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Abstract

Imprinted genes play crucial roles in regulating numerous biological processes in mammals, particularly during early embryogenesis, where they determine allelic expression and silencing through epigenetic modifications, thereby governing embryonic and placental growth and development. Aberrant expression of imprinted genes in the placenta and embryo is closely associated with fetal growth restriction, developmental arrest, and thyroid detoxification disorders. Therefore, in-depth investigation into the regulatory mechanisms by which imprinted genes control embryonic and placental development holds significant guiding importance for preventing intrauterine growth retardation, birth defects, and later-life diseases in mammals. This review summarizes the main characteristics of imprinted genes, the erasure and re-establishment of genomic imprints in gonads, epigenetic modifications, and recent advances in understanding how imprinted genes regulate mammalian embryonic and placental development.

Full Text

Regulatory Mechanisms of Imprinted Genes in Mammalian Embryonic and Placental Development

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Abstract: Imprinted genes play crucial roles in regulating numerous life processes in mammals. During early embryogenesis, imprinted genes determine allele-specific expression and silencing through epigenetic modifications, thereby regulating embryonic and placental growth. Aberrant expression of imprinted

genes in the placenta and embryo is closely associated with fetal growth restriction, developmental arrest, and thyroid detoxification disorders. Therefore, in-depth exploration of the regulatory mechanisms of imprinted genes in embryonic and placental development holds significant implications for preventing intrauterine growth retardation, birth defects, and late-onset diseases in mammals. This review summarizes the main characteristics of imprinted genes, the erasure and re-establishment of imprinting in gonads, related epigenetic modifications, and recent research progress on how imprinted genes regulate mammalian embryonic and placental development.

Keywords: imprinted gene; mammalian; embryo; placenta; epigenetic modification

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Imprinted genes typically refer to homologous genes where only one parental allele is expressed while the other is silenced, resulting in differential expression patterns of the two parental alleles in offspring somatic cells. Since their discovery, researchers have conducted extensive studies on the number of imprinted genes in mammals, their regulatory mechanisms, and their roles in modulating various tissues and organs. The expression of imprinted genes in the placenta is influenced by multiple factors including fetal sex, gestational period, maternal age, and delivery mode [?]. As the foundation of life, the developmental status of the placenta and embryo is inextricably linked to postnatal health in mammals. Therefore, exploring the regulatory mechanisms of imprinted genes in placental and embryonic development can provide a scientific basis for modulating postnatal growth and preventing diseases. Accordingly, this review synthesizes literature on the main characteristics of imprinted genes and recent research progress on their roles in mammalian embryonic and placental development, aiming to establish a foundation for systematic investigation of these regulatory mechanisms.

In 1960, Crouse first proposed the concept of genomic imprinting while studying *Sciara* (fungus gnats), discovering that only the maternal X chromosome allele was transcriptionally active while the paternal allele remained permanently silenced [?]. At that time, "genomic imprinting" described paternal-specific chromosome loss involved in sex determination in arthropod species [?]. With advancing research, genomic imprinting now describes parent-of-origin-specific

gene expression determined by epigenetic modifications, and genes exhibiting this phenomenon are termed imprinted genes. Under normal circumstances, imprinted genes express only one parental allele while the other is silenced through a series of epigenetic modifications. Distinct from sex-linked inheritance, genomic imprinting belongs to the field of epigenetics within non-Mendelian genetics. In the imprinting system, genes with paternal allele suppression and maternal allele expression are defined as paternally imprinted genes, whereas those with paternal allele expression and maternal allele suppression are maternally imprinted genes. The genetic theory of genomic imprinting posits that maternally imprinted genes promote fetal and placental growth, while paternally imprinted genes restrict fetal growth [**?**].

The earliest research on mammalian genomic imprinting can be traced to 1983, when McGrath and Solter discovered that parthenogenetic mouse embryos containing two copies of the same parental genome exhibited double expression of one parent' s genes and absence of the other' s. Although these composite embryos could develop briefly, they ultimately died, leading to the speculation that both maternal and paternal genomes are essential for offspring survival [**?**]. Subsequently, mammalian genes including insulin-like growth factor 2 (IGF2) [**?**], insulin-like growth factor-2 receptor (IGF2R) [**?**], and H19 [**?**] were identified in mice. By November 2015, the number of confirmed imprinted genes in humans and mice, including protein-coding genes, non-coding RNA transcripts, small nucleolar RNAs (snoRNAs), and micro RNAs (miRNAs), had reached 100 and 151 respectively, with numbers continuing to rise (http://www.mousebook.org/imprinting-gene-list, http://igc.otago.ac.nz/home.html). As research expanded, imprinted genes were subsequently discovered in pigs, cattle, and sheep, while studies also suggested that egg-laying mammals such as platypus and echidna may lack imprinted genes [**?**].

Main Characteristics of Imprinted Gene Expression

Although imprinted gene expression does not fully conform to classic Mendelian inheritance patterns, it differs distinctly from ordinary gene expression patterns.

Occurring in Gene Clusters

Imprinted gene clusters typically contain multiple imprinted genes and at least one non-coding RNA (ncRNA) imprint. All clusters possess an imprinting control region (ICR), usually 1–5 kb in length, where the ICR from one parental allele is marked by DNA methylation. These differentially methylated regions (DMRs) create differential expression between parental alleles, thereby regulating imprinting throughout the entire cluster. Additionally, each cluster contains at least one ncRNA expressed from the maternal allele and multiple paternal protein-coding genes. Finally, imprinted gene clusters may be regulated through four mechanisms: (1) differential methylation of CpG islands (CpGs) or promoters to form heterochromatin through closed chromosome conformation; (2)

differential binding of silencing factors to cis-acting silencing elements, where binding to unmethylated elements suppresses gene expression; (3) blocking of shared enhancer elements through CTCF binding to insulators [?]; and (4) coordinated regulation of sense gene expression by antisense transcripts combined with methylation of CpGs or promoters.

Temporal Specificity of Expression

While ordinary gene expression levels typically correlate with replication timing in the cell cycle, imprinted genes do not follow this pattern. Instead, they exhibit the distinctive characteristic of asynchronous replication of parental alleles.

Spatial Specificity of Expression

Imprinted genes show imprinted expression in some tissues but biallelic expression in others. Research has found that the paternally imprinted gene solute carrier family 22 member 3 (Slc22a3) exhibits specific imprinting in the placenta during early mouse embryonic development, whereas the maternally imprinted gene solute carrier family 38 member 4 (Slc38a4) is expressed in all mouse tissues except liver and intestine [?]. The paternally imprinted gene growth factor receptor-bound protein 10 (Grb10) is expressed in the mouse brain, while the maternal allele is expressed in nearly all other tissues and organs [?].

Erasure, Re-establishment, and Epigenetic Modification of Imprinting

Imprinting is established during gametogenesis in offspring, representing a dynamic process of DNA methylation that comprises three components: erasure of imprinting in the gonads, re-establishment of imprinting, and maintenance after re-establishment (Figure 1 [Figure 1: see original paper]) [?]. Methylation levels differ significantly between male and female gametes, with eggs showing low methylation and sperm showing relatively high methylation, though both are lower than somatic cells. These differences are believed to be the mechanism underlying gametic imprinting [?].

The first-generation imprinting carried by gametes from parents is maintained during fertilization and cleavage, only to be erased in the gonads through large-scale demethylation from the 8-cell stage to the blastocyst stage.

Regarding re-establishment of imprinting (acquiring the second-generation imprint), current perspectives suggest that paternal imprinting reconstruction occurs before spermatogenesis, while maternal imprinting occurs after oogenesis [?]. Researchers have found in mice that demethylation is completed between embryonic days E12–13. Primordial germ cells (PGCs) migrate from the epiblast to the gonads 7 days after mating, develop into gametes in the gonads by day 10.5, enter meiosis in female germ cells by day 13.5, while male germ cell mitosis is suppressed. During this process, germ cells undergo important

epigenetic reprogramming. On day 8 post-mating, the organism facilitates CpG migration through reduced DNA methylation and histone modifications (likely a passive process) [?]. After migration to the gonads around day 10.5, CpGs undergo active and rapid demethylation, though ICRs retain methylation marks for approximately one additional day. Studies indicate that activation-induced cytidine deaminase (AID) contributes to this second methylation wave, and histone replacement also plays an important role in this active process [?]. Parental imprints are erased during demethylation, demonstrating that parental epigenetic inheritance has minimal direct impact on offspring.

Figure 1. The methylation degree of cells in different stages of embryonic development and its imprinting status [14]. Legend: 5-methylcytosine; PGCs: primordial germ cells; Gametogenesis; Germ cells; Fertilization; Zygote; Morula; Blastocyst; Implantation; Gastrula; Birth.

Regulation of Embryonic and Placental Development by Imprinted Genes

Studies have shown that imprinted genes can regulate both maternal nutrient supply to offspring through the placenta [?, ?] and embryonic growth and development in mice (gene targeting experiments) [?], while also participating in various biological processes in embryonic cells [?]. For example, the imprinted gene solute carrier family 22 member 2 (Slc22a2) encodes organic cation transporters [?], while Kcnq1 and Kcne2 encode potassium ion transporters [?], and specific potassium channel blockers inhibit chorionic gonadotropin secretion in human syncytiotrophoblasts [?], thereby regulating maternal nutrient and metabolite transport. The imprinted gene solute carrier family 38 (Slc38) transporter family primarily regulates sodium-dependent amino acid transport systems in the placenta, with Slc38a4 encoding neutral and basic amino acid transporters. Its isoform Slc38a4/Snat4 has been confirmed in human placenta [?] and detected in rat and mouse placentas [?], suggesting that imprinted genes control nutrient transfer between mother and offspring by regulating amino acid transport across the placenta. The imprinted gene Cdkn1c encodes a cell cycle inhibitor whose expression negatively correlates with vascular endothelial growth factor expression [?], enabling Cdkn1c to regulate angiogenesis in embryonic tissues with rich blood supply and proliferative endometrium through vascular endothelial growth factor modulation. Additionally, studies have found that the imprinted gene Grb10 plays an important role in mediating insulin and insulin-like growth factor regulation of cell proliferation and apoptosis [?]. Furthermore, literature reports that IGF2 serves as the primary mitogenic signal for ventricular cardiomyocyte proliferation [?]. Research has also shown that the imprinted gene Gatm regulates creatine synthesis [?] while participating in embryonic tissue and organ formation. Moreover, at least 25% of imprinted genes encode antisense RNAs (e.g., IGF2R encoding Air), small nucleolar RNAs (e.g., SNRPN encoding HBII-52 and HBII-85), and small RNAs (e.g., Rrl1 encoding miRNA-127 and miRNA-136) [?].

Current understanding of imprinting mechanisms primarily derives from six imprinted regions, including four maternally imprinted regions (IGF2r/Air, IC2/Kcnql, Gnas, and PWS/AS) and two paternally imprinted regions (IGF2/H19 and Dlkl) [?]. Among these, the H19/IGF2, Dlk1-Dio3, and paternally expressed gene 10 (Peg10) imprinting regions are the main regulators of embryonic and placental development.

H19/IGF2 Imprinting Region

The H19 and IGF2 genes form a mutually imprinted region (IGF2/H19) located on human chromosome 11 [?] and mouse chromosome 7. The H19/IGF2 imprinting region is believed to participate in placenta formation and embryonic development. Imprinting restricts H19 expression to the maternal allele, while IGF2 is transcribed exclusively from the paternal allele [?]. The H19/IGF2 imprinting mechanism model (Figure 2 [Figure 2: see original paper]) comprises an ICR, flanking genes, downstream enhancers, CTCF, and a distal chromosome interaction complex controlled by a cohesive complex [?]. Recent experiments have demonstrated that paxillin serves as this interactive complex, regulating long-range interactions between H19 and IGF2 [?]. CTCF binds to the unmethylated maternal ICR and block (protein sequences generated by multiple sequence alignment without gaps), functioning through enhancers positioned at the IGF2 promoter [?]. Paternal methylation of the H19 ICR inhibits CTCF binding, allowing enhancers to activate the paternal IGF2 promoter [?]. Maintaining this imprinting pattern is critical for embryonic cell growth and development [?].

Figure 2. H19/IGF2 imprinting mechanism model [38].

Deletion of the ICR in the H19/IGF2 imprinting region leads to tissue-specific loss in mesoderm [?], suggesting its involvement in embryogenesis. Angiolini et al. [?] found that H19 mRNA upregulates many genes related to cell migration, angiogenesis, and placental blood flow, with H19 knockout causing abnormal hyperplasia in placental layers. Therefore, H19 plays an important role in modulating placental function and embryonic growth, development, and behavioral development. IGF2 transcripts are specifically expressed in embryonic labyrinthine trophoblasts [?], primarily regulating nutrient supply-demand balance between placenta and embryo [?] and participating in compensation of active amino acid transport systems [?]. The IGF2 promoter P0 controls mouse labyrinthine trophoblast cells, and deletion of promoter P0 reduces IGF2 mRNA expression in the placenta and decreases passive diffusion function [?]. Moreover, serum concentration and mRNA expression levels regulated by the paternal IGF2 gene positively correlate with infant birth weight [?]. Fetal growth restriction is also associated with the effects of 5-methylcytosine at the DMR of placental and umbilical cord IGF2 genes [?, ?], indicating that IGF2 participates in embryonic blood flow and nutrient supply.

Dlk1-Dio3 Imprinting Region

The Dlk1-Dio3 imprinting region is located on human chromosome 14, mouse chromosome 12, and sheep chromosome 18, showing high conservation among these three mammalian species. This region contains three paternally expressed protein-coding genes—Dlk1, paternally expressed gene 11 (Peg11), and Dio3—along with several maternally expressed non-coding transcripts such as maternally expressed gene 3 (Meg3)/Gtl2 (gene trap locus 2), miRNAs, and C/D snoRNAs [?]. In the 1980s, scholars discovered that uniparental diploid mice obtained through hybridization experiments all died perinatally with developmental defects in multiple organs including placenta, cartilage, osteogenic tissue, and skeletal muscle [?], suggesting that the Dlk1-Dio3 imprinting region is crucial for regulating embryonic and placental growth and development in mice. Peg11 is primarily expressed in embryonic and placental tissues [?] and participates in information transfer between placenta and embryo in eutherian allantoic placentas [?]. Dio3 encodes type 3 deiodinase to degrade thyroid hormones. Studies have found that type 3 deiodinase is highly expressed in placentas and uterine tissues of healthy mammals, likely to protect embryonic tissues from damage caused by excessive thyroid hormone concentrations [?]. Additionally, newborn mice lacking the Dio3 gene develop central hypothyroidism later in life and even develop thyrotoxicosis [?]. Gtl2 is expressed as early as mouse embryonic day E3.5 in an imprinted manner [?]. Knockout of a 10 kb region spanning the paternal chromosome Gtl2 DMR to exon 5 causes severe growth retardation and high perinatal mortality [?], while knockout of a 5 kb region from exon 1 to exon 5 on the maternal chromosome completely suppresses downstream long non-coding RNA expression and also leads to perinatal death [?], indicating that non-coding RNA transcripts within the Dlk1-Dio3 imprinting region participate in regulating placental and embryonic growth. After Meg3 knockout, vascular endothelial growth factor and its type I receptor expression increase significantly in mouse embryonic brains [?], with increased cerebral blood vessels [?], demonstrating that Meg3 participates in neural and metabolic regulation and may play a role in tumor suppression [?].

Peg10

Peg10 is located on human chromosome 7, mouse chromosome 6, and bovine chromosome 4. Its expression is primarily distributed in placenta, ovary, testis, heart, lung, brain, and other tissues, playing important roles in labyrinthine trophoblast formation, embryonic development, gestational metabolism, and establishment of normal pregnancy immune tolerance. Loss of DNA methylation at the Peg10 gametic DMR reduces embryonic developmental capacity and decreases labyrinthine trophoblast volume [?]. Reports indicate that abnormal Peg10 methylation can cause abnormal placental development in cloned cattle and increase early abortion risk [?]. Peg10 knockout leads to placental developmental defects [?], embryonic abnormalities, absence of embryonic glioblasts and labyrinthine layers, and even early embryonic death [?]. Main-

taining Peg10 at appropriate levels can promote synthesis of progesterone and chorionic gonadotropin, facilitating placental implantation and embryonic development. Increased Peg10 expression during early and mid-pregnancy is associated with early decidual and villous trophoblast differentiation, development, and placenta formation, with the Peg10 ICR considered a key regulator of mid-pregnancy placental function [?]. Decreased Peg10 expression in late pregnancy [?] is closely associated with placental calcification and glucose transport [?]. Abnormal Peg10 expression in late-pregnancy placental tissues not only reduces placental efficiency and fetal-to-placental weight ratio [?] but also increases risks of preeclampsia and intrauterine growth restriction [?].

Regulation by Other Imprinted Genes

Paternally expressed gene 1 (Peg1) is located on human chromosome 7 and expressed in all fetal tissues [?]. Experiments show that Peg1 expression in placental tissue does not depend on methylation level changes in the promoter region but may involve regulation by the paternally expressed non-coding RNA Mest1t1/Peg1-As between two Peg1 promoters during growth and development [?]. Paternally expressed gene 3 (Peg3) is located on mouse chromosome 7, and Peg3 knockout reduces placental volume [?]. Reports indicate that mice with Peg3 mutations have smaller placentas and lower birth weights [?], while other studies have found that high Peg3 expression in human placenta is influenced by promoter methylation and positively correlates with infant birth weight [?]. L3mbtl1 is a paternally expressed gene located on human chromosome 20, expressed in early germ cells and germline stem cells. L3mbtl1 deficiency inhibits germline stem cell chromatin transcription and affects embryonic stem cell differentiation into trophectoderm. Downregulated L3mbtl1 expression in early-pregnancy placental tissues may increase risks of miscarriage and embryonic arrest [?]. The Mash2 gene can regulate trophoblast development, which is crucial for placental growth [?]. Genes in the Kcnq1 cluster are only imprinted in the placenta, maintaining imprinted expression in embryos mutated by DNA methyltransferase 1 (Dnmt1) [?], with loss of the Kcnq1 gametic DMR closely associated with trophoblast giant cell expansion [?]. Phlda2 gene expression is upregulated in placentas of infants with intrauterine growth restriction [?], suggesting its role as a negative growth regulator. In early mouse embryos, Pgc7/Stella can protect 5-methylcytosine from oxidation catalyzed by TET (ten-eleven translocation) proteins [?], indicating that Pgc7/Stella may regulate imprinting status during embryonic development by modulating DNA methylation [?].

In summary, mammalian placental and embryonic growth and development are regulated by multiple imprinted genes, whose functional abnormalities can lead to restricted embryonic development. The expression patterns of imprinted genes in placenta and embryo differ significantly from those in adult tissues, demonstrating the crucial regulatory functions of imprinted genes in mammalian placenta and embryo. However, current research primarily focuses on humans

and mice, with most findings based on these two models. Strengthening research on imprinted genes in embryonic and placental development of agriculturally important livestock (pigs, cattle, sheep, etc.) will help improve their reproductive performance, reduce abortion losses, and decrease birth defects in offspring. Additionally, except for early-discovered imprinted genes such as H19, IGF2, and IGF2r—whose sequences, ICRs, and DNA methylation status have been thoroughly studied—the imprinting mechanisms of most other imprinted genes remain unclear. Research on interactions between imprinted genes and the placenta/embryo is also limited. Addressing these gaps, future research hotspots will likely include complete identification of imprinted genes in different mammals, mechanisms and interactions among different imprinting clusters, and the regulatory roles and mechanisms of different imprints in reproductive organ development.

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