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Review

Gene expression in placentation of farm animals: An overview of gene function during development

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Abstract

Eutherian mammals share a common ancestor that evolved into two main placental types, i.e., hemotrophic (e.g., human and mouse) and histiotrophic (e.g., farm animals), which differ in invasiveness. Pregnancies initiated with assisted reproductive techniques (ART) in farm animals are at increased risk of failure; these losses were associated with placental defects, perhaps due to altered gene expression. Developmentally regulated genes in the placenta seem highly phylogenetically conserved, whereas those expressed later in pregnancy are more species-specific. To elucidate differences between hemotrophic and epitheliochorial placentae, gene expression data were compiled from microarray studies of bovine placental tissues at various stages of pregnancy. Moreover, an in silico subtractive library was constructed based on homology of bovine genes to the database of zebrafish — a nonplacental vertebrate. In addition, the list of placental preferentially expressed genes for the human and mouse were collected using bioinformatics tools (Tissue-specific Gene Expression and Regulation [TiGER] — for humans, and tissue-specific genes database (TiSGeD) — for mice and humans). Humans, mice, and cattle shared 93 genes expressed in their placentae. Most of these were related to immune function (based on analysis of gene ontology). Cattle and women shared expression of 23 genes, mostly related to hormonal activity, whereas mice and women shared 16 genes (primarily sexual differentiation and glycoprotein biology). Because the number of genes expressed by the placentae of both cattle and mice were similar (based on cluster analysis), we concluded that both cattle and mice were suitable models to study the biology of the human placenta.

Keywords: Epitheliochorial placenta; Gene expression; Transcription factors; Placenta-specific genes; Farm animals

Contents

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1. Introduction

Adequate placentation is crucial for maintenance of pregnancy. Communication between the chorionic epithelium and endometrium promotes fetal development and survival by providing nutrition, gas transport, immunological and physical protection, and waste product removal [1,2]. Furthermore, the placenta secretes a wide range of molecules important to support pregnancy, e.g., hormones (estrogens, progesterone, placental lactogens, etc.) [1–4].

Epitheliochorial placentation occurred as a specialization from an ancestral hemotrophic placenta [5]. During evolution, a common ancestor with a bipotential placenta type (hemotrophic and histiotrophic) evolved into four branches [5]. The two low branches of eutherian evolution are composed only of a hemotrophic placenta type, and the other two by a miscellaneous category (between hemotrophic and histiotrophic placental types [5]; Fig. 1). Furthermore, evolutionary pressure for development of the epitheliochorial placenta could be a consequence of the need for more efficient placental transport [6], increased maternal control over the vascular supply to the conceptus [7], or as a strategy for immunological defense [8].

In epitheliochorial placentation, the maternal epithelium is preserved, whereas in the hemotrophic placenta, trophoblast cells invade maternal tissue up to the endothelial layer [2]. Therefore, the epitheliochorial placenta is considered a less invasive placenta, because fetal cells do not bypass the endometrial basal membrane [9,10]. Notwithstanding, there is migration of fetal cells toward maternal tissues, i.e., binucleate trophoblast cells in cattle and sheep, with synepitheliochorial placentae [2]. Migration of these cells facilitated the exchange of hormones between maternal and fetal tissues [9–15].

Moffett and Loke [8] raised the question regarding whether the ability of invasion of trophoblast cells was controlled by specific gene expression in those cells, specifically expression of major histocompatibility complex (MHC) class I classical and nonclassical. Trophoblast cells downregulated expression of the classic form of MHC class I and upregulated nonclassical isoforms [16]. In humans and mice, expression of nonclassical molecules was widely reported and the specific biological role of these nonclassical MHC is still under investigation. The human leukocyte antigen (HLA) G was heavily expressed by the human placenta; it was also expressed in two main isoforms (membrane bound and soluble [17]). The HLAG can interact with inhibitory receptors of natural killer (NK) cells, e.g., immunoglobulin-like transcript (ILT) -2 and -4 [18]; these receptors were also present on other immune cells (i.e., macrophages and dendritic cells [19]). Furthermore, HLAG was detected systemically in pregnant women [20] and probably had a role in pregnancy-related immune changes in human. Local and systemic effects of HLAG expression during pregnancy are not yet fully understood, but the lower expression of HLAG can activate uterine natural killer cells against trophoblast cells, and thereby induce trophoblast invasion [21].

Although maternal fetal interactions vary broadly among species, some characteristics of placentae are maintained, e.g., occurrence of imprinted genes [2,22]. Allelic expression of specific genes may explain the parental conflict theory, i.e., that paternal genes will maximize fetal development to increase nutrient supply to the fetus, even to the detriment of the dam's life, for example insulin growth factor 2 (*IGF2*) [23]. Conversely, the dam will protect herself by suppressing expression of growth-induced genes by the maternal allele [23]. The imprinting status of certain genes would confer to the dam greater control over fetal development, without deleterious effects on fetal development or the life of the dam [5].

Recent activities, especially the increased use of assisted reproductive techniques (ARTs) in livestock, i.e., in vitro fertilization (IVF) or cloning by somatic cell nuclear transfer (SCNT), highlighted the importance of adequate placental function to pregnancy success (at all stages of pregnancy). There is a clear association between ARTs and placental defects [24–26], emphasizing the need to elucidate similarities and differences of placental anatomy and function for species other than just humans and mice [24,26].

One consequence of producing embryos by SCNT was deregulation of gene expression, especially during the preimplantation period, compared with producing embryos by IVF, AI, or natural service [26]. Disrupted gene expression in SCNT embryos may occur due to failures of nuclear reprogramming and/or suboptimal in vitro embryo culture conditions [27,28]. For example, abnormal expression of imprinted genes, e.g., imprinted maternally expressed transcript (non-protein coding) gene *H19* and insulin growth factor 2 receptor (*IGF2R*) by SCNT embryos,

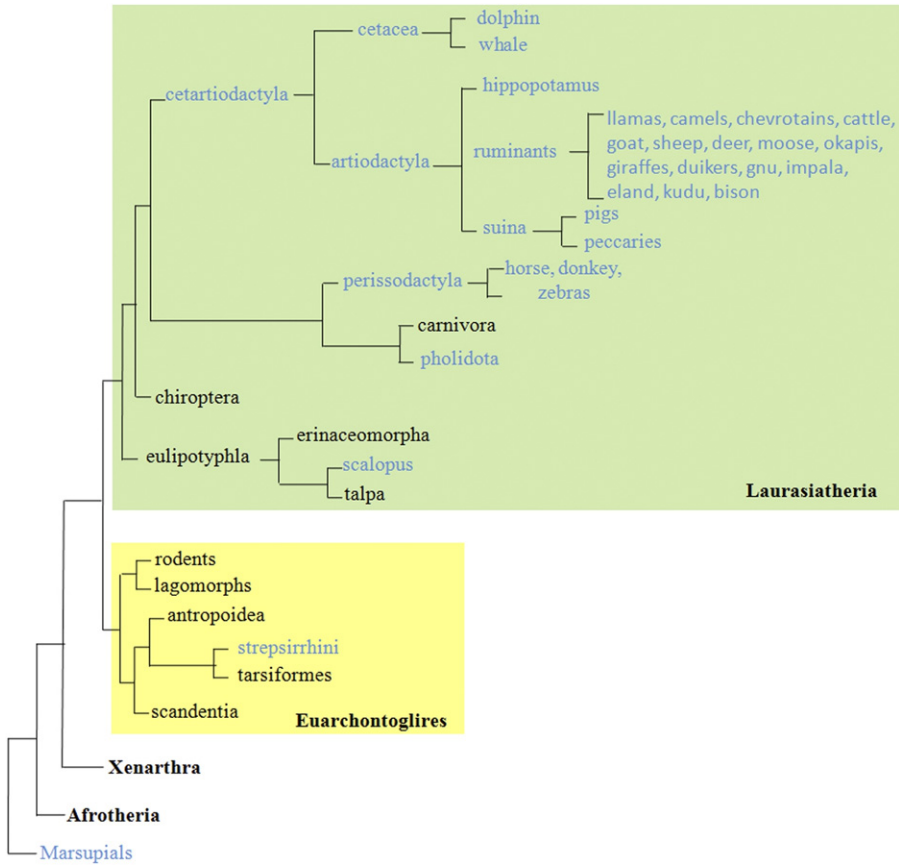

Fig. 1. Phylogenetic tree of therian mammals. Eutherians are the union of Laurasiatheria (green), Euarchontoglires (yellow), Xenarthra, and Afrotheria clades, Marsupials are an out-group. Blue subscriptions are therians with histiotrophic placenta and black hemotrophic. Phylogenetic model according to Vogel [5].

caused pregnancy losses from preimplantation to neonatal life in sheep, cattle, and mice [25,29].

The purpose of this review is to compile current data regarding gene expression of placenta among livestock (represented mainly by cattle) and to compare that with humans and mice, highlighting similarities and differences with regards to placental type.

2. Genes and early development: from pluripotency to established pregnancy

Expression of a triad of transcription factors, namely POU domain, class 5, transcription factor 1 (*POU5F1*), Nanog homeobox (*NANOG*), and SRY (sex determining region Y)-box 2 (*SOX2*), was essential for mainte-

Table 1
Expression of transcription factors at four-cell, eight-cell, and blastocyst stages of cattle, pigs, horses, humans, and mice [30,32,34–38].

Species	Four-cell stage			Eight-cell stage			Blastocyst stage		
	POU5F1	*NANOG*	*SOX2*	*POU5F1*	*NANOG*	*SOX2*	*POU5F1*	*NANOG*	*SOX2*
Cattle	N/A	N/A	N/A	N/A	N/A	N/A	ICM/TE	ICM	+
Pigs	+	–	–	+	+	+	ICM/TE	ICM	+
Horses	N/A	N/A	N/A	N/A	N/A	N/A	ICM/TE	ICM/TE	TE
Humans	+	+	+	+	+	+	+	+	+
Mice	N/A	N/A	N/A	N/A	N/A	N/A	ICM	ICM	+

+, gene expressed but spatial expression unknown; –, gene not expressed; ICM, gene expressed by cells of inner cell mass; N/A, not applicable; *NANOG*, Nanog homeobox; *POU5F1*, POU domain, class 5, transcription factor 1; *SOX2*, SRY (sex determining region Y)-box 2; TE, gene expressed by epithelial trophectoderm cells.

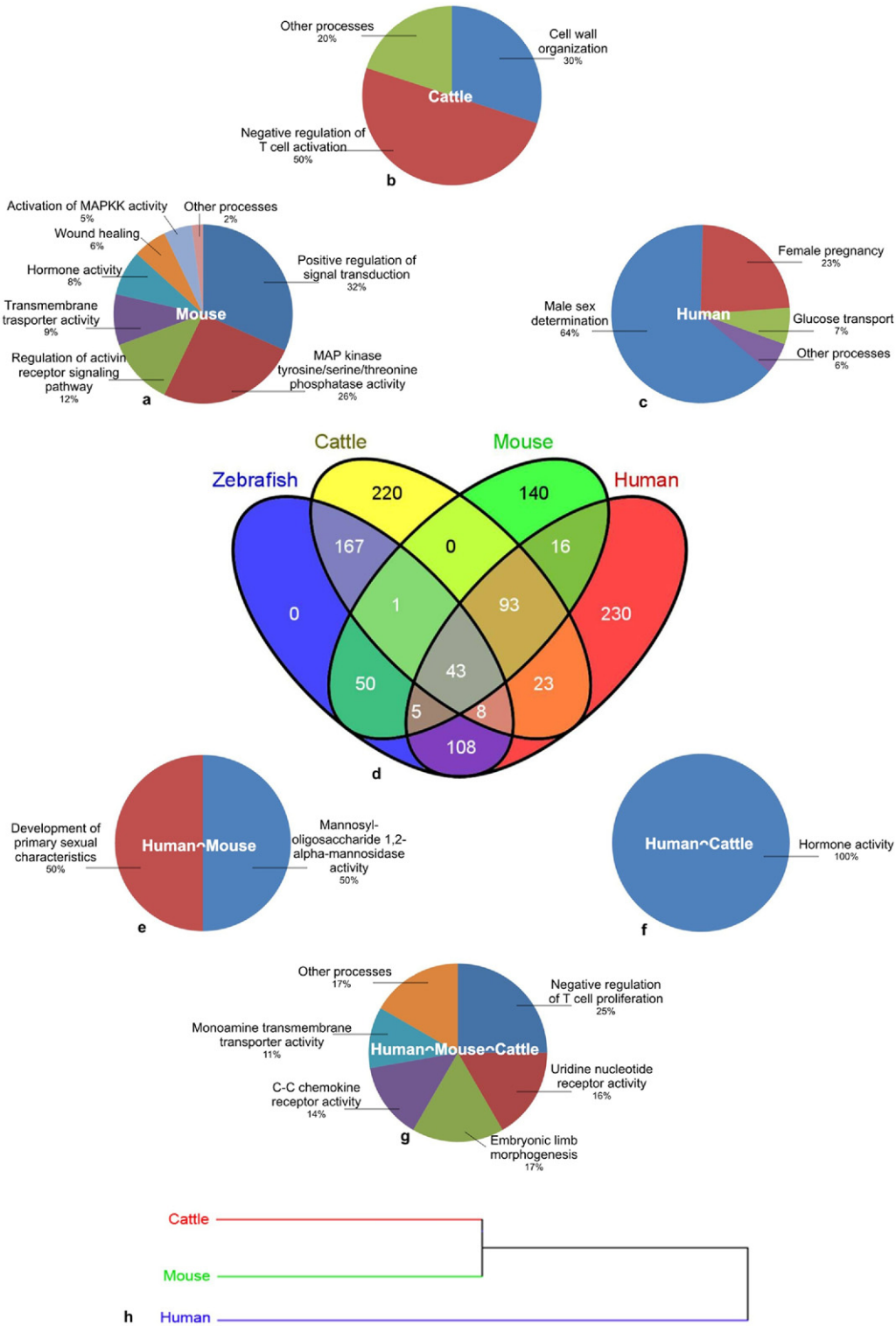

Fig. 2. Ontology of placental genes of humans, mice, and cattle, compared with a zebrafish orthologous database. (a) Ontology of genes in a mouse cluster. (b) Ontology of genes in cattle cluster. (c) Ontology of genes in human cluster. (d) Venn diagram of placenta preferential expressed genes in humans and mice, bovine placental genes from array studies, and zebrafish orthologous. (e) Ontology of common genes among human and mouse clusters. (f) Ontology of common genes among human and cattle clusters. (g) Ontology of common genes among human, mouse, and

nance of self-renewal and pluripotency of embryonic stem (ES) cells and inner cell mass (ICM) cells [30]. Transcription of *POU5F1*, *NANOG*, and *SOX2* were tightly regulated by each other, in a regulatory loop manner [30–32]. According to Adachi [32], downregulation of *POU5F1* in human ES cells led to *SOX2* and *NANOG* downregulation. In addition, lower expression of *NANOG* caused downregulation of *POU5F1*, but not *SOX2*. However, downregulation of *SOX2* induced significant decreases in *NANOG* expression.

Furthermore, upregulation of *SOX2* resulted in decreased expression of *POU5F1* and *NANOG*. Synergistically, *POU5F1*, *NANOG*, and *SOX2* regulated transcription of their target genes. It was noteworthy that these three factors interacted with 3%, 9%, and 7%, respectively, of the promoter regions of approximately 18 000 genes in human ES cells [33]. However, expression of these transcription factors did not happen in the same manner in all mammals. For example, porcine embryos expressed *POU5F1* at both the four and eight cell stages of embryonic development, whereas expression of *NANOG* and *SOX2* started at eight cell to blastocyst stages [30,34]. To date, there are apparently no data regarding expression of *POU5F1*, *NANOG*, and *SOX2* in bovine or equine embryos until the blastocyst stage, when *POU5F1* and *NANOG* were expressed by both trophectoderm and the inner cell mass. Moreover, in mice, expression of *POU5F1* was reported only at the eight cell stage [30], with no data for expression of *NANOG* or *SOX2*. At the blastocyst stage, all three transcription factors were expressed in bovine, porcine, equine, and murine embryos, albeit with some spatial differences (Table 1).

Little is known about mechanisms underlying pluripotency of embryonic stem cells (ES cells) in farm animal species. For example, the optimal time to initiate a blastocyst-derived cell culture for establishing ES cell lines is unknown [39]. A better understanding of how ES cells maintained their undifferentiated status could elucidate core mechanisms to establish ES cell lines in species of interest, e.g., cattle and pigs [30].

Protocols to establish ES cell lines in farm animals could be used to develop animal models, other than those involving primates or mice, for example, to study human genetic disorders and cellular therapy. Moreover, ES cell lines could be used to produce transgenic animals (to improve specific traits and to use them as bioreactors for the biopharmacy industry [39]).

Characterization of the bovine genome [40] revealed that humans and cattle shared 1791 genes, whereas humans and rodents shared 1481 orthologous genes, making cattle 21% more similar to humans than mice. Based on genetic similarities between cattle and humans, the former were a suitable model for human genetic research, such as gene therapy [41].

3. Gene expression on placentation and embryonic development

In general, developmentally regulated genes were largely conserved phylogenetically across placental types. Nevertheless, genomic mechanisms that lead to emergence and diversification of the eutherian placenta remain unknown [42].

In mice, during early pregnancy, the decidua and the placenta mainly express genes that have eukaryote ancient origins [42]. Later in pregnancy, gene expression is more based on rodent-specific genes that appeared later in evolution. Similarly, in humans, ancient genes are mainly expressed in early stages of gestation, whereas the expression of primate-specific genes arise during later stages of pregnancy [42]. Consequently, it is not surprising that genes expressed during mouse development are expected to be present in other mammals.

To understand similarities and differences among placental types, we searched for published data on placental gene expression, focusing on human, murine, and bovine models. In the present study, microarray data in gene expression of placenta were compiled into a list of genes expressed in placental tissues at various stages of pregnancy in cattle [4,43–50]. Microarray data alone highlighted genes involved in cell metabolism, the cell cycle, and other core cellular processes not specifically involved in placental function. Also, the wide variety of protocols for producing and analyzing data regarding global expression experiments did not make microarray data a tissue-specific gene expression database. To minimize this effect, we searched the expression of the listed genes on the database of zebrafish as a strategy to generate in silico a subtractive library for placental genes in cattle.

cattle clusters. (h) Distance analysis of developmental status of placental genes in human, mouse, and cattle. (a–c) and (e–f) Percentages in graphics are represented by number of daughters in each mother functional group of total daughter functional groups in each gene cluster. H, human; M, mouse; C, cattle; Z, zebrafish; ∪, intersection among groups.

Likewise, using the Tissue-specific Gene Expression and Regulation (TiGER; http://bioinfo.wilmer.jhu.edu/tiger/) database [51], we recovered a list of preferentially expressed genes in the human placenta, and using Tissue-Specific Genes Database (TiSGED; http://bioinf.xmu.edu.cn/databases/TiSGeD/index.html) to human and mouse [52]. In TiSGED a specific measure value (SPM) varying from 0.0 to 1.0 (whereas genes with higher SPM values are more likely to be specifically expressed in a given tissue than genes with lower values of SPM) is required before gene list acquisition; for our analysis, the SPM was set at 0.8. This setting excluded some genes commonly expressed in the mouse placenta, e.g., insulin growth factor 2 (*IGF2*) did not appear in the mouse list. The SPM value for *IGF2* is 0.6, compared with human which is 0.8. The SPM values suggest that *IGF2* may be not as specific to the placenta in mouse as it is in human. A comparison of placental gene expression among these four species was performed using the generated database (Fig. 2).

Based on ontology analysis, genes commonly expressed by more than one species (e.g., cattle, humans, mice, and zebrafish) participated in core cellular processes such a biosynthesis of hormones and cytokines, regulation of cell cycle and apoptosis, and organelle organization (Supplementary Files 1 and 2; online version only).

Humans, mice, and cattle shared a total of 93 genes expressed by their placentae. Based on ontology analysis, most of those genes were related to immune system modulation ("C-C chemokine receptor activity" and "negative regulation of T cell proliferation"). For example, V-set and immunoglobulin domain-containing 4 (*VSIG4*) negatively regulated T-cell activation [53], and was highly expressed by endometrial macrophages in the pregnant cow [54]. Another example was *CD274* (also known as programmed cell death 1 ligand 1); it was suggested to promote and enhance induced regulatory T-cells (iTreg) through antagonism of AKT/mTOR cascade in naive T-cells on nonhematopoietic tissues [55,56]. Moreover, blocked or absent expression of CD274 during pregnancy in mice led to increased maternal rejection in allogeneic, but not syngeneic, pregnancies [57].

Genes characteristic of the development of primary sexual characteristics and cellular pluripotency, e.g., zinc finger protein 42 homolog (*ZFP42*) [35], and T box gene 3 (*TBX3*) [58], were commonly expressed by humans and mice. Also, ontology highlighted genes related to protein glycosylation processes (mannosidase, alpha, class 1A, member 2 [*MAN1A2*], and mannosidase, alpha, class 1C, member 1 [*MAN1C1*]). Recently, *in vivo*-derived blastocysts produced in cows with elevated circulating progesterone concentrations had decreased expression of mannosidase, alpha, class 1C, member 1 (*MAN1C1*) among downregulated genes, compared with blastocysts recovered from cows with physiologic blood progesterone concentrations [59], suggesting the embryonic protein glycosylation may be a maternal hormonally-controlled process in the cow.

Finally, cows and women shared expression of 23 genes by their placentae (compared with 16 genes shared between mice and women). Of these 23 genes, 22 had hormone activity ontology, including insulin growth factor 2 (*IGF2*), insulin (*INS*), placental lactogens (chorionic somatotropin hormone 1 [*CSH1*] and StAR-related lipid transfer [START] domain containing 8 [*STARD8*]).

Using cluster analyses, the distance of bovine and murine placental gene expression were compared in relation to that of humans. Since both cattle and mice had a similar distance relative to humans in regards to placental gene expression (Fig. 2h), we inferred that cattle might be as appropriate as mice as a suitable model to study human placental biology and disorders. Therefore, the specific choice of a cow or mouse to test a given hypothesis should be made according to how target genes or cellular processes in humans are similar to the cow or mouse.

3.1. Gene expression and trophoblast invasion

Gene expression seemed to change according to placental morphology [60]. Perhaps marked differences between placental gene expression are needed to regulate trophoblast invasion [42]. The level of invasiveness in the epitheliochorial placenta is lower than the hemochorial placenta [2]. Although trophoblastic cells do not invade beyond the maternal basal membrane in cattle, in humans and mice, trophoblast cells are bathed by maternal blood in the decidua [2].

Decades ago, Mossman [1] said that "chromosome-mediated fetal membrane defects" were responsible for fetal pathologies, abnormalities, or even death, and concluded that very little was known about the genetics of fetal membranes. Although much knowledge regarding genes expressed in human, mouse, and bovine placentae has been published, there are few comparative studies among these species [40,48,60–62]. For example, based on global gene expression analysis from human and bovine placental/endometrial macrophages, cells in both species were activated in a similar manner, despite differences in placental morphology [54,63].

Moffett and Loke [8] suggested that an epithechorial placenta provided a better immunological barrier between mother and fetus when compared with hemotrophic placenta. Based on the gene expression analysis [54,63] highlighted above, although the epithechorial placenta is not as invasive as hemochorial placenta, immunological events, at least on the basis of gene expression, were very similar between the two placental types. Therefore, this information should contribute to understanding some placental disorders, e.g., preeclampsia, which are closely associated with reduced cell infiltration into the uterus [8].

3.2. Imprinted genes

Approximately 200 genes in the mammalian genome are imprinted. More than 70 imprinted genes in mice and at least 50 in humans have already been reported. For most genes, imprinting status is conserved between the mouse and human. Furthermore, for some genes, the imprinted status is also reported to be conserved in other species, e.g., cattle. Several genes had exclusively imprinted expression in placenta or early embryos in humans and rodents [62,64,65].

Many imprinted genes, e.g., *IGF2* [66], are involved in the control of fetal growth and placental development. All imprinted genes have functional nonequivalence according to their allelic origin (maternal or paternal); this is also true for placental imprinted genes.

There is a pronounced difference between imprinted and methylated genes. The imprinting status relates to the monoallelic expression of a specific gene, whereas methylated genes are inactive in all cells, but can be made active or inactive by signals in differentiated cells [67]. Imprinted genes are differentially methylated in one region (DMR) of one allele.

One evolutionary explanation for this hypothesis is that by restricting fetal growth, females have a longer reproductive lifespan, assuring their reproductive success. In contrast, having more numerous and stronger progeny is more advantageous for males [64]. This sexual antagonism was clearly evident in the large numbers of genes with imprinted expression in the placenta, i.e., *H19*, *IGF2*, *INS* and MAGE-like 2 (*MAGEL2*) [65], more than in any other tissue. Alterations in expression of imprinted genes may lead to fetal and placenta growth abnormalities (e.g., in IVF and SCNT embryos), due to abnormal cellular nuclear reprogramming [64,68,69].

Genomic imprinting is well studied in mice and humans, both of which have invasive hemochorial placentation [22,66,69–71]. Regarding farm animal species (epitheliochorial placentation), studies have focused on cattle, including comparisons between cloned and noncloned pregnancies [4,48,49].

Specific characteristics of large offspring syndrome (LOS) produced by ARTs in ruminants had similar clinical and experimental phenotypes as those in humans. Furthermore, IFV/SCNT-derived animals also had disrupted expression and/or effects of *H19* and *IGF2*, similar to the human [72]. It is noteworthy that large offspring syndrome (LOS) was a common syndrome for SCNT outcomes, mostly associated with altered levels of *IGF2-H19* genes [25,29].

4. Conclusions

Despite substantial diversification of placental morphology, gene expression was relatively similar among placental types. Although mice are the most widely used model to study the biology of placenta for human disorders, cattle also share a large number of genes preferentially expressed by the human placenta. Therefore, in addition to the mouse, cattle can be also a suitable model for placental studies, despite differences in morphology and cellular invasion. Moreover, identifying genes specifically expressed by the bovine placenta would help to identify markers of gene regulation in bovine embryos produced by ARTs, and should increase the efficiency of using these techniques in livestock.

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