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DEVELOPMENTAL GENETICS

Different Influences of Genomic Imprinting on the Development of Parthenogenetic Cell Clones in C57BL/6 and CBA Mice

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Abstract—Clonal analysis of parthenogenetic chimeric mouse embryos C57BL/6(PG) ⟷ BALB/c has shown that parthenogenetic cell clones C57BL/6 are present in the brain, liver, and kidneys of 14- and 18-day-old embryos. The content of the parthenogenetic component (PG) in these organs on day 18 was lower than on day 14, and, in some 18-day-old embryos, parthenogenetic cell clones were absent from the liver and/or kidneys. These data suggest that, during the embryogenesis of parthenogenetic chimeras, parthenogenetic cell clones of mostly endodermal and mesodermal origins were actively eliminated. Therefore, in such parthenogenetic adult chimeras, parthenogenetic clones of mostly ectodermal origins were preserved. In parthenogenetic chimeras CBA(PG) ⟷ BALB/c, parthenogenetic cell clones were actively eliminated at early embryonic stages, and, as a result, they were absent at the post-implantation stages. Hence, during development of parthenogenetic cell clones, the effects of genomic imprinting are expressed unequally in C57BL/6 and CBA mice.

Key words: genomic imprinting, parthenogenesis, chimeric mice, clonal analysis.

Both chromosome sets, maternal and paternal, are necessary for normal mammalian development. The mechanism regulating functional differences of parental genomes in placental mammals is called genomic imprinting (Surani *et al*., 1984). The mammalian genes inherited from the mother or father in a repressed or "silent" state are called imprinted genes. Unlike most genes expressed in a biallele manner in the somatic diploid cells, the imprinted loci are expressed in a monoallele manner: one of two parental alleles, maternal or paternal, is in the repressed, or inactive, state. It was shown repeatedly that genomic imprinting is determined by DNA methylation: specific methylation of cytosine bases of the key regulatory element of imprinted genes turns off the expression of the maternal or paternal allele (Surani *et al*., 1990, 1993; Razin and Cedar, 1994; Feil and Khosla, 1999).

During development, the expression of the genes of imprinted loci has tissue- and stage-specific characteristics. For example, the same gene may behave as an imprinted (inactive) gene in a certain cellular system and at a certain developmental stage, and also be expressed in other cellular systems or in the same cellular system but at another developmental stage. As a result of the differential expression of the genes of many imprinted loci, a corresponding balance in gene activity arises, which is necessary for the normal proliferation and differentiation of diverse cell clones during embryogenesis (Konyukhov and Platonov, 2001).

The death of parthenogenetic mammalian embryos is a direct consequence of genomic imprinting. Therefore, parthenogenetic mouse embryos obtained as a result of artificial activation towards development are a convenient model for studying the effect of genomic imprinting on mammalian development. The diploid parthenogenetic mouse embryos die, as a rule, soon after implantation and rarely reach the 25 somites stage. Artificial delay of implantation prolongs the development of diploid parthenogenetic mouse embryos (Kaufman *et al.*, 1977). The use of growth factors also makes it possible to obtain more advanced development of parthenogenetic mouse embryos (Penkov and Platonov, 1999). The data obtained in our laboratory suggest that 5-azacytidine-induced DNA demethylation can also prolong the development of diploid parthenogenetic mouse embryos (Penkov *et al*., 1996).

Chimeric mice are used for studying the developmental potencies of different parthenogenetic cell clones (PGCC). Chimeras consist of two or more genotypically different parental components and are widely used in developmental genetics of mammals to determine the place of action in genes and their effects (McLaren, 1976; Konyukhov *et al*., 1988). The chimeric mice consisting of parthenogenetic and normal cells are called parthenogenetic chimeras. These chimeras, usually produced by aggregation of parthenogenetic hybrid embryos with normal mouse embryos of a certain inbred strain, are capable of developing to term and sexual maturity, and the PGCCs are included in practically all tissues and organs, including the gonads, and produce completely functional gametes (Stevens *et al*., 1977; Surani *et al*., 1977; Stevens, 1978).

Genomic imprinting leads to a steady decrease in the content of PGCCs in the tissues of chimeras during

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development (Nagy *et al.*, 1987). The initial distribution (allocation) of parthenogenetic cells in the preimplantation embryo is accidental (Clarke *et al.*, 1988; Thomson and Solter, 1988), but, thereafter, they are progressively eliminated, first of all, from the trophoblast and, somewhat later, from the yolk sac endoderm, and, still later, from the yolk sac mesoderm. By the middle of gestation period, the PGCCs are practically absent from all extraembryonic tissues (Nagy *et al.*, 1987; Surani *et al.*, 1988; Thomson and Solter, 1989). In the embryonic tissues, the parthenogenetic cells continue to normally function until the middle of the gestation period, and, thereafter, their total contribution decreases. Parthenogenetic cells of endodermal and mesodermal origins are subject to the most intense elimination, while those of ectodermal origin are subject to the least intense elimination. The most intense elimination of PGCCs takes place between days 13 and 16 of the embryogenesis, specifically in the skeletal muscle between days 13 and 15, when the fusion of myoblasts begins (from day 14). However, no noticeable elimination of PGCCs was observed in the pancreas until day 15, when elimination of the parthenogenetic cells appears to be complete only at the moment of birth. In the liver, unlike the muscles and pancreas, the elimination of PGCCs is long-term and continuous. The contribution of PGCCs in the large intestine, kidneys, and urinary bladder is insignificant, unlike in the brain, where the percentage of parthenogenetic cells is usually high. The rate of PGCC elimination in the nervous tissue is the lowest, and, hence, the percentage of parthenogenetic cells in the brain is also high. Therefore, the distribution of PGCCs in the tissues of adult chimeras is unequal since the contribution of PGCCs in the formation of different tissues and organs is different (Nagy *et al.*, 1989; Fundele *et al.*, 1989, 1990, 1991). In the case of a high content of parthenogenetic cells in the tissues of chimeric mice, their growth and development are usually suppressed (Paldi *et al.*, 1989).

Diploid parthenogenetic embryos of hybrid mice (CBA × C57BL/6)F_1 or (C57BL/6 × CBA)F_1 are often used to produce parthenogenetic chimeras, since the diploid parthenogenetic embryos of such hybrids are capable of a rather stable preimplantation development *in vitro* and reach the somite stages after transplantation in the uterus of pseudopregnant females. The dynamics of elimination of parthenogenetic cells during development is, on the whole, similar in chimeras obtained with the use of hybrids of different mice as a parthenogenetic component (Fundele *et al.*, 1991). At the same time, the use of embryos of inbred mice is sometimes preferable, since the genetic environment can modulate the effects of genomic imprinting (Allen and Mooslehner, 1992; Latham, 1994; Chaillet *et al.*, 1995).

It was shown in our laboratory that the diploid parthenogenetic mouse embryos of various inbred strains have different developmental potencies (Penkov and Platonov, 1992; Penkov *et al.*, 1996). Thus, the development of diploid parthenogenetic C57BL/6 and CBA embryos markedly differs: the former develop to the blastocyst stage *in vitro* in 95% of cases but die soon after implantation, while the latter reach the blastocyst stage only in 23% of cases, but, after transplantation of the blastocysts in the uterus, 26% of implanted embryos reach the somite stages (Penkov and Platonov, 1992; Penkov *et al.*, 1995, 1996). Therefore, it can be expected that the developmental potencies of the different PGCCs of these two inbred strains in chimeras are noticeable different: genotypically different parthenogenetic cells may be eliminated in embryogenesis at a different rate.

MATERIALS AND METHODS

The inbred mouse strains C57BL/6 (*C*/*C, Gpi-1*^{bb}), CBA(*C*/*C, Gpi-1*^{bb}), and BALB/c (*c*/*c, Gpi-1*^{aa}), contrasting in pigmentation and glucose phosphate isomerase (GPI), and hybrid females (C57BL/6 × BALB/c)F_1 and (CBA × BALB/c)F_1 were used as recipients for the transplantation of the embryos in the uterus. The method of production of chimeras was described elsewhere (Isaev *et al.*, 1997). The day that the copulative plug was found in pseudopregnant females was considered day 1 of gestation. The developmental stages were identified by the normal tables (Dyban *et al.*, 1975).

Chimeric embryos C57BL/6(PG) ⟷ BALB/c that were 14 and 18 days old were used for clonal analysis taking into consideration the fact that intense elimination of PGCCs is completed in the majority of organs and tissues of chimeras by the perinatal period (Fundele *et al.*, 1990, 1991). Since we were unable to obtain postnatal (newborn) chimeras CBA(PG) ⟷ BALB/c (Isaev *et al.*, 1999) in our previous study, we planned on obtaining only 14-day chimeric embryos of this type.

Clonal analysis was carried out by electrophoretic division of the GPI isozymes on acetate-cellulose plates, since this method allows processing of microsamples (Brown *et al.*, 1990). The following organs were chosen for analysis: right and left halves of the brain, both kidneys (separately), and liver. We have already shown that in adult chimeras C57BL/6(PG) ⟷ BALB/c the parthenogenetic component was absent in the kidneys and liver (Isaev *et al.*, 1999).

After electrophoresis and staining, the acetate-cellulose plates were fixed in 5% acetic acid and dried. The resulting electrophoregram was cut into 5 mm wide bands and placed in a quartz cuvette filled with mineral oil. The electrophoregrams were scanned on a densitometric attachment of a Gilford spectrophotometer (France) at the wavelength 560 nm. Tracing paper was superimposed on the densitograms obtained, and the contours of optic density peaks were outlined. These contours were cut out and weighed on a torsion balance. The ratio of clones was calculated using the formula:

$$P = \frac{B}{A+B} \times 100\%,$$

where P is the percentage of PGCCs in the studied sample; B is the weight of cut-out contour of the peak corresponding to the isozyme GPI-1B (marker of C57BL/6 or CBA parthenogenetic component); and A is the weight of a contour of the peak corresponding to the isozyme GPI-1A (marker of normal BALB/c component).

RESULTS

We obtained and analyzed 14- and 18-day-old embryos C57BL/6(PG) ⟷ BALB/c (ten of each) and also obtained seven 14-day-old embryos as a result of the aggregation CBA(PG) and BALB/c morulas.

In order to obtain 14-day-old parthenogenetic embryos of two types, similar numbers of morulas were aggregated, and the aggregated embryos developed *in vitro* to the blastocyst stage at an equal rate, although the percentage of implanted C57BL/6(PG) ⟷ BALB/c embryos was much higher than that of CBA(PG) ⟷ BALB/c embryos. The percentage of live 14-day-old C57BL/6(PG) ⟷ BALB/c embryos was also 1.5 times higher than that of CBA(PG) ⟷ BALB/c embryos. In half of the live C57BL/6(PG) ⟷ BALB/c embryos (five out of ten), PGCCs were found in tissues; i.e., these five embryos were chimeric. The same percentage of chimeras was also found among the live 18-day-old C57BL/6(PG) ⟷ BALB/c embryos. But no parthenogenetic components were found in the studied tissues of all seven live CBA(PG) ⟷ BALB/c; i.e., chimeras were absent among the live embryos (Table 1).

When 14-day-old C57BL/6(PG) ⟷ BALB/c were isolated, the sites of implantation that did not contain live embryos were represented by decidual capsules. At the same time, of 20 implantation sites that did not contain live 14-day-old CBA(PG) ⟷ BALB/c embryos, six contained embryos that died after placenta formation. Hence, the high contribution of parthenogenetic CBA cells in the chimeric embryo and their subsequent intensive elimination leads to the death of CBA(PG) ⟷ BALB/c embryos soon after the beginning of organogenesis. In the embryos with a lower content of PGCCs, they are already completely eliminated from the organs and tissues by day 14, so that, up to that time, only monocomponent BALB/c embryos could be found. In five out of ten 14-day C57BL/6(PG) ⟷ BALB/c embryos, the isozyme analysis revealed the presence of PGCCs in all studied organs (Table 2).

All 14-day C57BL/6(PG) ⟷ BALB/c embryos, except the chimeric embryo 14B6(PG)10, which had the greatest contribution of the parthenogenetic component, had no morphological defects and were at stages 18–19. The extraembryonic membranes and placenta were well developed. The embryo 14B6(PG)10 was at stage 14, and its parietosacral length was only 5 mm. The tail was almost the same lengthas the body. It was difficult to prepare homogenates of individual organs of this embryo; therefore, the total homogenate was used for isozyme analysis. Despite a high contribution of the parthenogenetic component to the brain, none of the chimeras showed the signs of eye pigmentation.

Most 18-day-old C57BL/6(PG) ⟷ BALB/c embryos were at stages 22–23 and had well developed fetal membranes and placenta. The embryo 18B6(PG)7 was at stage 18 and had no morphological deviations, and its parietosacral length was only 8 mm. Isozyme analysis revealed the presence of a parthenogenetic component in organs of five embryos (Table 2). Since in all 18-day-old embryos, just as in the 14-day-old ones, no eye pigmentation was observed, the head of the chimeric embryo 18B6(PG)5 was used for histological analysis, and, hence, no isozyme analysis of its brain was performed. Histological analysis of the eyes of this embryo did not reveal pigmented cells in the retinal pigment epithelium. At the same time, no traces of cell-death were found in this tissue.

All seven 14-day-old CBA(PG) ⟷ BALB/c embryos showed no morphological defects and were at stages 18–19. Isozyme analysis did not reveal the presence of the parthenogenetic component in the brain,

Table 1. Embryogenesis of parthenogenetic chimeras

Chimeras	Embryos		Number of:		
	aggregated	developed to the blastocyst stage	sites of implantation	live embryos	chimeras
	Day 14 of development				
C57BL/6(PG) ⟷ BALB/c	86	79 (92)	34 (39.5)	10 (12)	5 (6)
CBA(PG) ⟷ BALB/c	92	81 (88)	27 (29)	7 (8)	0 (0)
	Day 18 of development				
C57BL/6(PG) ⟷ BALB/c	108	91 (84)	27 (25)	10 (9)	5 (5)

Note: Numerals in parentheses designate the percentage from the number of aggregated embryos.

Table 2. Content of parthenogenetic component (GPI–1B) in chimeric embryos C57BL/6(PG) ⟷ BALB/c, %

Chimeras	Brain		Kidneys		Liver
	left half	right half	left	right	
	Day 14 of development				
14B6(PG)2	37	29	35	29	24.5
14B6(PG)3	31	37	54	58	43.5
14B6(PG)5	15.5	18	16	14	24
14B6(PG)6	38	24	29	31	27
14B6(PG)10	Total homogenate-79				
	Day 18 of development				
18B6(PG)1	14	16	0	0	0
18B6(PG)2	34	27	0	0	10
18B6(PG)5	N/d	N/d	0	0	23
18B6(PG)7	42	45	48	28	43
18B6(PG)9	5	6	0	0	5

Note: (N/d) not determined, isozyme analysis was not carried out.

liver, and kidneys. No signs of eye pigmentation were observed.

DISCUSSION

Experiments with transgenes demonstrated that the activity of some of them in a transgenic organism may depend on the influence of line-specific modifier genes (Sapienza *et al*., 1987; Allen *et al*., 1990; Surani *et al*., 1990). It was shown that the level of methylation of the transgene *RSVIgmyc* differs in mice of inbred FVB/N and C57BL/6 strains (Chaillet *et al*., 1995). It was also reported that the genetic environment can modify the imprinting of endogenous genes in mice of diverse inbred strains (Babinet *et al*., 1990; Forejt and Gregorova, 1992; Reik *et al*., 1993). In experiments with nuclear transplantation, it was shown that the cytoplasm of C57BL/6 oocytes supported the development of androgenetic embryos to the blastocyst stage better than the cytoplasm of DBA/2 oocytes (Latham and Solter, 1991). The differences in the capacity for parthenogenetic development in early embryos of the inbred strains C57BL/6 and CBA described in our laboratory (Penkov and Platonov, 1992; Penkov *et al*., 1996) also suggest the influence of the genetic environment on the effects of genomic imprinting.

In our previous studies (Isaev *et al*., 1997, 1999), we demonstrated that, in chimeric mice C57BL/6(PG) ⟷ BALB/c, PGCCs of predominantly ectodermal origin were preserved: epidermal melanocytes and retinal pigment epithelium and brain cells. The data presented here suggest that, in 14-day-old C57BL/6(PG) ⟷ BALB/c embryos, the PGCCs are present not only in the brain, but also in the kidneys and liver (Table 2), while in the 18-day-old embryos of this kind, they were absent, as a rule, in the kidneys and/or liver. Elimination of the parthenogenetic cells from the liver could continue even after the birth of chimeras; therefore, in adult chimeras C57BL/6(PG) ⟷ BALB/c, the PGCCs were absent in the kidneys and liver. Thus, our data suggest active elimination of parthenogenetic C57BL/6 cells during development in the tissues of endodermal and mesodermal origins.

Despite the significant contribution made by PGCCs to the brain (the organ of ectodermal origin), no signs of eye pigmentation were observed in 14- or 18-day-old C57BL/6(PG) ⟷ BALB/c embryos. No pigmented cells were found in serial section of the retinal pigment epithelium in 18-day-old embryos 186(PG)5, whose chimerism was confirmed by the presence of the parthenogenetic component in the liver. At the same time, we described pigmented cells in the retinal pigment epithelium of adult parthenogenetic C57BL/6(PG) ⟷ BALB/c chimeras (Isaev *et al*., 1999). The lack of eye pigmentation in 14- and 18-day-old chimeric embryos could be due to a delayed differentiation of PGCCs in the retinal pigment epithelium and/or the later expression of the genes responsible for pigmentation.

In cases where there are a large number of parthenogenetic cells in the tissue of chimeric mice, their growth and differentiation is usually suppressed (Paldi *et al*., 1989). The embryos 14B6(PG)10 and 18B6(PG)7, in which the contribution of the parthenogenetic component was significant (Table 2), significantlylagged behind other chimeric embryos. Such developmental suppressionappears to cause the death of chimeras even before birth.

In a previous study, we demonstrated that the preimplantation development of the chimeras CBA(PG) ⟷ BALB/c and C57BL/6(PG) ⟷ BALB/c proceeded in

a similar way, while the postimplantation period was much different: despite the high number of CBA(PG) ⟷ BALB/c embryos in the blastocyst stage, the number of newborns was very low, and there were no chimeras among them (Isaev *et al*., 1999). In this study, we did not find chimeras, even among the 14-day-old CBA(PG) ⟷ BALB/c embryos (Table 1). Thus, despite the absence of differences in preimplantation development of chimeric C57BL/6(PG) ⟷ BALB/c and CBA(PG) ⟷ BALB/c embryos, their postimplantation development is much different due to the high mortality of the CBA PGCCs.

The big contribution of parthenogenetic cells to a chimeric embryo at the late morula or blastocyst stage leads to the suppression of development and death of chimeras in early postimplantation stages, just as in the case of diploid parthenogenetic embryos. The death rate of chimeric CBA(PG) ⟷ BALB/c embryos was higher than that of C57BL/6(PG) ⟷ BALB/c embryos.

Thus, the effects of genomic imprinting are expressed unequally at the cellular level in parthenogenetic C57BL/6 and CBA mice. The parthenogenetic CBA cell clones of endo-, meso-, and ectodermal origins are actively eliminated at the early embryonic stages, as a result of which the CBA(PG) ⟷ BALB/c embryos die more frequently than the C57BL/6(PG) ⟷ BALB/c embryos. In live 14-day-old CBA(PG) ⟷ BALB/c embryos, in which the contribution of the parthenogenetic component appeared to have been small initially, the CBA PGCCs are completely absent. At the same time, the parthenogenetic C57BL/6 cell clones are eliminated from the tissues and organs of the C57BL/6(PG) ⟷ BALB/c embryos gradually throughout the embryogenesis, and PGCCs of mainly endodermal and mesodermal origins are eliminated.

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