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SIGNIFICANCE OF GENE IMPRINTING IN LIFE OF BIOTA

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ABSTRACT

This review covers some important roles of gene imprinting in life of biota which is usually reflected on their progeny. Gene imprnting is associated with different metabolism processes in plants and mammals. It is also thought to be involved in hybrid vigor of crop plants, beside its association with crop adaptation to tolerate abiotic and biotic stresses. In endospermic cereals, the ratio of 2:1 gene expression of maternal to paternal genes is regulated via gene imprinting through developmental stages. The X-chromosome in some insects is also controlled by gene imprinting. In human, the frequent of early loss of fetus in women is related to gene imprint from the mother. Chronic diseases such as cancer, alzheimer, Parkinson, diabetes and blood groups are related to direct gene impringting. Noncoding DNA (98.3%) has been known recently to be related to human health and diseases. Noncoding different RNAs are also included in different cases of life of biota. Researchers should re-check their results about many of previonly obtained conclusions in this primely important topic.

Keywords

Methylation, RNAs, RdDM, Human Chronic Diseases

Introduction

Our today's knowledge in epigenetics and gene imprinting goes back to the discovery of transposable elements in maize cells by B.McClintock in 1950's and to D. Barlow who proposed imprinting genes in 1993 that have arisen from a defense mechanism targeted the inactivation of retrotransposons. So, she suggested that there should be maternal-specific and paternal specific factors involved (Elsahookie, 2013 a).

This means that epigenetic mechanisms are due to transposable elements (TEs) that can reduce transposition and genomic modifications. When TEs are silenced, DNA methylation will be higher. DNA methylation has been reported to play an important part in hybrid vigor (Elsahookie, 2013b; Elsahookie, 2019). The research articles published on epigenetics, genomics, and gene imprnting are more to be precisely counted. Bressman and Zhu (2014) mentioned a total of 14000 articles published on genomics in two years only. Gene regulation associated with epigenomics have several features to be driven away from the original affecting genes. These different features take place through chromatin modification by DNA methylation with some interference of long and short noncoding RNAs (Grossniklaus and Paro, 2014).

The mechanisms of imprinted genes play different important roles in life developments of several living beings including human. Among those mechanisms, endosperm size of kernels in maize, heat and drought tolerance in plants, and some characteristics of embryos in mammals. Luger et al (1997) reported that DNA, the carrier of genetic information in eukaryotes is condensed into nucleosomes in which ~ 140 bp of DNA is wound twice around octamers of four core histones; H_2A,

H_2B, H_3, and H_4. Meanwhile, the conserved epigenetic mark 5- methylcytosione (5mC) on DNA facilitates the regulation of gene expression and the formation of heterochromatin and has been identified in several genera and species of plants and mammals (Li and Zhang, 2014). However, in maize, some genes which encode for methyltransferases catalyze DNA methylation (Li et al, 2014). The adjustment of chromatin structure is another feature of epigenetic regulation in which results in functional changes in gene expression. This mechanism takes place through protein complexes which can alter DNA nucleosomes resulting in changes in some metabolic and/or phenotype of the living being (Elsahookie, 2013 a, b).

Molecules of iRNAs and ncRNAs are involved in many epigenetic mechanisms. One of the most extensive articles published on maize hybrid vigor and its relationship to imprinted genes was reported by Zhang et al (2011) which they gave a detailed survey on mechanisms of imprinted genes in maize kernel and endosperm through their analyses on the reciprocal crosses of the famous American maize hybrid B73×Mo17. This review article covers some and important roles of imprinted genes in some plants and mammals developmental processes, and their reflections on crop breeding methodologies. Several researcher have published thousands of articles on the importance of gene imprinting in regulating processes in different genera and species of biota.

Scanning of Gene Imprinting

Zhang et al (2011) calculated the expression ratio between the maternal and paternal alleles at each SNP site in dissected endosperm tissue of the maize hybrid, of both reciprocals (B73×M017 and M017×B73). They found that the majority of 11370 genes at 10 DAP endosperm exhibited a matemal to paternal ratio of 2:1. At the same time (10 day after pollination), they obtained at total of 149 million 100-bp paired –end reads depencling on mRNA-sequence. In the triploid endosperm, they found a significant number of SNP sites (1686 of total SNP in 699) genes were deviated from the expected ratio in both B73×M017 and M017×B73. However, among 699 genes, 127 showed maternally preferred expression, whereas 572 genes were paternally preferred. They concluded that such a kind of deviated expression cannot be explained by inbred-allelic differences, because the same patterns were shown in both directions of reciprocal crossing. Hence, most likely explanation is that the expression of genes with a deviating allelic expression ratio is affected by the parental origin of the alleles. They found a set of high-confidence imprinting genes indicating that the level of actively expressed allele was at least five times more than that of the repressed allele randomly tested eight candidate imprinted genes, four MEGs and four PEGs by reverse transcription (RT-PCR) of 10 DAP endosperm, and they found that the eight genes have the same parent-of-origin dependent expression.

Methylation of DNA

The process of DNA methylation is an important process in gene imprinting and X-chromosome inactivation (Wang et al, 2016). The most common methylation in higher plants and mammals is cytosine methylation (Elsahookie, 2013 b). Eichten et al (2013) identified about 700 differentially methylation regions (DMR) by establishing genome-wide maps of DNA methylation in maize inbreds of the well-known hybrid B73×Mo17. Maize inbreds differ in number of DMRs, SNPs, and DNA methylation levels which appear when inbreds of elite maize hybrids tested. These cases are thought to be involved in a way or another with the hybrid vigor of different crop hybrids (Elsahookie et al, 2018; Elsahookie et al, 2019). They also reported that imprinted genes appear in a form of clusters around the genome of maize, and that the embryo and endosperm of maize kernels showed different DMRs, and that maternal alleles were had less methylation than paternal alleles. These results explain that the processes taking place in the kernel of hybrids are so complex. On the other hand, different tissues may exhibit different DNA methylation as was found by Eichten et al (2013) when they sequenced genome-wide DNA methylation in leaves, immature ear, embryo and endosperm of maize inbreds; B73 and Mo17.

Similar results on these two inbreds were found by Zhang et al (2011).

DNA methylation in maize has been studied by several researchers. DNA methylation is a genetic mark of gene imprinting. Epigenetic change could be transmitted to next generation offspring without changing the number or sequence of DNA nucleotides. Methylation of DNA occurs in different stages of plant or animal developmental processes. This confirm that methylation is so crucial to all living beings. Chan et al (2005) showed that methylation level differs with different tissues and stage of development. They reported different levels of methylation which was higher in maize bracts> ear sheath leaves > tassels.

RNAs of Eukaryotes

Only parts of DNA and RNA are coding for proteins. Guttman et al (2013) reported that the majority of eukaryotes RNA do not encode proteins. This part of RNA is called ncRNA, and this involves the long noncoding RNAs (lnc RNAs) which they are in general more than 200 nt in length (Yamada, 2017), and the small RNAs (sRNAs) of about 20-24 nt (Eichten et al, 2011; Eichten et al, 2013; Elsahookie, 2013). These noncoding RNAs regulate expression at the transcriptional or posttranscriptional level. Short noncoding RNAs are divided into micro RNAs (miRNAs) and small interfering RNAs (siRNAs) (Elsahookie, 2013a) and circular RNAs (circRNAs) which are all single-stranded (Lai et al, 2018). These noncoding RNAs were reported to play important roles in several processes in mechanism of organs and tissues in several living beings (Elsahookie et al, 2018; Elsahookie et al, 2019).

Transposable elements (TEs) composing a large part of the genomes of biota. The genes of lncRNA contain more TEs than do the protein-coding genes (Wang et al, 2017), and they have important role in stress mechanisms in plants. In maize, lncRNAS, miRNA, and siRNAs have been reported to be found in embryo and endosperm tissues (Elsahookie, 2013a; Elsahookie, 2013b; Elsahookie et al, 2018; Elsahookie et al, 2019).

The small RNAs of 20-24 nt long from the complex called (RISC), RNA-induced silencing complex in plants. This complex plays an important part in stress tolerance in plants with other proteins and/or compounds (Elsahookie, 2013a).

In was found that miRNAs have profound relationships in plants and animals, such as biotic and abiotic stress tolerance, and disease resistance or even immunity. Olejnicza et al (2018) explained that miRNA has been found to be involved in disease and stress tolerance in maize. These newly discovered findings were not thought to be exist years before. On the other hand, Chavez-Hernandez et al (2015) found that miRNA in maize was related to hormone depletion in embryo genesis, and that miRNA can be differentially expressed under different phytohormone and light intensity levels, and that expression differed according to different maize genotypes.

As it was reported previously, siRNAs are of 20-24 nt long. These endogenous RNA transcripts are involved in RNA-directed DNA- methylation (RdDM) which plays an important role in stress tolerance in plants (Elsahookie, 2013 a,b). RdDM-associated siRNAs are of great importance in adaptation of plants to biotic and/or abiotic stresses (Li et al, 2017; Elsahookie et al, 2019). On the other hand, Ge et al (Ge et al, 2017) found that siRNAs were associated with maize embryo development by targeting transcripts of genes involved in this process, and even in maize embryonic callus formation.

The third class of endogenous noncoding RNAs, the circRNAs, have also received prime attention in research through last years. These molecules were found to be involved in transcriptional and posttranscriptional regulation of gene expression (Chen et al, 2018; Zhang et al, 2019; Yu et al, 2020). Tang et al (2018) stated that circRNAs participate in various regulatory mechanisms in maize including responses to heat, cold, and drought stresses. However, intra-species extensive variations are exist in the expression of circRNAs in maize (Yu et al, 2020). Meanwhile, Zhang et al (2011) reported that circRNAs, most of which were differentially expressed under drought stress have been identified in *Zea* and *Arabidopsis*, but circRNAs and sRNAs were negatively correlated. Drought, salt, and heat stresses are challenging

towards doubling food productivity in the world growing population. Janni et al (Janni et al, 2020) suggested using available natural or induced variations in crop plants to have a breakthrough in global food production. Elsahookie et al (2021) reported natural existing variations in some crosses of inbreds of the genus *Zea* that their microgameto-genesis were tolerant to atmosphere temperature through time of pollination exceeded 50 °C.

Gene Imprinting in Mammals

Gene imprinting mechanisms have been active in many genera and species of animal kingdom. X-chromosome deletion in some insects is one of familiar imprinted genes (Kimball, 2021). In mice, Bartolomei et al (Bressman et al, 2014) reported that some genotypes of mice showed parental-specific inheritance of phenotypes. From these studies, the hairpin-tail mouse come to light, which carried a large deletion of chromosome 17 and demonstrated midgestation overgrowth and lethality when maternally transmitted. On the other side, paternal inheritance of the same deletion resulted in viable and fertile mice. Ivanova et al (2020) have generated genome-wide DNA methylation and whole transcriptome dataset from gametes to blastocysts in both pig and cow. In oocytes of both genera, a distinctive bimodal methylation landscape was present, with hypermethylated domains prevalent over hypo-methylated domains similar to human.
Thamban et al (2020) explained that gene imprinting takes-place in insects, plants, mammals, and human. The phenomenon includes X-chromosome inactivation and paramutation, which are the most studied cases. In case of chromosomal sets during development, result in functional non-identified more than 130 imprinted genes in mouse, most of them were found in cluster forms. Gene imprnting has important roles in creating phenotypic variations among many genera of plants and animals, including human. Creeth et al (2018) and Angiolini et al (2021) found that gene imprinting in mouse was very clear and important in placental passive permeability in the mouse.

Gene Imprinting in Human

Gene imprinting is becoming an interesting area of science in several genera in mammals, including human. This phenomenon causes the parental origin-restricted expression of a growing number of genes in mice and human due to germline-derived differential DNA methylation at specific regions. Takahashi et al (2019) reported that zinc finger protein 57(ZFP 57) is critical for maintainance of the epigenetic memory during post-fertilization reprogramming, yet, incomplete penetrance of ZFP 57 mutation in humans and mice suggests additional effectors. They revealed that ZNF 445/ZFP 445, which they trace to the origins of imprinting, binds imprinting control regions in mice and humans. Meanwhile, Shi et al (2019) reported that over 80% of ZFP 57 targets are TEs, but ZFP 57 is not essential for their repression, though, the loss of ZFP 57 influences imprinted genes as expected. Another form of gene imprinting in humans was studied by Demond et al (2019). They reported that maternal effect mutation of the subcortical maternal complex (SCMC) of the human oocyle can cause early embryonic failure, gestational abnormalities, and recurrent pregnancy loss. These cases are associated with DNA methylation abnormalities at imprinted genes in conceptfuses. They have identified a patient to be homozygous for an inactivating mutation in the human SCMC. They have concluded that the integrity of the SCMC is essential for *de novo* methylation in the female germline. These findings have important implications for understanding the role of the SCMC in DNA methylation and for the origin of imprinting defects, for counseling families, and will help inform future therapeutic approaches. This is in agreement with that reported by Kimball (2021) on human placental tissue and its importance in fetus nourishment.

Syndromes, Tumor Suppressors and Blood Groups

Hundreds of imprinted genes have been identified in mammals and humans. Gene imprinting require DNA-and–histone methyation. Kimball (2021) reported that this phenomenon start in the germline; pollens and ovules in plants, and sperms

and ova in humans and other mammals. It maintained in the embryo through mitotic divisions of somatic cells. The deletion of a part of chromosome 15 causes two different syndromes in human:

1- Prader-Willi syndrome, if that happens on father's chromosome.
2- Angel-man syndrome, if that happens on mother's chromosome.

Kimball (2021) attributed both syndromes to the loss of imprinted genes exist at that lost part of the chromosome. On the other hand, if methylation is reduced, proto-oncogenes will be highly expressed, and that could lead to cancer. Increased methylation will decrease expression of tumor suppressor genes. This explains that mechanism and degree of methylation should be always well-balanced. In human blood groups, if we have an individual with AB blood group, this means that he obtained genes of both parents (A and B blood graups). Another example; if an individual with haemoglobin S and haemoglobin A, he will have equal amounts of both haemoglobins as he inherited from his parents. This implies that cells of this individual will have same number of imprinted genes for each type of haemoglobin or blood group. Sites which have these changes are usually C_5 and G_5 sites called CpG. This will prevent binding transcription factors to those promoters, and that gene expression will be shut-down. Another example in human, the insulin production, the maternal genes that control insulin production that imprinted in a male, will be expressed in any of that male offspring that inherit those genes. That is for imprinting is considered a reprogramming process that makes things fit that individual, a male or a female.

The most interesting finding is what was recently reported by Mackenzie and Kolb (Mackenzie and Kolb, 2021) on the activity in gene expression of the DNA. They stated that human genome-wide analysis took about 13 years with a cost of 2.7 billion US dollars to identity ~ 3 billion base pairs. Some researchers predicted human genes to be around 300,000, and other as low as 40,000, but today, our genome shows that it contains only roughly 21,000 genes !. This number of genes is very close to fruit fly or the mouse!. Human genome contains two sections of genetic material; the coding and the non-coding genome. The coding genome represents only 1.7% of our DNA, and the rest (98.3%) is not coding any proteins. On the other hand, scientists found that non-coding genome is actually responsible for the majority of information that impacted disease development in human. This new finding have made it clear that the non-coding genome is actually far more important than previously thought. Mackenzie and Kolb (2021) added that short regions of DNA called: enhancers switches genes on and off in different tissues at different times. These enhancers are needed to shape the embryo, and they have been changed very little during evolution. Klien et al (2021) stated that regulating proteins in the epigenome program are so important, and the absence of them will disrupt that replication program. Disrupting this epigenome in human stem cells will prevent these cells to develop into liver, kidney, heart, and neuron cells.

Finally, gene imprinting has many important roles in life developments in plants and mammals, including human. One of the most important phenomenon in some crops productivity is hybrid vigor. Gene imprinting, SNPs, gene activation and inactivation though transcription and posttranscription, lncRNAs, ncRNAs, cirRNAs, siRNAs with differential degrees of DNA and cytosine methylation, all are thought to be involved in many roles in developmental tissues and organs of biota. The ratio of 2:1 maternal to paternal endosperm genes is due to gene imprinting. Gene imprinting has an important role in abiotic and biotic stresses in crop plants. In some insects, such as bees, the X-chromosome is controlled by imprinted genes. Placental tissues that connect the human fetus with his mother is associated with gene imprinting. Frequent early loss of fetus is usually related to mother's family history. The newly discovered information about the relationship of non-coding DNA (98.3%) to human health and diseases should be given more interest to focus on many human chronic diseases with this high part of non-coding DNA. The exact time of gene activation and inactivation should be well understood to help solve most of our challenging problems in human life, and our animals and plants.

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