—Mini Review—

Sexual Dimorphism during Early Embryonic Development in Mammals

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Abstract: *Although most sexual dimorphism appears after gonadal differentiation, some occur at earlier stages of development. One example of this phenomenon is the skewing of the sex ratio of embryos due to the glucose concentration of the culture medium. This skewing occurs because male and female embryos differ in their abilities to metabolize glucose. Another example is the sexually dimorphic expression of the bovine embryo-derived signal for maternal recognition of pregnancy, IFNT. The difference in expression of X-linked genes between male and female embryos, that results from incomplete X-chromosome inactivation, is considered to be involved, either directly or indirectly, in the sexual dimorphism that appears during early development.*

Keywords: *Sexual dimorphism, Sex ratio, X-chromosome inactivation*

Introduction

In the livestock industry, the sex of offspring is a key factor that affects the management practices of farmers. For instance, female offspring benefit dairy farmers because they can produce milk, whereas male calves, which typically have a larger carcass size than female calves, are preferred by beef producers. Therefore, the mechanism of sex determination and subsequent control of the sex of offspring generate great research interest.

Sexual dimorphism typically appears after gonadal differentiation. Sex-related hormones, such as estradiol and testosterone, secreted from differentiated gonads of both sexes influence the expression of sex-specific phenotypes. Moreover, these hormones affect the expression of sex-specific behaviors by changing brain function (masculinization and feminization) [1]. In addition, some differences between male and female embryos are seen earlier during development, before gonadal development, and their early appearance implies the involvement of factors other than gonadal hormones. One widely known example of this phenomenon is the sex-ratio skewing of embryos that occurs during early development *in vitro*. Here we summarize previous reports that focus on the sexually dimorphic events that occur during the early development of mammalian preimplantation embryos, and on the mechanisms that underlie these events.

Sex-ratio Skewing

In mammalian species, approximately the same numbers of sons and daughters are typically born. However, Tivers and Willard [2] proposed that in polygynous species such as deer, the dams in optimal body condition tend to produce male offspring, which would likely become elite breeding males. As a result, these dams would pass on their genes to greater proportions of subsequent generations. In contrast, dams in poor body condition tend to have female offspring because their daughters would likely have greater reproductive success than their sons. This hypothesis of sex-ratio skewing provides a rationale and motivation for the study of sex control in livestock species.

Various mechanisms have been suggested to be involved in sex-ratio skewing in mammalian populations. These include: differences in sperm mobility, such that sperm of one sex are more likely to move directly toward and therefore arrive at oocytes, depending on the conditions prevailing in the female reproductive tract; differences in fertilization, such that sperm of one sex are more effective once the egg has been reached; differences between XX and XY embryos in rates of development or sensitivity to conditions within the female reproductive tract, leading to selective loss of embryos of one sex prior to implantation; and sex-associated selec-

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tive fetal resorption or abortion after implantation. These same mechanisms might also lead to sex-ratio skewing during embryonic development *in vitro.*

An earlier mini-review by Iwata addressed various studies of factors that directly affect the sex of resulting embryos (namely, sperm mobility and fertilization) and therefore occur prior to embryogenesis. Another review [3] suggested that external factors such as the maternal diet play a key role in selective fetal resorption or abortion after implantation. Here we summarize previous studies on the sex-ratio skewing which occurs during early embryonic development prior to implantation.

Sex-ratio skewing in mammalian embryos

The relationship between sex ratio and growth rate during *in vitro* culture was first elucidated in mice [4]. In that study, 8-cell mouse embryos were cultured to the blastocyst stage and then allocated into three groups according to the time of blastocoel formation (growth rate). After embryo transfer, the sex ratio of the offspring from the fast-developing embryos was skewed toward male, whereas that of slow-developing embryos was significantly shifted toward female. This bias occurs in other species *in vitro* and *in vivo*. Embryos collected from bovine uteri on day 7 after superovulation (that is, *in-vivo*–derived embryos) showed skewing of the sex ratio toward male (but without significance) when a donor yielded embryos of at least three different developmental stages [5]. Bovine embryos produced *in vitro* on day 7 or 8 post-insemination show a clear correlation between sex and stage of embryonic development [6, 7]. Similar skewing of the sex ratio also occurs at earlier developmental stages in bovine embryos produced *in vitro* [8]. In sheep, the sex ratio of fast-developing blastocysts is skewed toward male [9, 10]. As in animal species, the likelihood of a liveborn human male is significantly greater than that of a female if embryonic development at the scheduled time of transfer is advanced [11, 12]. In contrast, some reports show data inconsistent with sex-ratio skewing during early embryonic development. For example, Ng *et al*. analyzed the sex of 213 babies born after 145 embryo transfers and failed to reveal any sex-associated differences in embryo cleavage rates between procedures that led to male compared with female infants [13]. Holms *et al*. demonstrated no difference between the cleavage intervals of male and female bovine embryos by observation in a time-lapse culture system [14]. These conflicting results may be attributable to difference between species, culture methods, or the developmental stage of the embryos observed.

The role of glucose metabolism in the mechanism of sex-ratio skewing

Because glucose is an energy substrate for not only somatic cells but also mammalian embryos, standard tissue or embryo culture medium includes glucose at the concentration found in normal human serum, 5.6 mM [15]. However, this excessive concentration of glucose is detrimental for early embryonic development *in vitro* in several species, including mice [16], rats [17, 18], hamsters [19], humans [20, 21], pigs [22], sheep [23], and cattle [24, 25]. Precisely how glucose inhibits the early development of mammalian embryos is not fully understood, but several studies have demonstrated various damaging effects of glucose. For example, the oxygen consumption of hamster embryos decreases dramatically only when both glucose and phosphate are included in embryo culture medium [19, 26]. Under this condition, phosphate stimulates cellular glycolysis by activating three enzymes: hexokinase, phosphofructokinase, and glyceradehyde-3-phosphate dehydrogenase [27]. This enhanced glycolysis subsequently inhibits mitochondrial respiration, in a process known as the “Crabtree effect” [28]. Moreover, other reports suggest that a high concentration of glucose in the culture medium leads to the production of oxygen radicals, which cause various types of cellular damage [29, 30]. Iwata *et al*. showed that the damage to bovine embryos generated through the addition of glucose to the culture medium was mitigated when the embryos were cultured under a reduced oxygen concentration [31]. Another study by the same group suggested that some of these free oxygen radicals are generated through the metabolism of hypoxanthine by xanthine oxidase [32].

These damaging effects of glucose depend on the species and developmental stage of the embryo, because the metabolic rate of glucose differs between stages of embryogenesis. For instance, glucose uptake from the culture medium is relatively low until the 16-cell to morula stage in bovine embryos. Glucose uptake then begins to increase with the initiation of compaction and continues to increase with the formation and expansion of the blastocoel [33]. The metabolism of bovine embryos increases with the uptake of glucose [34], and this change in glucose metabolism is coincident with genomic activation in the embryo [35]. In the case of cattle, early embryonic developmental stages (that is, until the 8- to 16-cell stage) utilize maternal-origin mRNA or protein. Later, the embryonic genome is activated, and the bovine embryo begins to produce enzymes [36].

These observations regarding the characteristics of glucose metabolism in mammalian embryos have led

not only improvement of *in vitro* embryo culture systems, but have also shed light on the mechanisms involved in sex-ratio skewing, which appears to be modulated by the *in vitro* environment [37]. Bredbacka and Bredbacka were the first to report that the presence of glucose in the embryo culture medium is involved in the sex-related differences in growth rates of bovine embryos produced *in vitro* [38]. In their study, the cell numbers of male and female embryos at 48 h post -insemination did not differ in glucose-free medium. However, in the presence of glucose (5.56 mM), male embryos had more cells than female embryos. Other studies have confirmed this effect of glucose on the skewing of the sex ratio of embryos *in vitro*. A time-lapse video recording system was used to demonstrate that in glucose-containing media more male than female embryos reached the morula and blastocyst stages [39]. In another study, the sex ratio of blastocysts on day 8 in the presence of glucose was biased toward male, although it was not skewed in either 8-cell embryos on day 3 or in morulae on day 6 [40]. This result was confirmed by another study, which reported the presence of glucose in the medium caused a sex-ratio imbalance on day 9 to 10, with fewer female embryos reaching the expanded blastocyst stage [41].

Although the involvement of glucose in sex-ratio skewing is evident, the mechanisms and threshold concentration that induce this effect had remained unclear.

It was demonstrated that when the concentration of glucose in the medium exceeded 2.5 mM, the sex ratio of bovine embryos at the blastocyst stage was skewed toward male [42]. Moreover, the effect of fructose, a hexose similar to glucose, on sex-ratio skewing of bovine blastocysts has also been investigated in the same study [42]. As with glucose, bovine embryo can uptake fructose at different rates [43], and including fructose in the culture medium improved the rate at which bovine embryos developed to the blastocyst stage [44]. As a result, fructose affected neither development rate nor sex ratio at same concentration of glucose (5.6 mM) [42]. Glucose and fructose have different transport mechanisms, and therefore potentially different rates of uptake and different metabolic fates. The first step of fructose metabolism, its conversion to fructose 6-phosphate, bypasses the limb of pentose phosphate pathway (PPP) and leads to entry directly into the Embden–Meyerhof pathway (glycolysis, Fig. 1). Supplementation of the culture medium simultaneously with glucose at a concentration that induced skewing of the sex ratio and dehydroepiandrosterone (DHEA; a noncompetitive inhibitor of glucose-6-phosphate dehydrogenase [G6PD], a 'gatekeeper' of PPP) or 6-aminonicotinamide (6-AN; a competitive inhibitor) prevented subsequent skewing of the sex ratio of bovine blastocysts [45]. Moreover, the total glucose metabolism in male bovine embryos was twice that in female embryos on day 7 post-IVF [46], but PPP activity was four times greater in female than in male embryos [46]. Taken together, these results suggest that the effect of glucose on sex-ratio skewing might be exerted through PPP rather than glycolysis (Fig. 1). A possible mechanism for the glucose-associated skewing of the sex ratio is that the high PPP activity in female embryos increases purine nucleotide synthesis, followed by inhibition of female embryo development by purine derivatives [47].

Sexual Dimorphism of Gene Expression during Early Embryonic Development

Why is the PPP activity of female embryos greater than that of male embryos? How does glucose in the culture medium cause skewing of the sex ratio of embryos? The answers to these questions may lie in epigenetic differences that occur during early embryonic development.

X chromosome inactivation

A key genetic difference between male and female organisms is the composition of their sex chromosomes. Because females have two X chromosomes (XX genome), they can potentially produce twice the amount of X-linked proteins that males (XY genome) can. In fact, however, the expression levels of almost all genes on the X chromosome are equal between males and females. This dosage compensation in gene expression is accomplished through 'X chromosome inactivation', genetic inactivation of one of the two X chromosomes, in females of almost every mammalian species [48]. X chromosome inactivation occurs during female embryo or conceptus development [48] and is essential for normal embryonic development [49–51].

The inactive X chromosome is characteristically heterochromatic and hypoacetylated [52–54]. Moreover, during the cell cycle, replication of the inactive X chromosome is delayed compared with that of the active X chromosome and autosomes [53, 55]. In the trophectoderm of mice, the paternal X chromosome is replicated late and transcriptionally inactivated, whereas in the embryonic ectoderm, inactivation occurs later and affects either the paternally or maternally derived X chromosome [56, 57].

Some of the molecular events involved in X chromosome inactivation are well understood. The X inactivation centre, a locus essential for the induction of X chromosome inactivation, is mapped to the X chromosome [58]. This region includes the gene involved in the X inactiva-

tion process, X-inactive specific transcript (*XIST*), which is transcribed only from the future inactive X chromosome [59]. Moreover, *XIST* RNA is not translated into protein and coats the inactive X chromosome *in cis* [60], with subsequent remodeling of the chromatin [61]. Therefore, *Xist* expression precedes X chromosome inactivation [62–64].

Expression levels of X-linked genes in embryos

The kinetics of the epigenetic changes associated with activation and reactivation of the imprinted paternal X chromosome during the development of preimplantation embryos have been investigated intensively in mice. Beginning at the 2-cell stage, *Xist* RNA is transcribed from the paternal X chromosome and covers it gradually. At the blastocyst stage, *Xist* RNA is lost, and the paternal X chromosome is reactivated in the inner cell mass, whereas the paternal X chromosome remains inactive in the trophectoderm [65–68]. The basic process of X-chromosome inactivation appears to be shared among mammalian species, but species-specific differences exist. In humans, *XIST* is expressed continuously from the 5- to 10-cell stage and onward [69]. In cattle, *XIST* transcripts are not detected in embryos at the 2- to 4-cell stage but are present in 8-cell stage embryos [70]. These differences are attributed to differences in the timing of zygotic genome activation. In mice, *Xist* expression begins at the same time as the major wave of zygotic genome activation is initiated [71].

Xist RNA is involved, at least, in the initiation of X chromosome inactivation, and *Xist* expression precedes the initiation of late replication and dosage compensation [51, 62, 63]. In cattle, late replication of one of the X chromosomes was present only in some blastocysts on day 8 of development but in all elongated blastocysts on days 14 and 15 [70]. These data suggest that even after the initiation of *XIST* expression, both X chromosomes in female bovine embryos are still active.

Several studies have investigated the expression of various X-linked genes during early embryo development before X chromosome inactivation. For example, the gene for hypoxanthine–guanine phosphoribosyltransferase (HPRT), which is involved in the salvage of purine derivatives, is expressed at higher levels in female than in male embryos from the 8-cell to blastocyst stages in mice [62, 64]; its gene expression is also up-regulated more in female than in male blastocysts in cattle [72]. In humans, the expression of HPRT is not sexually biased in embryos on day 2, but on day 3 female embryos show greater expression of this gene than their male counterparts [73]. The enzymatic activity of phosphoglycerate kinase, which is involved in glycolysis and is the product of an X-linked gene, is higher in female than in male mice [74]. In the preceding section, we reviewed studies showing that excessive glucose in the embryo culture medium leads to skewing of the sex ratio, and noted that higher PPP activity in female embryos is a possible mechanism for this phenomenon. Entrance into the PPP is controlled by G6PD, and its enzymatic activity is higher in bovine female embryos than in male embryos [75]. In addition, the G6PD gene is X-linked and its expression is also higher in bovine female embryos than in male embryos [72, 76, 77]. These findings suggest that having both X chromosomes active is closely involved in the sex skewing of early-stage embryos.

Several reports provide data supportive of this possibility. G6PD is an enzyme involved in the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is a principal substance for reducing oxidative stress. When cultured under heat stress (41°C), female mouse embryos have less H_2O_2 than male embryo, and the sex ratio is skewed toward male. Moreover, inhibition of G6PD with DHEA abrogated all heat-stress-associated differences in the embryos [78]. Kimura *et al.* focused on the enzyme, O-linked GlcNAc transferase (OGT), which is involved in protein glycosylation, whose gene is located on the X chromosome [79](Fig. 1). When glucosamine, a substrate of OGT, was added to the culture medium for bovine 8-cell to blastocyst-stage embryos, the sex ratio of the developed blastocysts was skewed toward male in a concentration-dependent manner. Moreover, addition of benzyl-2-acetamido-2-deoxy-α-D-galactopyranoside, an inhibitor of OGT, to culture medium containing glucosamine at a concentration that had previously skewed the sex ratio prevented this glucosamine-associated effect [79]. The authors of that study suggested that when glucosamine is present in the bovine embryo culture medium, proteins in female embryos, such as transcription factors, are highly glycosylated and therefore impaired the development of those embryos.

In contrast, Jiménez *et al.* focused on X-linked inhibitor of apoptosis protein (XIAP) [80]. The expression of this gene is higher in female bovine embryos than in male embryos. In their research, the sex ratio of bovine blastocysts was skewed toward female under hyperglycemic conditions (20 to 30 mM), and the number of apoptotic cells was increased. Moreover, when mouse embryos were cultured in the presence of 20 mM glucose and then transferred to recipient dams, more female than male embryos implanted. Therefore, the authors surmised that the higher expression of XIAP in female may inhibit

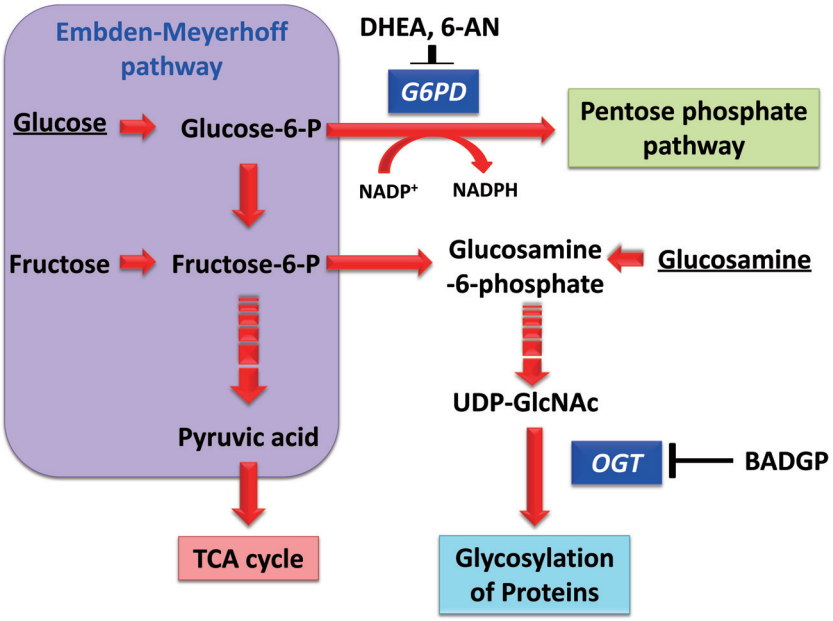

Fig. 1. Metabolic pathway involved in the sex-ratio skewing of embryos. Underlined substrates cause the sex-ratio skewing of embryos when added into the embryo culture medium at appropriate concentrations. Glucose skews the sex ratio of embryos toward male, however, fructose does not. Glucose is phosphorylated by hexokinase and then utilized both in the Embden-Meyerhoff and pentose phosphate pathways. Fructose is also phosphorylated by hexokinase, but it is utilized only in the Embden-Meyerhoff pathway. The enzymes in blue boxes are X-linked and are involved in the sex-ratio skewing of embryos. The inhibitors of these enzymes (DHEA, 6-AN and BADGP) abrogate their effects.

the hyperglycemia-associated programmed cell death that occurs during preimplantation [80]. The existence of such a mechanism would account for the significant decrease in the number of male children born to diabetic mothers [81].

Sexually Dimorphic Expression of Genes That Are Not X-linked

In previous sections, we have described various sex-related events that occur before gonadal differentiation and the evidence linking them to the sexual dimorphic expression of the genes located on the X chromosome before its inactivation. However, some events cannot solely be explained by X chromosome inactivation, suggesting that some genes that are not located on the X chromosome are expressed in a sex-dependent manner. One example of this is the sexually dimorphic production of interferon tau (IFNT), which is a key factor for maternal recognition of pregnancy in ruminants and is secreted from bovine embryos [82].

Sexually dimorphic production of IFNT

In mice and humans, embryos implant into the uterine endometrium just after hatching from the zona pellucida. However in ruminant ungulates such as cattle, implantation occurs at approximately 30 days post-estrus, whereas the bovine estrous cycle is 21 days in length. Therefore, to inhibit a return to estrus, the growing conceptus in the bovine uterine cavity needs to signal its presence to the mother. This signaling substance is IFNT, a protein similar to IFNW, and it has antiviral activity as do other type-I interferons [83–89]. IFNT is secreted from the trophectoderm of embryos and inhibits regression of corpora lutea by modifying the secretion pattern of the luteolytic hormone $PGF_{2\alpha}$, which is secreted from the uterine endometrium [90–94]. Secretion of IFNT is detected first in the culture medium of blastocysts [95–97], and production peaks just before the implantation [98]. When implantation initiates, the production of IFNT is down-regulated dramatically [99]. Therefore, IFNT plays important roles in the maternal recognition of pregnancy in ruminant ungulates.

With respect to the production of IFNT, the study of Flint *et al.* made an interesting finding [100]. They noted that IFNT (measured as antiviral activity) was present in the uterine flushings of culled red deer hinds carrying female but not male conceptuses. As in red deer, female bovine blastocysts secrete higher concentrations of IFNT than do male blastocysts [40]. From these studies, it is clear that the secretion of IFNT, a signal for the establishment of pregnancy in ruminant ungulates, is sexually dimorphic.

Are the IFNT genes located on the X chromosome? Because the IFNT genes are located as clusters on an autosome (chromosome 8) [101], two active X chromosomes appear not to be directly involved in this sexual dimorphism. For example, Kimura *et al.* showed that female bovine blastocysts produced higher amount of IFNT than did male blastocysts on day 9, however, this sex-associated difference was absent in conceptuses on day 14 [102]. This pattern of sexually dimorphic expression of IFNT is coincident with the process of X chromosome inactivation. De la Fuente *et al.* showed that the X chromosome inactivation in cattle is accomplished by 14 days post-fertilization [70]. These data suggest that X-linked genes might be involved indirectly in the sexually dimorphic expression of IFNT.

Of the hundreds of genes encoded on the X chromosome, one that may play a key role in embryonic development is *G6PD* [103]. The deletion of the *G6pd* causes embryonic lethality in mice and severely affects the development of trophectoderm, from which IFNT is secreted, in cattle [104]. Therefore, the sexually dimorphic expression of IFNT may be an indirect effect of the greater expression of G6PD in female embryos than in male embryos due to the presence of two active X chromosomes in female embryos. In one study, addition of DHEA or 6-AN, inhibitors of G6PD, to the culture medium for bovine embryos abrogated the sexually dimorphic expression of IFNT [45], but that study did not address how G6PD might cause the sexually dimorphic expression of IFNT. The expression of IFNT genes is regulated by many transcription factors [105–111]. In comparison, G6PD is a rate-limiting enzyme of PPP and is involved in the production of cellular NADPH [112, 113], which regulates the activity of proteins through control of the cellular redox state [114–116]. Together, these findings imply that a difference in the redox state between male and female embryos would give rise to sexually dimorphic expression of IFNT.

Microarray analysis has revealed sexually dimorphic expression of genes in embryos

Is *IFNT* the only gene that shows sexually dimorphic expression even though it is located on an autosome? A recent global analysis of genes expressed in male and female mouse embryos revealed that nearly 600 genes show sex-associated differences in expression, and 11 of these genes show greater than 2.5-fold differences. Of these 11 genes, 6 are located on autosomes [117]. In the case of cattle, the results are much more dramatic: almost one-third of the transcripts detected show sexual dimorphism (2921 out of 9322 transcripts). This result suggests that sex chromosomes impose extensive transcriptional regulation on autosomal genes [118]. Together, these studies indicate that sexual dimorphism of gene expression appears throughout the entire genome during early embryonic development.

Conclusion

Above, we have reviewed various studies addressing the sexual dimorphism that occurs before gonadal differentiation during embryonic development. This phenomenon is attributed to the lack of X chromosome inactivation. During the early stages of development, both of the X chromosomes in female embryos are active, and dosage compensation of X-linked genes has not yet been accomplished. This difference in the expression of X-linked genes drives sexual dimorphism such as sex-ratio skewing. Moreover, recent studies have revealed that numerous autosomal genes are regulated sexually in embryos. The studies we have reviewed here are useful foundations not only for the investigation of the regulation of gene expression in embryos and embryonic stem cells, but also for research into the control of the sex ratio of domestic animals.

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