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Dissection of the maternal effects on puberty onset by embryo transplantation in mouse

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ABSTRACT. Puberty onset in mammals is affected by multiple genetic and environmental factors. Among which, the maternal effect could have played a considerable role. In our previous study, we found that the F1 offspring from reciprocal crosses between C3H/HeJ (C3H) and C57BL/6J (B6) mice differed significantly in the timing of puberty in both sexes, though they had identical genomic background. In order to dissect the causative factors to such phenomenon of maternal effect, embryos from reciprocal crosses of C3H/HeJ and C57BL/6J mice were collected and transplanted to the uterus of either strain of mothers, and the puberty onset of pups were compared between different recipient mothers and egg origins. The results showed that the male pups from C3H recipient mothers attained puberty onset earlier than those from B6 recipients significantly, while the female pups did not show such difference. On the other hand, the egg origin made no difference in the puberty onset of either sex, yet it influenced the birth weight of female pups significantly ($p<0.05$). The manipulation of embryo transplantation delayed the puberty onset of pups dramatically. A mitochondria substitution strain between B6 and C3H (BmC), which had the genome background of B6 and a mitochondrial hyplotype of C3H, had the same phenotype of puberty onset as B6. The integrated results indicated that the uterine environment was the major causative factors to the maternal effect on the differential puberty onset in reciprocal crosses of F1 hybrids between B6 and C3H mice.

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INTRODUCTION

Puberty onset in mammals is affected by multiple genetic and environmental factors, and precocious puberty can influence the children physically and psychologically in modern society. Large efforts had been made to elucidate the molecular mechanism of puberty onset, some important puberty-related genes such as GPR54 (1), KISS1 (2), and GNRHR (3) have been defined as mutations on them were able to result in puberty failure. A number of chromosomal loci including 2p13-2q13 (4), 16q21, 16q12, 8p12 (5), 6q21 (6, 7) and 9q31.2 (7) have been discovered to be related to the timing of menarche by genome-wide linkage scan or genome wide association study in human. The accumulating evidence proved that the puberty onset in mammals could be controlled by complicated gene network composed of multiple pathways, among which a tumor supressor gene (TSG) network had been put forward to play an important role in the regulation of puberty onset (8). Although a lot of achievements have been made to explain the genetic mechanism underlying this complex trait in mammals, some other factors such as perinatal and/or environmental exposure still need to be revealed.

The environment in which the fetus develops is critical for its survival and long-term health. Several epidemiological studies in human indicated that environmental factors such as maternal nutrition and behavior might programme persisting changes in the fetal reproductive axis by influencing the pre-natal growth trajectory and physiology of the major organ systems of the body (9). Data from animals showed that pre-natal environment in which fetus grew played an important role in the development of hypothalamic-pituitary-gonadal axis which was crucial for sexual maturation and fertility (10).

Evidence from a number of animal models supported the hypothesis that maternal exposure to suboptimal factors such as malnutrition, stress, specific sexual hormone, and glucocorticoid during gestation could impact the puberty onset of offspring. Léonhardt found that pups of both sex from mothers exposed to food restriction during gestation and lactation delayed their puberty onset in rats, and their circulating levels of gonadotropins and leptin were altered dramatically (11). Increased nutritional demand on the mother by increasing litter size also alters sexual development of offspring (12). The puberty was substantially delayed by increased exposure to glucocorticoids during pre-natal life more evidently in female offspring in rats, while reduction of exposure to maternal glucocorticoids advanced the puberty onset in male offspring (13). A maternal diet high in n-6 polyunsaturated fats administered during pregnancy induced precocious puberty in female rat offspring, while n-3 polyunsaturated fats did not have such effects (14).

In our previous studies, we generated reciprocal crosses between C3H/HeJ (C3H) and C57BL/6J (B6) mice to investigate genes regulating the onset of puberty. Besides a puberty-related quantitative trait loci on ChrX was discovered in F2 hybrids (15), we also found that the F1 off-

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spring from different cross differed significantly in the puberty onset in both sexes, though they had identical genomic background (p<0.01) (16). The influence of the mitochondria haplotype could be roughly excluded as such distinction disappeared in differently crossed F2 progeny. This kind of phenomenon could either result from different egg origin, or from distinct uterine environment in which the fetus developed provided by different mothers. In order to dissect the causative factors underlying such difference, embryos from reciprocal crosses of C3H/HeJ and C57BL/6J mice were collected and transplanted to the uterus of either strain of mothers in the present study, and the onset of puberty was investigated in these pups to clarify the major causative factors to the maternal effect on the differential puberty onset in reciprocal crosses of F1 hybrids between B6 and C3H mice.

MATERIALS AND METHODS

Animals and housing

Parental mice C57BL/6J (B6) and C3H/HeJ (C3H) were obtained from Shanghai SLAC Laboratory Animal Co. Ltd. (Shanghai, P.R. China). All mice used in this study were housed in standard polysulfone microisolator cages with hardwood chips (SLAC Laboratory Animal Co. Ltd.) and were allowed unlimited access to water and food (SLAC Laboratory). Animals were maintained on a 12 h light: 12 h darkness schedule at a mean ambient temperature of 23-25 C. All animal housing and care procedures were conducted in accordance with the Experimental Animal Management Ordinance of P.R.China (1988).

Embryo transplantation

To obtain reciprocal F1 hybrid embryo from B6 and C3H parental strain, either B6 or C3H female mouse aged 8-12 weeks used as a donor was induced superovulation by 5 IU of pregnant mare's serum gonadotropin (PMSG) by ip injection, and followed by an i.p. injection of 5 IU of hCG post PMSG administration 48-52 h later. After hCG injection, the female mouse was placed in a separate cage with an alternative male mouse (B6 female with a C3H male, and *vice versa*) to generate B6C3H or C3HB6 F1 hybrid zygotes. The female mouse was checked for vaginal plug in the next morning, and was sacrificed by decapitation 46 h post hCG injection if a vaginal plug was observed. The oviduct of the donor female mouse was removed and torn open of the infundibulum. The two-cell embryos were flushed off the oviduct by human tubal fluid (HTF) buffer (100 ml HTF included NaCl 640 mg, KCl 35.6 mg, KH2PO4 16.2 mg, $MgSO_4$ 7H2O 29.4 mg, NaHCO3 190 mg, glucose 100 mg, Na-pyruvate 2.5 mg, Ca-lactate pentahydrate 46 mg, streptomycin 5 mg, penicillin 7.5 mg, 0.5% phenol red 0.2 ml, 20 mM 2-ME 10 µl, 100 mM EDTA, 50 µl, BSA 300 mg) and collected in HTF buffer.

The recipient mouse was pseudopregnant female B6 or C3H aged at 8-12 weeks plugged by a vasectomized B6 male 2.5 days previously. The recipient was anesthetized by i.p injection of 0.5% sodium pentobarbital and exteriorized the ovary, oviduct, and part of the uterine horn. The 2-cell embryos were transferred through the wall of the oviduct of recipients. Both reciprocal crosses of F1 hybrid embryos were transferred to either B6 or C3H recipient simultaneously, with 4-6 embryos in each oviduct. After the transferring process, the ovary, oviduct, and uterine horn were put back into the abdomen, and the skin was closed. The recipient was placed in a separate cage after recovering from anesthesia on a 37 C plate, and kept separately till delivery.

The cross-fostering and assessment of puberty onset in the embryo-transplanted offspring

In order to eliminate the effect of post-natal mothering on the trait in the pups, the embryo-transplanted pups were separated from their recipient mother on the day after their birth and fed by a lactating B6 female mouse who had delivered within 5 days until weaning. The pups were weaned at between the age of 20 to 21 days, and males and females were then housed separately.

Beginning on the day of weaning, mice were examined daily for the puberty onset by vaginal opening (VO) in female and balano preputial separation (BPS) in male from 08:00 h to 11:00 h, and the date of VO and BPS, together with their concurrent body weight were recorded.

The genotyping of the pups from recipient mother

As both of the reciprocal crosses of F1 hybrid embryos were transferred to a recipient simultaneously, the pups had to be genotyped for the parents they came from. A single nucleotide polymorphism (SNP) A9349G on the mitochondrial haplotype between B6 and C3H was genotyped in the embryo-transplanted pups by PCR-ligase detection reaction methods (17).

The construction of mitochondrial substitution strain between B6 and C3H

The mitochondrial substitution strain C57BL/6J-Mit$^{C3H/HeJ}$ was generated to investigate the influence of the mitochondrial haplotype on the puberty onset in mice. C57BL/6J-Mit$^{C3H/HeJ}$ was derived from 10 sequential backcrosses (N10) of C3H to B6. C3H was used as maternal strain, and B6 as the recurrent paternal strain. After 10 generation of backcross, the N10 mouse had mitochondrial haplotype from C3H and genome DNA mostly from B6 (with less than 0.1% residue C3H genome), and its mitochondrial haplotype was examined by the SNP A9349G between B6 and C3H.

Statistical analysis

All procedures were performed using the SPSS statistical software (SPSS version 13.0, SPSS Inc., Chicago, IL, US). The VO age of female and BPS of male pups were compared between those from different recipients (B6 or C3H), as well as between distinct egg origins using two-way analysis of variance. The puberty onset, body weight at birth and puberty onset of mitochondrial substitution strain C57BL/6J-Mit$^{C3H/HeJ}$ and B6 were analyzed and compared by unpaired t-test. The impact of embryo transplantation manipulation on the puberty onset age were analyzed and compared between the embryo transplanted and naturally pregnant pups by unpaired t-test. p<0.05 was considered significant.

RESULTS

The puberty onset of mitochondrial substitution strain C57BL/6J-Mit$^{C3H/HeJ}$ (BmC)

After 10 generation of back-crossing to B6 male, a mitochondrial substitution strain C57BL/6J-Mit$^{C3H/HeJ}$ (BmC) was generated. The genome of BmC was analyzed by genotyping of 36 microsatellite markers on 19 chromo-

Table 1 - *The body weight at birth, the body weight and the age at puberty of B6 and mitochondria substitution BmC mice.*

Strain	Birth weight (g) (mean±SD)	Weight at PO (g) (mean±SD)	Age at PO (days)
B6 ♀	1.352±0.101	13.13±1.21	27.83±1.52
BmC ♀	1.42±0.146*	12.77±1.52	27.41±1.54
B6 ♂	1.357±0.108	17.62±1.22	32.23±1.88
BmC ♂	1.509±0.155*	17.55±1.00	32.22±1.88

*$p<0.05$, compared between B6 and BmC mice. PO: puberty onset.

somes, and all of them had a B6 allele. The mitochondrial haplotype of BmC was verified by sequencing 500 bp DNA fragment including the 2 SNP (A9349G, T9461C, respectively) and a deletion (9821, 9822) between B6 and C3H, and the sequence was identical to C3H (data not shown).

The body weight at birth, the puberty timing and concurrent body weight of BmC mice was compared with B6. BmC mice attained puberty onset at the similar age as B6 mice and had identical concurrent body weights to the latter in both genders, with a slight difference in birth weight (Table 1). Given that BmC differed from B6 in the mitochondrial haplotype, which had no effect on the puberty timing, mitochondria could be excluded as a regulatory factor on this trait.

The difference of puberty onset of embryo-transplanted pups from different recipient mothers and from different egg origins

Embryos of reciprocal crosses between B6 and C3H were transferred into the uterus of either B6 or C3H recipient simultaneously; pups were clarified for the egg resource by detection of the SNP on the mitochondrial haplotype. The VO timing of the female and the BPS timing of male pups were compared between different recipients, and between distinct egg origins. The male pups from C3H recipient attained puberty onset earlier than their B6 peers significantly, while the female pups were not affected in VO by their recipients. The egg origin made little difference to the trait in both sex of pups (Fig. 1).

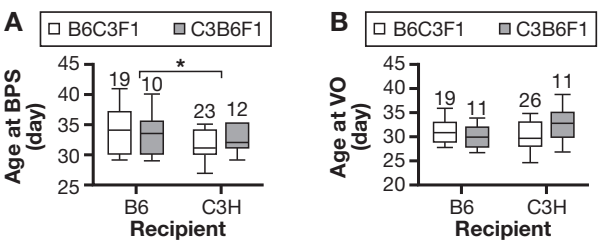

Fig. 1 - *The onset of puberty [defined as balano preputial separation (BPS)] of male pups (A) and the onset of puberty [defined as virginal opening (VO)] of female pups (B) from different recipients. Two-way analysis of variance was performed to analyze the association between age at BPS and recipient, and between age at BPS and egg types. B6C3F1 referred to the pups with B6 egg and C3B6F1 with C3H egg. Whiskers indicate the min to max values. The number above the bar represents the number of mice tested. *Statistically significant (p<0.05) between compared groups (B6 vs C3H).*

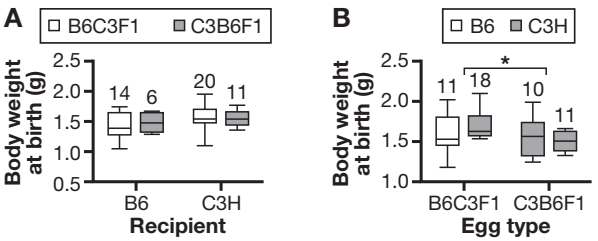

Fig. 2 - *Body weight at birth of male (A) and female (B) pups. Two-way analysis of variance was performed to analyze the association between birth weight and recipient and egg types. B6C3F1 referred to the pups with B6 egg and C3B6F1 with C3H egg. Whiskers indicate the min to max values. The number above the bar represents the number of mice tested. *Statistically significant (p<0.05) between compared groups (B6C3HF1 vs C3B6F1 pups in famale).*

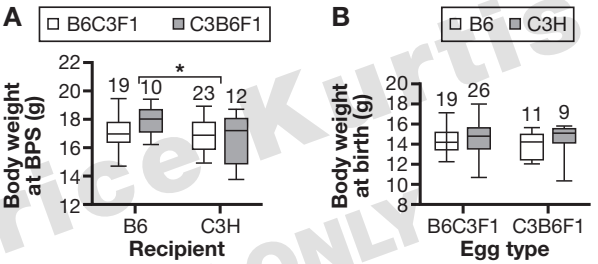

Fig. 3 - *Body weight at balano preputial separation (BPS) of male (A) and virginal opening (VO) of female (B) pups. Two-way analysis of variance was performed to analyze the association between body weight at BPS or VO and recipient and egg types. B6C3F1 referred to the pups with B6 egg and C3B6F1 with C3H egg. Whiskers indicate the min to max values. The number above the bar represents the number of mice tested. *Statistically significant (p<0.05) between compared groups (B6 vs C3H).*

The difference of body weight of embryo-transplanted pups from different recipient mothers and from different egg origins

The body weights at birth and puberty onset were also compared between pups from distinct recipient mothers to see if the body weight was the causative factor to the discrimination of puberty onset. The result showed that the body weight at birth of female pups was influenced by the egg origin significantly; while the body weight at BPS of male progeny was associated with their recipient mothers (Fig. 2 and 3).

The impact of embryo transplantation manipulation on the puberty onset age

Both male and female pups from embryo transplantation attained puberty onset later than their naturally pregnant peers.

In order to investigate the impact of embryo transplantation manipulation on the puberty onset, the reciprocal crosses of F1 were compared between the embryo transplantation pups and their naturally pregnant peers. Both male and female pups from embryo transplantation attained puberty onset much later, and the female were more susceptible than the male pups (Table 2).

Table 2 - *Comparison of the age at puberty onset between pups from embryo transplanted and naturally pregnant groups.*

Gender	Egg origin	Transplanted group PO (days)	Naturally pregnant group PO (days)	Difference in PO (days)
♀	B6C3HF1	30.73±2.73 (no.=19)	26.44±3.19 (no.=90)	4.29**
♀	C3HB6F1	31.55±3.08 (no.=11)	25.00±2.74 (no.=55)	6.55**
♂	B6C3HF1	32.88±3.31 (no.=19)	29.45±1.98 (no.=103)	3.43**
♂	C3HB6F1	32.82±2.70 (no.=12)	28.38±2.98 (no.=64)	4.44**

**$p<0.01$, compared between embryo transplanted group and naturally pregnant group. PO: puberty onset.

DISCUSSION

The phenotypic distinction in puberty onset was observed between reciprocal crosses of C57BL/6J and C3H/HeJ F1 mice, yet they had the same genomic background in our previous study (16). This phenomenon of maternal effect could be ascribed to mitochondrial haplotype (18) and uterine environment (19, 20) from different recipient mothers, or the egg origin (21-23). We employed embryo transplantation to clarify the predominant causative factor from the uterine environment and egg origin. The uterine environment provided by recipient mothers may vary with the genetic background of recipient mothers, as well as environmental factors (19). C3H female mice onset VO earlier than B6 females by 5-6 days, and the male pups that have developed in the uterus of the former generate their puberty onset earlier than their counterparts with B6 recipient mothers and the difference is independent of their embryo types. Therefore, we assume that the genetic background of the recipient mothers have taken part in the regulation of the uterus environment. The effect of the mitochondrial haplotype on this trait was investigated in a mitochondria substitution strain between B6 and C3H (BmC), which had the genome background of B6 and a mitochondrial hyplotype of C3H, and they had the same phenotype of puberty onset as B6, which coincided with our previous genetic analysis (16). The collective results indicated that the uterine environment was the major causative factors to the maternal effect on the differential puberty onset in reciprocal crosses of F1 hybrids between B6 and C3H mice.

On the other hand, we also found that the egg origin influenced the birth weight of female pups significantly ($p<0.05$; in male pups, $p=0.06$), which implied that the different expression of some imprinted genes might have played a role. Fetal growth is largely controlled by some imprinted genes, such as *Igf2* and *H19* (24). Imprinted genes are only expressed from either maternal or paternal alleles, as B6C3F1 and C3B6F1 pups inherited opposite maternal or paternal alleles from their parents, the difference of imprinted genes between B6 and C3H mice could have brought about developmental distinction between these two kind of fetus. For example, the gene of Igf2 varied between C3H and B6 mice in 2-bp insertion in its 3' UTR (http://www.sanger.ac.uk/cgi-bin/modelorgs/mousegenomes/snps.pl) which might result in a modest difference of the gene expression level between the two mice. It is suspected that the downregulation of IGF2 is the cause of intrauterine growth restriction in human (25). However, the impact of imprinted genes on puberty onset has not been observed in our case, as the puberty timing of B6C3F1 and C3B6F1 pups was at the similar age.

Puberty is the final stage of maturation of the hypothalam-pituitary-gonadal axis, symbolized by the pulsatile release of GnRH by GnRH neuron (26). Many factors are subject to act on the GnRH neuron to influence the initiation of puberty. The perinatal maternal nutritional statuses were closely related to the puberty onset and fertility of offspring (11, 27-29). In order to eliminate the impact of post-natal mothering on the trait, cross-fostering was carried out by identical females (B6) at litter size of 6-8 in our experiment. The recipient mothers were fed ad libitum during pregnancy, and the pups had identical birth weight between B6 and C3H. However, the male pups from C3H recipients attained puberty onset earlier than their counterparts from B6 dams and they had smaller concurrent body weight as well, which implied that the prenatal programme of the puberty onset was independent of the growth rate. However, female pups did not show the difference in the VO significantly between distinct maternal origins, which differed from the results obtained from the naturally pregnant pedigrees (16). We assumed that the manipulation of embryo transplantation might be the main cause. We compared the puberty onset age between the mice that were conceived by embryo transplantation and conceived spontaneously. The former male postponed their puberty onset as long as 3-4 days, the female did even worse in both cross (4-6 days) (Table 2). The tremendous delay in puberty onset caused by the manipulation of embryo transplantation could have masked the differences made by different recipient mothers, especially in female pups. Data from human implied that infants conceived by assisted reproductive technology ART were at a higher risk of intrauterine hormonal disorder which might influence the development of endocrine system and the maturation of endocrine-control systems of fetal (20). The elevated βhCG level was observed in ART pregnancies and was supposed to play an etiologic role (30). In our manipulation, though hCG was only used to help superovulating the donor female mice, without given to the recipients, it was unclear whether it impacted the microenvironment inside the ovum. Some chemicals used in the i*n vitro* fertilization process could inhibit embryo development (31), though the mentioned glucosamine was not employed in our manipulation, the potential effect of medium and buffer used on the oocyte development deserved awareness. Moreover, metabolic alteration was also manifested in ART offspring in mouse, which provided another possible cause of the altered puberty onset age in our case (32).

Although our study did not address the molecular or cellular mechanism the maternal effect could have performed by, we speculated that the different physiological status of C3H and B6 pregnant dams might have played a role. The maternal plasma levels of glucose, leptin and corticosterone were regarded as to affect fetal-programming pre-natally (19). The recipients of B6 and C3H have different genetic background and should have distinct baseline of physiological parameters. As they were fed *ad libitum* during gestation, the fetuses were exposed to the average levels of glucose and leptin of different recipients. The regulation of mammal fetal growth involves many multidirectional interactions between the mother, placenta, and fetus (18). The dissection of protein expression pattern and hormone secretion level in the placenta, the influences of different recipients on the hypothalamic-pituitary-gonadal axis in offspring can help to elucidate the mechanism of maternal effect on puberty onset.

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