NON-MENDELIAN INHERITANCE: GENOMIC IMPRINTING

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ABSTRACT

Genomic imprinting is a form of non-Mendelian inheritance. It refers to a parental-specific difference in the behaviour of homologous chromosomes or loci. Genes are expressed from two alleles; one maternal and one paternal. But in minor cases, genomic imprinting causes the differential expression of a gene according to its maternal or paternal origin. In this paper, we will discuss examples and the possible molecular mechanisms of imprinting.

Key Words: Genomic imprinting, Non-Mendelian inheritance, Methylation

INTRODUCTION

Progress in molecular techniques has given us some of the most interesting scientific insights on the inheritance of gene expression. With every new data, mechanisms other than Mendelian Inheritance are being discussed and we are being acquainted with new terms. In the last couple of years, in addition to Mendelian inheritance, the mechanism of a epigenetic inheritance known as genomic imprinting has been the focus of interest.

Mammalians have two sets of chromosomes, each set inherited from one parent. There are two copies of each autosomal chromosome. Normally both copies, the paternal and maternal alleles of genes are expressed equally. According to a new concept, a mechanism named as "genomic imprinting" the allele-specific expression of a gene, depends on whether the gene is inherited from the father or mother. There are functional differences between the maternal and paternal genomes. There is a chromosomal memory through which the chromosome remembers its parental origin. Genomic imprinting, implies that the phenotype observed for a particular gene varies, depending on the sex of the parent from which the gamete containing that gene is originated (1-4).

The term "imprinting" was first used in 1930, by K.Lorenz to describe observations about animal behavior (5). He described changes in phenotypical behavior by stating offspring were "imprinted" to act in a certain way. Later in 1960 H.V. Cruse and in 1989 C. Sapienza used this term to describe a form of chromosomal behavior which was identified in the homopteran scale insect Sciara. Embryos of the Sciara that are triploid for the X chromosome, having two paternal and one maternal copy; inactivate or eliminate one or both paternal copies at the eight-cell stage. In contrast the single maternal X chromosome is always retained in an active form. In 1986 Surani used the term genomic imprinting to describe the functional differences between the maternal and paternal genoma resulting in the differential expression of parental alleles (1).

The different observations that are referred to as genomic imprinting fall into four classes which can be summarized as the following (6):

1- Differential phenotypic effects of parental alleles: The best examples for this group are parthenogenetic (gynogenetic) and androgenetic embryos (7). In mice it is possible by pronuclear transplantation to construct zygotes in which all nuclear genes both set of haplaid chromosomes are derived entirely from either the mother or the father. Those with only paternally derived chromosomes are called androgenetic embryos while, those with two sets of maternally derived chromosomes are called gynogenetic embryos (5). Both types of embryos are morphologically and functionally different from each other. Androgenetic embryos have relatively normal development of membranes and placentas but very poor development of embryonic structures; conversely, the gynogenetic embryos have relatively good embryonic development but very poor development of placenta and membranes. Both conditions are lethal for the embryo (8). From these pronuclear transplantation experiments it is concluded that the paternal genes are responsible for the development of the placenta and membranes,

while maternal gene expression is mainly responsible for embryonic development. There has been similar examples described in humans (9). Hydatidiform mole, triploid pregnancies, Uniparental Disomy (UPD), Prader-Willi Syndrome (PWS), Angelman Syndrome (AS) and Beckwith-Wiedemann Syndrome (BWS) can be given as examples for differential phenotypic effects of parental alleles in humans. Hydatidiform mole is a tumor characterized by a severe hyperplasia of cytotrophoblast in the placental tissue. Most complete moles are diploid and karyotypically normal but usually all chromosomes are of paternal origin (9). Cytogenetic studies of spontaneous abortions have shown that at least 50% of first trimester pregnancy loss results from chromosomal aberrations. Uniparental disomies and autosomal disomies make up much of this 50%. Uniparental disomy is the condition that arises when both homologues of a chromosome pair originate from the same parent in a diploid offspring (10). As a result of Robertsonian or reciprocal translocations both copies of a whole chromosome or part of the chromosome may be derived from one parent resulting in UPD. Experiments done on mice have shown UPDs involving a parental gene set will end up in phenotypically large offsprings, while UPDs involving a maternal set of genes will end up in phenotypically small ones (3,5,11). PWS Syndrome and the AS can be examples of a UPD-like genomic imprinting in humans. Although there are phenotypic differences between both syndromes, they both have a similar deletion at the same gene loci (12). The deletion 15q11-13 has been shown by DNA markers to be on the paternal allele in PWS(13). The syndrome is characterized phenotypically by marked hypotonia in infancy, moderate developmental delay, obesity with hyperphagia beginning in early childhood, hypogonodotrophic hypogonadism, small hand and feet (2,4,5,11,12). Angelman Syndrome is a very different clinical disorder and is also associated with deletions of region 15q11-13, indistinguishable from those in PWS except that they occur on the maternal chromosome. Clinical features of the disease include, unusual and frequent laughter, a happy disposition, bizarre repetitive symmetrical ataxic movements, a specific face with a large mouth, red cheeks, mental retardation and rarely observed seizures (5). Another genetic syndrome involving the 11p15.5 loci is Beckwith-Wiedemann Syndrome. In this syndrome there is a duplication of the 11p15.5 loci on the paternal chromosome. So there are two paternal chromosomes and one maternal chromosome; as a result we end up with a trisomy of this genetic region. Clinical phenotype is characterized by numerous congenital abnormalities, including examphalos (umbilical sac containing parts of the gut and liver), macroglossia (large tongue) and gigantism. Also the association with embryonal tumors is of considerable interest (9,11,12). It should be remembered that the 11p15.5 chromosomal loci is thought to have some role in certain kinds of cancer.

2- Monoallelic expression:

The phenomenon of genomic imprinting has been, and still is the topic of many scientific studies. Today six endogenous imprinted genes are indentified in mice (14):

Igf2 (Insulin-like growth factor 2)
Igf2r (Insulin-like growth factor 2 receptor)
H19 (codes for embryonic RNA)
Snrpn (codes a part of a ribonucleoprotein that catalyzes RNA splicing in the brain)
ins 1 (a functional retroposon for ins 2)
ins 2 (insulin 2 gene)

Igf2 and Snrpn are activated only paternally (the active genes are on the paternal chromosome) while Igf2r and H19 genes are activated maternally. The ins1 and 2 genes where shown to be paternally imprinted in the yolk sac but not in the pancreas. This is an example of variable imprinting of a gene (14). In all cases the repressed locus shows a complete absence of messenger RNA. This means that the cellular transcription machinery must be able to discriminate between the maternal and paternal gene copy. Inbred mice, which are genetically identical at all loci are used for these experiments. So this functional difference in gene expression cannot be due to nucleotide sequence differences (15).

Barlow has emphasized two important factors in his experimental imprinting model (16): The imprinting box and the imprinting factor. The imprinting box is the DNA sequence being imprinted. The imprinting factor is the gene locus of the sequences and the modifications on this region. Barlow stated four important properties:

a- The imprinting box and imprinting factor are functionally reversible
b- The imprinting factor may change the transcription
c- The imprinting factor changes and modifies the imprinting box during gametogenesis and is lost in the gametes of the next generation
d- The imprinting factor is inherited chromosome-specifically in a diploid embryo

These properties of the imprinting box and imprinting factor show great similarities with the DNA methylation in mammals. Studies in the past two years show that DNA methylation plays an important role in the phenomenon of genetic imprinting (16,17,20). The imprinting box cannot transcribe mRNA. As a result it is concluded that the cellular transcription machinery can identify between the maternal and paternal gene. The DNA methyltransferase enzyme is responsible for DNA

methylation (16-18). This enzyme has been shown to be directly involved in DNA methylation which is a key event in the imprinting process (16-18).

Gene expression in mammals is dependent on parental origin. In diploid cells the imprinting boxes have been genetically identified (Gene loci are imprinted according to parental variations). The mammalian development regulates the position of the DNA sequence in the imprinting box by differential methylation of active and inactive loci (8,18,19).

Imprinting in humans is not observed in all members of a family or all chromosomes. The imprinting effect may be observed in only one gene, in a group of genes, in a chromosomal loci or in a whole chromosome.

3- Allele-Specific Methylation:

Genomically imprinted genes represent a class of sequences that are localized in a region of an allele and are expressed in a allele specific manner. As mentioned before there is a direct association between methylation and the expression of these genes. DNA methylation plays an important role in two key events. Methylation of the maternal allele preserves its activation while methylation of the paternal allele suppresses its transcription (15,20).

Tissue specific genes and housekeeping genes have CpG islands in their promotor regions (21-23). The methylation of these islands causes transcriptional inactivation of the gene involved. Studies in mice have shown that increase in methylation and chromatin condensation shows parallelism with the suppression of the paternal H19 gene (5,6,15,17,21,24-27).

There are models showing different allele-specific methylation patterns (21,22,27-29). One possibility is that the allele-specific DNA methylation observed in somatic cells is inherited from the gametes and is retained during embryogenesis. Another possibility is gametes from the very beginning. The cis-acting regulatory element acts as an imprinting activator in the gametes (21,28,29). There is no evidence that imprinting observed on homologue regions is preserved in all tissues or in all members of a species through out its life span.

To day, many studies are being done on site-specific DNA methylation changes in gametes and the embryo (2,4,6,20-22,24-26,28). De-novo methylation events occurring following fertilization have also been observed. There is an overall DNA methylation loss in the blastocyst stage. The second de-novo methylation event occurs at gastrulation. But this event is found to be lineage specific (21). There is not much information on the differences of methylation patterns between parental genomes during preimplantation development (21).

Experiments done on mice, cats and marsupialls lead to the conclusion that the parental X chromosome inactivation in extraembryonic tissues may be a result of genomic imprinting (30). In humans it was shown that imprinting occurred in extraembryonic tissues only randomly. Results of studies done on the embryonic development of mice reveals that imprinting shows tissue-specific differences (30-35).

4- Monoallelic changes in the genome:

A maternal allele loss with a paternal allele duplication or a paternal allele loss with a maternal allele duplication is observed (5,9,36-39). Typical examples will be: BWS, Fragile X Syndrome, Rhabdomyosarcoma, Osteosarcoma and Retinoblastoma (36-43).

Genomic imprinting is the focus of interest of many scientists in the field of genetics and molecular biology. Most studies have been done on animal models (mainly mice) and some studies have been done on maize and drosophila (17,44). Molecular studies are being done on humans, in cases that show phenotypical differences which are reflected as clinical diseases. Even though this event is shown to happen during gametogenesis there are experimental studies stressing its importance in the development of cancer (9,40-42,45). Experiments and investigations done up-to date were mainly to form a hypothesis for this phenomenon. Hopefully in the future the whole process will be stated out and will help in our understanding of genetic disease and cancer.

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