore, the possibility that triggering the cyclin B synthesis in mouse oocytes may be independent of and may precede MPF activation cannot be excluded. Because newly synthesized cyclin B is immediately complexed with p34^{cdc2} (Hampl and Eppig, 1995), the amount of newly made inactive pre-MPF at the time of breakdown of the nucleus (when it becomes available for CAK) could, under these conditions, be relatively higher in oocytes in which GVBD occurred later.

One of the aims of this study was to search for the putative genes affecting the rate of the first meiosis of mouse oocytes. It seems that the most important genes in this respect may be those coding the proteins directly involved in cell cycle control, namely the cyclins and cyclin-dependent kinases (Pines, 1993), especially those implicated in M-phase regulation. The cyclin E locus (*Ccne*) has been detected in the mouse on chromosome 7 between *D7Rp2* and *Lhb/Klk1* (Johnson *et al.*, 1996). According to the position of these loci (Lyon and Kirby, 1996), the cyclin E locus should be located about 15–17 cM from the centromere (Fig. 1). This is not only within the region delimited for the putative gene investigated in this study, but very close to one of its more probable positions in terms of its linkage to *Gpi-1* (about 14 cM from the centromere). It seems possible, therefore, that *Ccne* may be one of the genes responsible for the differences in the duration of the first meiotic M-phase between KE and CBA oocytes. Cyclin E may be a component of cytostatic factor (CSF) (Rempel *et al.*, 1995; Hartley *et al.*, 1996). Cytostatic factor activity is responsible for metaphase II arrest in unfertilized eggs (Sagata *et al.*, 1989;

Colledge *et al.*, 1994; Hashimoto *et al.*, 1994). However, it may also influence the timing of first meiosis, since in mouse oocytes lacking the primary component of CSF, the *c-mos* proto-oncogene product, the period of maturation between GVBD and first polar body extrusion is increased (Hashimoto *et al.*, 1994) as in KE oocytes. We are in the process of using DNA probes, especially those specific for the region close to *Ccne* as well as other regions not covered in this study, to broaden and verify the data presented here.

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