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Review

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

Anjana Munshi①, Shanti Duvvuri

Department of Genetics, Shadan PG Centre for Biosciences, Khairtabad Hyderabad 500016, *India*

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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① Corresponding author. E-mail: durani65@yahoo.co.in; Tel: +91-040-2776 2776

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 on each of the two inherited sister chromatids, must be erased in the germ cells of each generation and then re-established such that the profiles of these cells affect the sex of individual in which they reside[6].

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