Genomic Imprinting—The Story of the Other Half and the Conflicts of Silencing

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Abstract: Genomic imprinting is an epigenetic mechanism that produces functional differences between the paternal and maternal genomes and plays an essential role in mammalian development and growth. There are a number of genes in our genomes that are subject to genomic imprinting where one parent’s copy of the gene is expressed while the other is silent. Silencing of one allele predetermines that any function ascribed to that gene are now dependant on the single active copy. Possession of only a single active allele can lead to deleterious health consequences in humans. If imprinted genes are crucial in mammalian development, one would also expect mutations in these genes to cause diseases. Since imprinting is an epigenetic mechanism, mistakes in maintaining epigenetic mark also cause imprinting disorders. Here we in this review focus on the current understanding of this unique genetic mechanism more than two decades after the first description of the imprinting phenomenon was given by McGrath and Solter. Although the possible molecular mechanisms by which imprinting is imposed and maintained are being identified, we have a long way to go in understanding the molecular mechanisms that regulate the expression of these oddly behaving genes, the function of imprinting and the evolution. Post genomic technologies might ultimately lead to a better understanding of the ‘imprinting effects’.

Keywords: imprinting; epigenetic; DNA methylation; histone modifications; non-coding RNAs; evolution

The first description of the imprinting phenomenon was given by McGrath and Solter in 1984[1] but the term ‘imprinting’ was actually used in a cytogenetic context by Helen Crouse in her study of chromosome elimination in Sciara[2-4]. It was later expanded by Surani et al.[5] in 1984 to describe the process by which some genes are presumably modified during gametogenesis in such a way that only paternal or the maternal alleles are expressed after fertilization or in other words, we are functionally hemizygous for imprinted genes. Although both copies of the gene are present, yet one is maintained in an inactive condition initiated in the germline of one parent. The latter is referred to as the ‘imprinted copy’. The mechanism of imprinting is largely unknown and is under intensive investigation. We are still in dark as to why imprinting exists as it renders the organism functionally haploid for these loci. This induction of functional haploidy has markedly increased vulnerability to many diseases such as cancer and neurobehavioral disorders. In addition to eutherian and metatherian mammals, imprinting has been reported in angiosperms as well[6,7]. Imprinting based regulation of entire chromosomes has long since been known in both insects (paternal genome elimination) and mammals (Non-random X-inactivation).

A gene may show its imprinted character only in certain cells during a specific time in development. There a gene can behave as imprinted in one tissue and be biallelically expressed in another[8]. At present

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80 of 30,000 genes in humans are known to be imprinted. The identification of further imprinted genes and the analysis of the control of their expression should eventually lead to the complete understanding of the mechanisms underlying genomic imprinting, its deleterious consequences, and the evolution of this unique form of gene regulation.

1 Establishment, Maintenance and Erasure of Imprinted Genes

The imprint mark is set during gametogenesis when the germline cells in the testes or ovaries are formed and the imprinted traits pass on to the progeny via the sperm and egg at sexual reproduction[9]. Effects of autosomal genomic imprinting are indifferent to the actual sex of the offspring because the parental origin of the allele is crucial. Traits influenced by maternally expressed genes are inherited down the matriline, whereas traits dependent upon the paternally expressed genes are inherited down the patriline[9]. The parental gametes must contain information that distinguishes the ‘sex’ of the imprinted genes for appropriate expression in the next generation. These marks, which differ within the offspring because the parental origin of the allele is crucial. Traits influenced by maternally expressed genes are inherited down the matriline, whereas traits dependent upon the paternally expressed genes are inherited down the patriline[9]. The parental gametes must contain information that distinguishes the ‘sex’ of the imprinted genes for appropriate expression in the next generation. These marks, which differ within the offspring because the parental origin of the allele is crucial. Traits influenced by maternally expressed genes are inherited down the matriline, whereas traits dependent upon the paternally expressed genes are inherited down the patriline[9].

ⅰ. Erasure requires passage through gametogenesis.

ⅱ. As far as the expression status of the imprinted genes is concerned, these can be on, off or monoallelically on. The biallelic expression of the imprinted genes does not mean that the imprint is erased. It may only mean that the mechanism that recognizes the imprint is not operational[8].

Once the imprints are founded, these markings must also be maintained in somatic cells throughout all subsequent cellular divisions so that the transcription machinery can appropriately interpret the information to effect accurate expression.

2 Mechanisms of Imprinting

Igf2 (paternally expressed) and Igf2r and H19 (maternally expressed) were the first imprinted genes, definitively identified in mouse[10,11]. Since then a number of imprinted genes have been added to the list by the advent of molecular and computational screens and large-scale microarray studies[12]. Currently, 100–200 imprinted genes are known in mammals and out of this, more than 70 are known to exist in mouse and a similar number in humans[13]. However, much effort has gone into determining the molecular and cellular mechanisms underlying the imprinting. Some of the molecular mechanisms known to imprint the genes are as follows:

2.1 DNA methylation

The imprinted domains of the two parental chromosomes carry different marks known as epigenetic modifications. These epigenetic modifications include DNA methylation at CpG dinucleotides, which helps to distinguish two parental chromosomes by the transcriptional machinery. Local sites with DNA methylation patterns that differ between the two parental chromosomes have been identified in several studies, and these differently methylated regions are thus implicated in the control of gene expression[14]. The differences caused by these specific tags, include germline imprints that are imposed during gametogenesis, and seem to be critical for setting up heritable allele-specific imprints after fertilization. In general, it seems that egg genome is under methylated in comparison to the sperm genome and in turn, both are less methylated than the DNA in somatic cells[15,16].

In majority of the cases, the imprinted genes tend to be organized into clusters and replicate asynchronously. This accounts for the shared regulatory elements involved in imprinting control. These shared regulatory elements can extend their effects over large
distances. For at least five of the imprinted domains, an imprinting control region (ICR) has been identified that regulates the allele-specific activity of imprinted genes in the cluster. ICRs usually carry a germline derived methylation imprint. For two of these regions ICR is methylated on the paternal chromosome and unmethylated on maternal chromosome, the other three carry maternally inherited methylation mark. Different ICRs do not resemble each other in sequence. The common feature they share is that they have a relatively high level of CpG dinucleotides and have simple sequence repeats in the vicinity. At present, we do not have a full understanding of the mechanisms of domain wide imprinting control and this may be different for different domains[17]. The ICR is also referred to as ‘differentially methylated region’ (DMR) and ‘differentially methylated domain’ (DMD). This corresponds to a 2 kb DNA fragment and is characterized by nuclease hypersensitivity[18]. The nucleosomes are loosely packaged in these hypersensitive sites.

An insulator model has been proposed for the regulation of the Igf2-H19 domain. Here the ICR functions as a methylation sensitive binding domain for the zinc-finger binding protein CTCF. In this case, ICR is located between Igf2 and H19 loci. When unmethylated on the maternal chromosome it binds CTCF and insulates Igf2 from downstream-shared enhancers, allowing expression from H19. A non-coding RNA is produced by the H19 transcription whose function is unknown. On the methylated paternally inherited ICR, CTCF cannot bind and hence enhancers are able to drive expression from the paternally inherited Igf2 allele[16] (Fig. 1).

Distinct enzymes involved in de novo and maintenance of DNA methylation have been identified and shown to play important roles in the establishment and heritable maintenance of methylation imprints.

2.2 Non-coding RNAs

Recent studies have indicated that non-coding RNA molecules might have a role to play in genomic imprinting. There are a significant number of imprinted genes that are transcribed to give a non-coding RNA. Non-coding RNA model for imprinting control has been proposed to explain imprinting at Igf2r and Dl K1-Gt12 imprinted loci[19,20]. A germline derived ICR has been identified within an intron of Igf2r gene. When unmethylated on the paternally derived chromosome, the ICR derives the expression of a transcript antisense to the Igf2r. This anti sense transcript seems to be required in cis of Igf2r and the other members in the cluster. The methylated maternal chromosome does not express the antisense transcript and thereby all the genes in the cluster go ahead with the transcription. Some classes of imprinted non-coding RNAs appear to have repressive effects only in trans[20].

The non-coding RNAs include antisense transcript, small nucleolar RNAs (Sno RNAs), micro RNAs, pseudo genes and other RNA of unknown function. The mechanisms by which these non coding transcripts operate and convey the imprinting signal is yet to be established although it is known that imprinted and random x-inactivation is associated with coating of the chromosome with xist RNA[21].

The role of non-coding RNAs in the regulation of mammalian gene expression is one of the most exciting challenges facing epigeneticists today[22].

2.3 Micro-imprinted domains and retro transposed genes

Most of the imprinted genes seems to be clustered but there are a number of imprinted genes that are isolated or in other words not associated with a cluster e.g. ARHI, Nap1 ls, TCE B36 and NNAT. The latter have been referred to as ‘singleton’. One recent finding is that these singletons have been found to reside within an intron of other protein coding genes, to form the so-called ‘micro-imprinted domains’. It remains to be seen whether this pattern has any potential for co regulatory activity for the host and the in-
Fig.1 The diagram shows a chromosome carrying two imprinted genes D & E

D is subjected to imprinting in the female germline and E in the male germline. D is imprinted when present on a maternally inherited chromosome and E is imprinted when present on a paternally inherited chromosome. The chromosome may pass through the male and female germline in successive generations: a man may hand over a chromosome inherited from his mother and a woman can transmit a chromosome, which she received from her father. Therefore, a mechanism must be present which erases the old imprint from the germline prior to establishing a new sex-specific imprint.
serted imprinted genes. In mouse, the micro-imprinted domains are paternally expressed. It is not known whether maternally expressed inserted genes exist or not[9].

In addition to this a few imprinted genes seem to have originated on account of a retrotransposition event[23]. In such cases, genes might acquire the imprint of the flanking region[24] or alternatively the gene might carry the imprint regulatory elements along with it during the transposition event[25].

The involvement of transposons in genomic imprinting is controversial. Recent studies on Arabidopsis at the MEDEA locus by Spillane et al.[26] show that transposons and tandem repeats are not involved in the control of genomic imprinting.

2.4 Histone modification & chromatin modeling

Histones are a dynamic component of chromatin. Individual histone molecules get modified as a result of modifications that occur to their individual amino acids especially at their tails. These include adding acetyl groups (CH₃CO) to lysines, phosphate groups to serines and methyl groups to lysines. These specific modifications can either stimulate or inhibit gene expression. Recent studies have shown that imprinting is controlled epigenetically by histone modifications and chromatin remodeling, which in turn can be modified by environmental factors or nutrition[27]. For example, methylation of lysine-4 in H3 is associated with active genes and methylation of lysine-9 in H3 is associated with inactive genes.

Pedone et al.[28] have shown an association between H19 bi allelic chromatin structure and histone acetylation. Their results are based on transformed mouse fibroblast cell line, where the first exon of the H19 gene has low levels of N-terminal lysine acetylation on the paternal allele. The allele-specific gene silencing in H19 is in part mediated by hypermethylation and histone deacetylation. In addition to this the paternally H19 silencing has been linked to methylation of histone H3 at lysine 9 at the N-terminal region. This is catalysed by the histone methylase suv 39HI. This label (H3 lysine methylation) can be recognized by heterochromatin protein 1 (HP1), a protein which has an association with heterochromatin formation and silencing. The histone H3 modification leads to repressive chromatin configuration at the ICR and its surrounding area in the paternal H19 allele[18]. Therefore, there is no reason to doubt the contribution of histone modifications that in turn leads to change in chromatin configuration, and genomic imprinting.

3 Imposition of Imprinting in Gametogenesis

The previous section have discussed as to how the differential methylation long-range regulatory elements and chromatin structure play a key role in the mechanism of imprinting. However, this does not explain the origin of parental differences in imprinting. There must be some mechanism that distinguishes between maternally and paternally inherited alleles: as chromosomes pass through the male and female germ lines: they must acquire some imprint to signal a difference between paternal and maternal alleles in the developing organism.

At the same time, there must be a mechanism to erase the imprints, when required, for instance a man passes on an allele, which he had acquired from his mother (Fig. 2). It seems that the old imprint is totally erased at an early time-point in the primordial germ cells (PGCs) of the developing foetus[6]. Researchers have reported that when the developing germ cells are entering the gonads, there is an apparently complete eradication of DNA methylation between 10.5 and 12.5 days post-coitum in mice[29].

After the imprint is erased in the PGCs, parent specific imprint is re-established during gametogenesis. This occurs in sperm postnatally within diploid gonocytes prior to meiosis and within oocytes arrested at the diplotene stage of meiosis[30]. A novel
Fig. 2  Schematic illustration of the $Igf2/H19$ domain on the two parental chromosomes, where the $H19$ gene is maternally expressed and $Igf2$ is paternally expressed under normal conditions

The differentially methylated region is located upstream of $H19$ gene. Enhancers are shown as triangles, downstream of $H19$. In the maternal allele the zinc-finger nuclear factor CTCF interacts with unmethylated DMR and provokes a maternal specific enhancer blocking the activity of DMR and allowing only $H19$ expression. In contrast, on the paternal allele, the CTCF cannot bind because of DMR methylation. As a result the enhancer blocking activity is lost and the downstream enhancers are able to drive expression from paternally inherited $Igf2$ gene over a long distance. Moreover, DMR and $H19$ gene are methylated and thereby $H19$ gene gets silenced on the paternal allele. (Drawing not drawn to scale)

male germ-line specific zinc-finger DNA-binding protein may play vital role in the process. This protein known as BORIS (brother of the regulator of imprinted sites), has the identical zinc-finger domains as CTCF (insulator protein involved in reading imprinting marks in soma)$^{[31]}$. BORIS and CTCF bind to the same DNA sequence on account of having identical zinc-finger domains. The two proteins might have evolved because of a gene duplication event. The expression of BORIS in testis is normally limited to the discrete period of spermatogenesis when the imprints are erased. It is hypothesized that BORIS may facilitate de novo establishment of the methylation imprints while CTCF maintains or reads these imprint marks pre- and postnattly$^{[31,32]}$. The DNA features that direct acquisition of methylation imprints are not clear.

In the oocytes, methyltransferases belonging to Dnmt3 family are required to set maternal specific methylation patterns for imprinted genes in mice$^{[33]}$. Dnmt3a, Dnmt3b and Dnmt3L seem to be operational here. Although Dnmt3L lacks a methyltransferase activity, yet it is essential. It probably provides sequence specificity for the other de novo methyltransferases, Dnmt3a and Dnmt3b, by directing them to the DNA regions requiring maternal methylation imprints$^{[33]}$.

Immediately after fertilization, the zygote faces a wave of global demethylation event, first in male pronucleus, followed by maternal pronucleus. Imprint marks that were established in the gametes must resist this demethylation process. Remethylation of the diploid genome occurs during gastrulation. These imprints are then maintained throughout the life span of the individual$^{[6]}$. The life cycle of the imprint (from germ line to embryo) is very complex and the details
of the mechanism involved in establishment and era-
sure of imprints are not very clear till date.

4 Evolution

The existence of the imprinted genes—together
with when in the past, why, and how they became
imprinted—is a mystery that continues to intrigue
evolutionary and developmental biologists and also
clinicians looking for answers for “non-Mendelian”
inherited human genetic disorders. While most studies
of mammalian imprinting have investigated the phe-
nomenon in mice or humans, recent studies involving
other diverse mammals, including monotreme (egg-
laying), marsupial (offspring carried in a pouch), and
eutherian (“placental”) have helped to unravel the
origins and mechanisms of the unique family of im-
printed genes. Recent focus on the physical structure
and biochemistry of imprinted chromatin domains is
also providing an image of parental differentiation
within the genome.

Noted biologists Randy Jirtle and Keith Killian
looked at marsupials and then at the platypus—an
egg-laying mammal—to see where imprinting
arose. They found that imprinting is absent in the
platypus, at least for the genes they looked at, but was
present in marsupials. Thus, imprinting appears to
have arisen more or less coincident with the origin of
live birth, before the common ancestor of marsupials
and placentals (http://www.edge.org/3rd_culture/haig/haig_index.html).

5 Parent-Offspring Conflict Theory

One theory about origin and importance of im-
printing which is now being accepted is that of par-
ent-offspring conflict theory by Robert L. Trivers.
According to this theory, the genetic interests of par-
ent and offspring are different, therefore the offspring
would manipulate the parents to ensure survival and
vice versa. This theory of conflict has been sup-
ported by David Haig’s work on genetic conflicts
during pregnancy. According to which the fetal genes
would be selected to extract more nutrients from the
mother than what is advantageous for the mother. The
placenta secretes certain allocreine hormones so that
the fetus has access to more glucose from the mother.
These make the mother insensitive to the production
of insulin. To counter act this, the mother-placenta
produces insulin degrading enzymes. Gestational
diabetes develops if the mother is unable to balance
this assault by the fetus developing resistance to
insulin. This parent offspring conflict theory is
currently being extended to complex social structures—
polygamy and monogamy which are/may be
controlled by multiple genetic and environmental
factors.

While pregnancy is considered a harmonious
process it is in fact a battle for resources between the
mother and her offspring. This is probably the reason
as to why only 22% of pregnancies reach the full term
and that while it is initially fetal-mother conflict later
on it is mother-fetal conflict. Apart from gestation-
al diabetes which develops when the mother is unable
to balance the resources there are other metabolic
disorders which arise in the mother during pregnancy
viz, morning sickness due to high level of hCG-hor-
mone which inhibits menstruation and preclampsia
causing hypertension.

For instance it is believed that the mother re-
leases certain sedatives in her breast milk like
benzodiazepines. This helps mother to keep the new
born quiet. In addition, the milk is relatively difficult
to be digested by the fetus and researchers suggest
that this strategy helps the mother to conserve energy
for other activities including next pregnancy.

The parent offspring conflict theory states that
because of multiple paternity the offspring’s are less
related to each other and more to the mother. In the
developing fetus, there is a conflict between the
paternal and the maternal genes. The paternally
derived genes try to extract greater resources from the

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mother. In turn, the mother tries to ensure equal distribution to all her offspring. In human beings, this is apparent in Prader-Willi syndrome where both the copies of chromosome 15q 11-13 are maternally inherited and the infant has a feeble cry and displays poor sucking. However if both the copies of the same chromosome are paternally inherited the infants are active and display strong sucking. Hence, the effects/activity of genes is dependent on whether they are maternally or paternally derived (http://en.wikipedia.org/wiki/Parent-offspring_conflict).

There is another hypothesis called ‘Ovarian time bomb’ (OTH) given by Varmuza and Mann [38] which states that imprinting evolved in mammals to prevent spontaneous development of unfertilized eggs and also trophoblastic disease of the ovaries.

The other hypotheses for the origin of imprinting are X-linked sex-specific selection (XSSH) and sexually antagonistic selection (SASH) [23].

For larger offspring to survive, especially in seed plants selection favours the offspring to acquire more resources from the mother [39]. However, selection may also favour the mother to allocate all her resources among her offspring. In addition, if there are several paternities between or even within broods there will be a conflict between the maternal and paternal genomes where selection usually favours the paternal genomes with regards to resource acquisition. With mathematical models supporting the concept of evolution of imprinting due to conflict over resources, it is speculated that through selection an allele can invade population if that allele augments the growth of offspring when paternally inherited and not maternally [40].

There are many reasons to believe that the sequence evolution of imprinted and non-imprinted genes is/maybe different. However, Spencer comments that though the expression of imprinted genes is non-Mendelian, their inheritance is normal. Therefore their population size should be the same as non-imprinted autosomal genes and the force of genetic drift is unaffected by imprinting. However, there should be differences in the effect of selection and mutation [41]. For example, lethal mutation in an imprintable gene will be hemizygous and when expressed will be similar to dominant recessive mutations in non-imprintable genes [42].

Experimental research concerned with testing the theory that conflict for resources has created an antagonistic coevolution between growth enhancers and suppressors. In addition, this conflict provided the conditions for the evolution of imprinting, and the conflict is still driving the evolution of imprinted genes.

If antagonistic coevolution was the driving force of evolution of imprinted genes, then it was suggested that there should be rapid rates of evolution in imprinted genes [43,44]. The evidence of this came from genomic sequence data of a number of unknown imprinting status genes in mammals like placental lactogenes 1 and 2, growth hormone, growth hormone releasing factor and prolactin, involved in maternal-fetal condition, show high rates of sequence evolution [45]. However, a comparative study of 22 imprinted genes in mouse and rat showed no rapid sequence evolution in comparisons with non-imprinted genes. Detailed studies of an imprinted gene-Igfr2 showed that the signal sequence (the part that controls the cellular localization) is evolving more quickly than that of non-imprinted genes, at a rate comparable to the rapidly evolving genes of the immune system [44,46].

Thus, it was suggested that the signal sequence concerning the cellular localization of Igf2r may be involved in antagonist coevolution [46]. It is suggested that under antagonistic coevolution, the imprinted genes may have lost their introns resulting in fewer and smaller introns due to selection for rapid transcription [47].

6 Conclusion

Genomic imprinting—an epigenetic modifica-
tion that inactivates one of the parental alleles after fertilization is currently under intensive investigation. How the imprints are read, and the message converted into activation or inactivation of a particular gene is not known. Recent years have seen unraveling of possible molecular mechanisms by which imprinting is imposed, regulated and maintained. Some of the common themes are becoming apparent i.e. the role of DNA methylation, histone modifications, chromatin modeling, transposition events and the function of non-coding RNAs. Methylation is a vital DNA modification that seems to be important for the regulation of many cellular functions including imprinting\cite{47,48}. In addition to this, insulator and antisense models have been suggested though not proven.

Depending upon whether a gene is to be expressed or silenced, specific tags are attached to the histone tails and the chromatin gets remodeled accordingly. This is another mechanism, which seems to mediate the parent-of-origin effect. As far as the role of non-coding RNAs is concerned to what extent, the genomic imprinting is controlled by non-coding RNA remains to be determined. It remains possible that RNA systems might provide solution to a wide range of previously intractable questions surrounding gene regulation; including genomic imprinting. Some genes have been shown to get epigenetically silenced when transposons get inserted in their vicinity\cite{49}. Role of transposons in imprinting needs to be further researched.

It would be interesting to investigate non-mammals for imprinted genes. It would also be interesting to see the differences in patterns of imprinting at a single locus in different species and if they have any relation to multiple paternities. The genetic conflict theory and other hypothesis like the ovarian time bomb\cite{38} have to be thoroughly investigated\cite{50}. These hypotheses are weak as they are limited to explaining selection in terms of growth enhancers and suppressors\cite{42}. Species level diversity should also be taken into account while studying evolution on imprinted genes.

Researchers have engineered chromosomal rearrangement in mice such that both the copies of chromosomes are inherited from the same parent. They have also looked at mice with reciprocal and Robertsonian translocations in their efforts to misexpress the imprinted genes\cite{12}. Other approaches including systemic differential expression and methylation and sequencing might be useful in identifying new imprinted genes. The use of microarrays together with chromosome rearrangement can help us in comparing the parent and offspring chromosomal transcripts\cite{12}.

Linking phenotype and genotype can help us in understanding not only the mechanism of imprinting but also developmental pathways. However, it is important to note that not all imprinted genes express a phenotype, therefore understanding the selective evolution process of imprinting and the bystander effect will amount to greater comprehension of the underlying mechanism of imprinting. A good model would be the use of knock out mice to understand isolated phenotypes of imprinted genes. It is imperative to discern the ‘imprinted gene control’ to understand genetic human diseases/disorders associated with imprinting\cite{12}.

The questions, which remain to be answered, are: Do we really need imprinting? Can we do away with imprinted genes? Advancements post genomics can help unravel the mysteries of evolution of imprinting. To some it maybe playing God but it would be interesting if we can predict this phenomenon and use it to our advantage. However, before we get to that stage a lot of research is necessary.

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Anjana Munshi et al.: Genomic Imprinting—The Story of the Other Half and the Conflicts of Silencing


基因组印记研究进展

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摘要：基因组印记是由于父源或母源的等位基因受到“标记”而发生的不符合孟德尔遗传定律的特殊遗传现象。父源或母源的等位基因通过某种特异的基因修饰机制，如DNA甲基化，非编码RNA的调节作用和组蛋白修饰等，抑制另一拷贝的表达。哺乳动物中的基因印记影响着其生长发育，正常印记模式的改变在临床上会引起许多疾病。文章总结了自印记现象被发现后十几年来的研究进展，包括印记的发生机制、发生途径、进化方式和起源理论。目前对基因印记的理解还不完善，后基因组技术的发展也许能够促进对其分子机制的进步揭示。

关键词：印记；表观遗传学；DNA甲基化；组蛋白修饰；非编码RNAs；进化

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