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The Mutations and Their Relationships with the Genome and Epigenome, RNAs Editing and Evolution in Eukaryotes

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<http://dx.doi.org/10.5772/49968>

“Mutations have been crucial for geneticists, as day and night for astronomers. Whithout the successions of days and night we would not know about stars. Whithout mutations we would know very little about inheritance and the existence of genes.”

Gustavo Hoecker Salas

(December 5, 1915- March 19, 2008)

National Prize of Science of Chile in 1989

1. Introduction

The idea of variation in nature is very old, in Heraclitus of Ephesus (504-500 BC) we find the first ideas of changes when he stated: “we never bathed in the same river”. However in the field of biology, the Greeks considered that the species were immutable. This concept changes with the first scientific ideas of organic evolutions and heredity. Lamarck proposed the first evolutionary theory where the organisms evolved from simple forms. Also he proposed an hereditary model in which the environmental influences are very important as an agents of evolutionary change and proposed the Theory of acquired characters. With the Mendelism advent, Lamarck’s Theory was left behind and all the mutations in the living organisms were attributed to Mendelian “factors”. However in recent years with the development of epigenesis, genomic imprinting and the horizontal transferances of the genes, Lamarck’s ideas have resurfaced.

The concept of mutation was coined by Hugo De Vries in 1901, whom worked with plants species of the genus *Oenothera* where he discovered some phenotypic hereditary characteristics that he coined as “mutations” and “mutants” to those individuals that have these phenotypic alterations. In opinion of De Vries, these mutations give origin to a new

species that he named “elementary species” [1], [2]. Thus, this gave birth to the saltacionist Theory of Evolution that he described in his book entitled “Mutations”. The harmony between Mutation Theory and Mendel model of heredity, the simplicity of the experimental method and the vast accumulation of supporting data, explain the big impact in the biological world [3]. Also, De Vries ventured with a hypothesis: “With the knowledge of the principles of the mutations will be possible in the future to induce mutations artificially” [4]. Wilhelm Johannsen argued that evolution consisted of discontinuous changes between “pure lines” and carried out their classic experiments in the beans *Phaseolus vulgaris*, through which coined the concepts of phenotype, genotype and gene [5]. Other important step in the advances of the genetics as an experimental discipline, was the establishment of relationships between mutations and genes discovered by Thomas Hunt Morgan in 1939 using *Drosophila* as biological material. Later Timoféeff-Ressovsky distinguished mutations at gene level and chromosomal aberrations. Morgan named mutations to these changes in individuals genes with variable effects [6]. Year later Morgan perfected the gene concepts as “the hereditary unit indivisible by recombination, located in the loci in a homologous chromosomal pair that can spontaneously mutate and belong to the linkage unit” [7]. In the framework of this concept the genes are located in a fixed position, specifically in a locus, concept coined by Morgan in 1915, and could change of position only by structural chromosomal reorganization [6]. This concept was accepted by the great majority of the scientific community of this time, prevailing until the discovery of transposable genetic elements in the second half of last century. However it is necessary to refer to some exceptions to the classic concept of the gene. Richard Goldschmidt in his book *Theoretical Genetics* denied the existence of an corpuscular gene; according to his opinion, in the chromosome only there is a definite pattern of changes that corresponds with the mutation and: “the mutation create the gene” [8].

Mutations have been historically the cornerstone of biological disciplines: in basic science, to understand biodiversity and evolution of species, in medicine to explain phenotypic variation and diseases, in education to justify the individual differences found between the students within a classroom and also in agriculture and veterinary in the improvement of plants and animals useful to man. Thus, Mutations have allowed the explosive growth of genetics as an experimental science. In multicellular organisms the cell differentiation requires a series of genetic and epigenetic changes. The mutations (epimutations) can occur also post transcriptionally in the different type of RNAs that constitute the epigenome. This article explores this theme, in the framework of the adaptation, phenotypic plasticity and evolution of eukaryotes.

2. Mutations at genome level

At the beginning of the genetics as an experimental discipline, mutations have been associated to the classic Mendelian genes and, with the advent of molecular genetics these genetic changes are produced in the coding area of the DNA. A gene occupied a definite place in the chromosome that was associated with a well determined phenotype, thus the

gene was simultaneously a unit of mutation and function and were indivisible by recombination [7]. Archivald Garrod in 1909 was interested in to explain the origins and inheritance of human diseases. Also he was the first proposing the concept that a gene is in direct relationship with the production of a specific protein and that establishes the genetic control of some inborn error of the metabolism. He showed that an alteration in an enzyme was linked to amino acid metabolism. In 1941 Beadle and Tatum postulated the hypothesis "one gene-one enzyme". Thus, each gene control the production, function and specificity of a particular enzyme. Studies conducted in different organisms proves that the capacity to synthesize the appropriate amino acid is caused by the modification or loss of a single enzyme. This concept was changed by Vernon Ingram who postulated the hypothesis "one gene-one polypeptide" in base to the sickle cell anemia disease in humans. Also Ingram postulated that this disease is caused by a single gene mutation which is lethal in homozygous with severe sickle cell anemia, and is semilethal in heterozygous that show an attenuated sickle cell anemia. Normal homozygotes individuals are normal for the form of their blood cells and their hemoglobin in an electrophoretic analysis migrated differently in comparison to those heterozygous individuals. The fingerprint show that the differences between normal and diseased individuals was only a single amino acids substitution in one of the beta chain of polypeptide. The glutamic acid in normal individuals is replaced by valine in individuals with sickle cell anemia. The difference between valine and glutamic acids is only one base in the codon. Moreover, the amino acid changes in one chain is independent of changes in the other chain, suggesting that the gene determining the alpha and beta chain are located in different loci. Thus one gene codes for one polypeptide and several polypeptides may be necessary for a functional enzyme of the organism. In 1961, Seymour Benzer studying the fine structure of genes by using mutants in the phage T4 of *E. coli*, use for first time the concept of cistron. Inside of a gene, there are different cistrons or "functional units". Benzer demonstrated the hypothesis of Ingram, the cistron corresponds to a sequence of nucleotides that code for a polypeptidic chain [9, 10]

The ideas about the genetic action and its mutability were complemented by Goldschmidt in 1940 [11] who defined the gene on the basis of its physiological action. With the first DNA sequencing by Frederick Sanger, it was clearly demonstrated by C. Yanofsky that the gene is a nucleotide sequence that encodes for proteins. Thus, within the genes there are information for the amino acid sequence of the primary structure of protein. [12] Any mutation at nucleotides of a gene may cause an alteration in the primary structure of the protein. Depending on the phenotypic effect causing these mutations can be lethal, semilethal, deleterious or innocuous (silent mutation). Many researchers were interested in inducing mutations with different agents in plants and animals such as Hermann Muller in *Drosophila*, Milislav Demerec in bacteria, Åke Gustafsson in barley, George Snell in mice, G.W. Beadle, E.L. Tatum in *Neurospora*, Lederberg and Tatum in *E. coli* [13].

An important step in the process of regulation of gene expression were the Jacob and Monod experiments in *E. coli*. Using mutations were able to establish the first model of expression and gene silencing in prokaryotes. Based in pioneering works of Calvin Bridges and Goldschmidt on the effects of homeotic mutation on development in *Drosophila*, García-

Bellido and Lewis proposed a model of gene regulation of development in eukaryotes [14, 15]. The homeotic mutations have been fundamentals to explain the genetic basis of development, adaptation and evolution in eukaryote organisms. However, in recent years have found that in regions of DNA does not code for proteins are transcribed an enormous amount of non-coding RNA (ncRNAs), which together with proteins, regulate gene expression. These RNA, including the rRNA and tRNA, together with the mRNA and chromatin are part of epigenome. The mutation at the level of the epigenome have been called epimutations and also cause phenotypic changes, including diseases but also evolutionary novelties that even can be inherited through a non-Mendelian pattern of inheritance. Then will delve into this important topic.

3. Epimutations at epigenome level

The concept of epigenome is a recent concept in genetics that arises with epigenesis concept. The epigenome involved the chemical changes at DNA level such as methylation and also histones acetylation, chromatin remodeling and phenotypic changes that originate by ncRNAs [16]. The epigenesis is a old concept that was coined in 1942 by Conrad H. Waddington to explain as an adults can be formed from a zygote by cell differentiation and gene regulation. In a multicellular organism each cell has an epigenotype that is determined by which genes are functioning in that particular cell. The differentiation of multicellular organisms is controlled by epigenetic markers and are transmitted through cell division. However, have been demonstrated that epigenetic changes in germ cell line could be heritable transgenerationally. Epigenesis is a heritable changes in the expression of genes that not involve a change in the nucleotide structure of DNA but only changes in the chromatin. These changes alter the capacity of genes to respond to external signals [17]. Epigenetic changes allows heritable or transgenerational modifications in the expression of genes without the need of mutations at DNA level and not necessarily following the Mendelian model of heredity. In classical model of Mendelian heredity a gene's effects were assumed to be independent of its parental origin, but is know that some genes have different effects depending if gene was inherited via a sperm or an egg. This process is know as genomic imprinting. At present there is a lot of evidence that genomic imprinting inclusive may influence human behavior. Is know that children who inherit a chromosomal deletion of 15q11-q13 from their father have behavior different of children who inherit a similar deletion from their mother [18, 19, 20]. Also, experimental animal models in mouse shows that in utero or early life environmental exposures produce effects that can be inherited transgenerationally and are accompanied by epigenetic alterations [21]. These changes in the epigenome have been named as "epimutations". In humans there are just a few reports that have been used to suggest inheritance of epimutations and the search of these epigenetic inheritance is under way [18]. Some evidences have been described in colorectal cancer [22, 23, 24, 25].

Epigenesis and epimutation concepts also extend to ncRNAs that have different functions and in human genome constitute about of 60% of the total transcriptional output [26, 27, 28,

29, 30]. The ncRNAs are short single-stranded between 18 to 30nt length such as micro RNA(miRNAs) Small interfering RNA (siRNAs), small nuclear RNA (snRNAs), Small nucleolar RNAs(snoRNAs), piwi- interacting RNAs (piRNAs) and long nc RNA (lncRNA) 200-2800 nt length. All these ncRNAs are hairpin that are paired in some places similar to tRNAs. The homologies detected between the ncRNAs with endogenous viruses, transposons and introns revealed that ncRNAs probably originates from RNA viruses [31]. In the eukaryote genome, the ncRNAs are located in the non coding areas of mRNAs, endogenous viruses, transposons and also transcribed from non coding DNA areas. The ncRNAs not transcribed for proteins and are characterized for a great variety of processes that included genomic imprinting, as enhancers of transcriptional regulation, mRNA processing and modification, sex determination by dosage compensation, protein degradation, oncogenic, tumor-suppressive, neural and synaptic plasticity of learning and memory and cognitive capacity by regulating dendrite morphogenesis during early development and also viral and transposons defense [28,29,30,32,33,34]. Most of the mRNA stability elements are considered to be located in the 5'- and 3'- untranslated regions (UTRs) of genes where are located ncRNAs [35, 36] In the following paragraphs are detailed the features and the functions of each ncRNAs in eukaryotes. Also describes the effects of the mutations in the origin of disease, and also in the adaptation and evolution of the species. In Table 1 are shows the principal hallmark characteristics of these smalls and long ncRNAs.

Name	Length in nucleotides (nt)	Principal functions	References
siRNAs	21-23 nt	mRNA cleavage	[41]
miRNAs	21-23 nt	Regulate developmental timing	[50-52]
piRNAs	29-30 nt	Transposons silencing in gametes	[61]
snRNAs	90-216 nt	Efficiency of splicing, maintaining telomeres	[69-70]
snoRNAs	< 70 nt	Guide methylation of rRNAs,tRNAs and other snRNAs	[69,72]
lnc RNAs	200-2800 nt	X chromosome inactivation, human brain development	[76,77,94]

Note: lncRNAs always act in Cis position in the chromosome and small ncRNAs in Trans position [76].

Table 1. Principal Hallmark characteristics of small and long non-coding RNAs

4. The mutations at non-coding RNAs level

4.1. Short interfering RNAs

The eukaryotic genome encode an ample amount of short interfering RNAs, in different cells and tissues principally miRNAs, siRNAs and piRNAs that have less than 200 nt length and are highly conserved. These short ncRNAs are engaged in specific gene regulation and modulate the development of several eukaryote organisms including mammals and are involved in gene silencing in higher eukaryotes [27,37]. They act by binding to complementary sites on targets mRNAs to induce cleavage or repression of transcription in

a specific manner. Thus these ncRNAs could participate in the degradation of some specific sequence of mRNA. Also, a mutation in proteins required for miRNAs function or biogenesis can affect animal development [37, 38, 39,40]. Generally the target genes and the mechanism of target suppression are unknown, the reason for this is that miRNAs have a very short sequence of nucleotides, and also the interaction of base pairs with target mRNAs may be affected by a protein complex [38]. Unlike miRNAs of animals, miRNA target of plants are more easily identified because of near-perfect complementarity to their target sequences and act as siRNAs and destroy its target mRNA [41]. In plants, the miRNAs target sites are generally found into the protein-coding segment of the target mRNAs but in animals are found in untranslated region 3'UTR [40, 41]. MiRNAs and siRNAs are processed from a double-stranded RNA precursors about 70 nt by a specific ribonuclease, DICER that excises long RNA into short duplexes of 21-23 nucleotides called siRNAs and miRNAs. Only one type of DICER is found in *C. elegans* and humans indicating that the same DICER is acting on both miRNAs and siRNAs precursors [42,43]. However, two mutants, Dicer 1 and Dicer 2, have been discovery in *Drosophila* . Dicer 1 block the production of miRNA precursors. In a different way, Dicer 2 block the processing of siRNA precursors [44]. The excised short RNAs are associated with an ARGONAUTE proteins and constitute an RNA-inducing silencing complex (RISC) that is able to target near- perfect complementary RNAs for their degradation or for the control of translation [38, 45]. In contrast to DICER , studies in *C.elegans* and in *Drosophila* embryos suggest that the maturation and function of siRNAs and miRNAs have different requirements for argonaute proteins [45]. Mutations in these proteins required for miRNAs function or biogenesis impair animal development [46]. Micro RNAs are highly conserved across a wide range of species, for this reason it is not uncommon that homologies have been described in miRNA binding sites [38, 47]. It was shown that a large subset of *Drosophila* miRNAs with homologs in the human genome is perfectly complementary to several classes of sequence motifs previously demonstrated to mediate in negative posttranscription regulation [48,49]. The functions of miRNAs began to be studied in the founding members of miRNAs was in *lin-4* and *let-7*, genes that regulate developmental timing, were discovery from molecular analysis on *Caenorhabditis elegans* [50, 51,]. Both are 21-22 nt RNAs associated with apparent precursor RNAs with stem-loop structure, and both mediate post-transcriptional regulation of target mRNAs via imperfectly complementary sites in their 3' UTRs [37]. MiRNAs play significant regulatory roles in physiological aspect of development and pathologies in plants, flies, fishes, and mammals [52]. In *C.elegans* miRNAs involves to *lys* mi RNAs that regulates left-right asymmetry in the nervous system [34], and in *Drosophila* *bantam* miRNA control tissue growth and apoptosis [39]; *miR-14* in *Drosophila* suppresses cell death and is required for normal fat metabolism control [53]. In *Bombix mori* has been discovered that miRNAs are relates with the molting stages and, based on the analysis of target genes, have been hypothesized that miRNAs regulate development on complex stages [54]. In mouse *miR-375* is involved in the pancreatic- islet-specific that regulates insulin secretion[55] and *miR-181* is important in hematopoietic differentiation [56]. In the sheep, the variety Texel, was identified the myostatin *GDF8* gene in chromosome 2 . This gene has direct relation with a major effect on muscle mass. Also have been discovery that this gene has relation with the coding of a miRNA which is highly expressed in the skeletal muscle. A transition of G to A in 3' UTR

occurs in an allele of the gene GDF8. This mutation inhibits the production of myostatin causing muscular hypertrophy [57]. MiRNAs also have a role in a normal development and function of heart muscle in vertebrates. In mouse embryos, overexpression of miRNA miR-1 in the heart, during mid-embryogenesis originated lethality due to cardiomyocyte deficiency and heart failure [58]. There are many evidences that mutations in miRNAs cause disease in humans. For example, karyotyping showing that chronic lymphocytic leukemia (CLL) has a genetic basis consisting in a deletion located in 13q14 chromosome. These deletion is associated to other diseases such as mantle cell lymphoma, multiple myeloma and prostate cancers [59]. In humans, has been demonstrated that the hemizygous and/or homozygous loss at 13q14 constitute the most frequent chromosomal abnormality in CLL. Also has been demonstrate that two mutation in miRNAs : miR15 and miR16 are located into a 30-kb deletion area in CLL. Both genes are deleted or down-regulated in the majority of CLL [42]. In plants many mRNA target encode transcription factors that are important in morphogenesis regulation and, due to the high complementarity with mRNA targets act as siRNAs guiding the destruction of their mRNA target. In plants, miRNA target sites are principally found within the protein-coding segment of the target mRNA, but in animals miRNA act in 3' untranslated region (3'UTR) [40,41,60]. A set of 3' UTR motifs, such as the Brd-box (AGCUUUA), the K-box (CUGUGAUA) and the GY-box (GUCUCC), were characterized as motifs involved in negative post-transcriptional regulation of genes in the enhancer of split and, Brd gene complexes of *Drosophila* the 5'ends of miRNAs may be important for target recognition [37]

5. Mutations in Piwi interacting non-coding RNAs

PiRNAs are other class of small ncRNAs molecules that have 29-30 nt length and form the piRNA-induced silencing complex (piRISC) protein in the germ line of many animal species. Piwi proteins bind to piRNAs, which map to transposons. PiRNAs are important regulators of gametogenesis and have been proposed to play roles in transposon silencing [61].

PiRNAs are produced by the primary processing of single-stranded transcripts of heterochromatic master loci [62] The piRISC complex protects the integrity of the genome from invasion of transposable elements and other genetic elements as viruses and silencing them. They express only in gonads, specially during the spermatogenesis regulating the meiosis. [63,64] but also has been described during de ovogenesis [61]. As a result of the loss of piRNAs silencing, in *Drosophila* piwi mutations lead to transposable element over expression and cause a transposition burst. PiRNAs mutants in females exhibit two types of abnormalities, over expression of transposons and severely underdeveloped ovaries [62,65].

Piwi proteins and piRNAs have conserved functions in transposon silencing in the embryonic male germ line. Piwi proteins are proposed to be piRNAs-guided endonucleases that initiate secondary piRNA biogenesis. The biogenesis and piRNA amplification is fundamental for the silencing of LINE1 transposons. Experimental data in mice in base to mutations in Mili and Miwi 2 alleles revealed that the defective piRNAs results in spermatogenic failure and sterility. [66]. The relevance of the non-coding genome in human disease has mainly been studied in the context of the widespread disruption of miRNAs

expression and function that is seen in human cancer. At present we are only beginning to understand the nature and extent of the piRNAs, snoRNAs, transcribed ultraconserved regions (T-UCRs) and large intergenic non-coding RNAs (lincRNAs) are emerging as key elements of cellular homeostasis [67]. Genomic imprinting causes parental origin-specific monoallelic gene expression through differential DNA methylation established in the parental germ line. However, the mechanisms underlying how specific sequences are selectively methylated are not fully understood. Has been found that the components of the piRNAs pathway are required for de novo methylation of the differentially methylated region (DMR) of the imprinted mouse *Rasgrf1* locus, but not other paternally imprinted loci. A retrotransposon sequence within a ncRNAs spanning the DMR was targeted by piRNAs generated from a different locus. A direct repeat in the DMR, which is required for the methylation and imprinting of *Rasgrf1*, served as a promoter for this RNA. Has been proposed a model in which piRNAs and a target RNA direct the sequence-specific methylation of *Rasgrf1*. [68]

6. Mutations in small nuclear ncRNAs

SnRNAs are short molecules of RNA that are located within the nucleus of cells and participate in a variety of processes such as RNA splicing, regulation of transcription factors (7SK RNA) or RNA polymerase II (B2 RNA) and maintaining the telomeres [69]. RNA-RNA interactions between snRNAs or between snRNAs and the pre-mRNAs play critical roles in the accuracy and efficiency of the splicing. The snRNAs also are combined with the protein factors, they make an RNA-protein complex called small nucleoriboprotein (snRNP). The presence of dynamic RNA-RNA interactions within a ribonucleoprotein (RNP) complex like the spliceosome suggests that the snRNAs themselves may need to adopt more than one RNA conformation in order to execute their functions during splicing. Not all of these interactions are established simultaneously, nor do they persist once established. Rather, interactions are formed, modified, disrupted, and replaced during spliceosome assembly and splicing. [70]. The complex structure of spliceosome and the varied interactions between their protein subunits make than any mutations in the nucleotide structure of the snRNAs cause alterations in some of its interactions and functions. Thus, it has been demonstrate that in yeast alternative RNA folding can cause cold sensitive function of RNA and that in the case of U2 snRNA, for which the potential to form the alternative structure is conserved, disrupting the alternative folding relieves the cold sensitive defect. This finding suggests that alternative RNA folding may provide a general explanation for the common occurrence of cold-sensitive mutations in RNA and RNA binding proteins [70]. In the yeast *Schizosaccharomyces pombe* there are pre-mRNA processing (prp) mutants that are temperature sensitive or cold sensitive for growth. Some these mutants accumulated the U6 snRNAs precursor at the nonpermissive temperature [71]. Small snoRNAs, are ancient ncRNA that guide the methylation of rRNAs, tRNAs and other snRNAs. These snoRNAs are less than 70 nt in length including 10-20 nucleotides of antisense elements for base

pairing rRNA processing involves a number of snoRNAs [69,72]. These activities involve direct base-pairing of the snoRNA with pre-rRNA using different domains. A mutation consisting of single nucleotide insertion in the guide domain shifts modification to an adjacent uridine in rRNA, and severely impairs both processing and cell growth [73]. Have been described that U3 and U14 snoRNAs have been implicated in processing steps leading to 18S rRNA formation in eukaryotes. In addition, 18S rRNA formation in vertebrates requires U22 snoRNAs, and in yeast it requires snR10 and snR30 snoRNAs. The role of snoRNAs in rRNA processing is distinct from the function of the majority of snoRNAs that serve as guide RNAs for rRNA modification. Mutations in U3 snoRNAs of *Xenopus* were tested for function in oocytes. The results show that U3 mutagenesis uncoupled cleavage at sites 1 and 2, flanking the 5' and 3' ends of 18S rRNA, and generated novel intermediates: 19S and 18.5S pre-rRNAs [74]. This study reveals that budding yeast snoRNAs gene promoters are typically demarcated by a single, precisely positioned binding site for the telomere-associated protein Tbf1, which is required for full snoRNAs expression. Tbf1 is known to bind to subtelomeric regions of *S. cerevisiae* chromosomes, where it contributes to the maintenance of telomere length and the regulation of telomeric gene silencing. The subtelomeric binding protein Tbf1 is a global transcriptional activator in budding yeast, where it activates snoRNA genes [75].

7. Mutations in macro or long non-coding RNAs

Macro or long coding RNAs are conserved and unlike the short RNA, always act in Cis position in the chromosomes and can be up to several hundred thousand nucleotides long, about 200-2800 nt. In the eukaryotic genome and, specially in mammals there are thousands of lncRNAs that are expressed in different cell lines and tissue and exhibit tissue-specific expression patterns. At moment there are a small amount of lncRNA in which are know in its function and stability, although it has been assumed that they are generally unstable. Recently a genome-wide analysis in the mouse neuroblastoma cells, using a custom ncRNAs array has been determined that lncRNA show a similar range of half-lives to proteins-coding transcripts, suggesting that lncRNAs are not unstable and also that the stability of lncRNAs is a regulated process and depend of where are located in the genome these lncRNAs. Thus, the intergenic RNAs show more stability than those originated from introns of mRNA [76]. Also it is known that in mammals these lncRNAs have different regulatory functions, principally X chromosome inactivation by heterochromatinization (Xist gene) and coats the inactive X chromosome from which it is transcribed. This represents part of the mechanism by which transcriptional silencing is achieved [77]. The lncRNAs roX in flies plays a role in dosage compensation in sex determination similar to XIST gene in mammals [78]. Also the lncRNAs are involved in the regulation of transcriptional and post transcriptional pathway programming, regulation of mRNA splicing, epigenetic gene activation in the regulation of Hox genes that regulate development and also in genomic imprinting and as enhancers of gene expression and in the length of telomere in the chromosomes [79,80,81,82,83,84,85,86,87,88,89,90].

In addition, several lncRNAs have been shown to be mis regulated in various diseases including cancer and neurological disorders [83,91]. One such alterations in an lncRNA, is Malat1 RNA (metastasis-associated lung adenocarcinoma transcript). Malat1 also is highly abundant in neurons and It is enriched only when RNA polymerase II-dependent transcription is active. Knock-down studies revealed that Malat1 modulates the recruitment of SR family pre-mRNA-splicing factors to the transcription site of a transgene array. Malat1 controls the expression of genes involved not only in nuclear processes, but also in the function of the synapse. In cultured hippocampal neurons, knock-down of Malat1 decreases synaptic density, whereas its over-expression results in a cell-autonomous increase in synaptic density. These results suggest that Malat1 regulates synapse formation by modulating the expression of genes involved in synapse formation. [91]. lncRNAs are present not only in animals but also in plants where they are involved in gene silencing and in the phenotypic plasticity [92]. In mouse a lncRNAs that has been coined as Rubie (RNA upstream of BMP4 expressed in inner ear) originate malformation in the vestibular apparatus. The Mutation is expressed in developing semicircular canals. However, was discovered that the SWR/J allele of Rubie is disrupted by an intronic endogenous retrovirus that causes anormal splicing and premature polyadenylation of the transcript. Rubie lies in the conserved gene desert upstream of Bmp4, within a region previously shown to be important for inner ear expression of Bmp4 [93]. Also in vertebrates and specifically in humans has been described mutations in transposable elements that are related to neurodegenerative diseases. The mutation was located in a degenerated long interspersed elements (LINES). This mutation expressed in the brain and causes lethal infantile encephalopathy suggesting that these repetitive elements are important in human brain development [94].

8. The RNA editing

The epimutations at ncRNAs are very important for the adaptation of organism and could be also heritable. Traditionally has been considered that mutations are nucleotide changes that occur at the DNA level and also that are the only new source of genetic variation. However, an special epigenetic regulatory mechanism was discovered from the mitochondria of protozoa *Trypanosome* where a number of genes are expressed in a unconventional manner, the nucleotide sequence of primary transcripts is modified post-transcriptionally through the insertion or deletion of Uridine. These nucleotide alteration was coined as RNA editing [95,96] and also should be considered as “post-transcriptional epimutations”. The RNA editing has been detected in unicellular and multicellular eukaryotes but not in prokaryotes. After this discovery, it was thought that this process affects only mRNAs, but now is known that also the editing occur in tRNAs, rRNAs and miRNAs [73,97,98,99]. In humans RNA editing is a change of adenosine to inosine mediated by the enzyme adenosine deaminase, acting on double – stranded RNA, where the inosine acts as guanosine [73,98]. In mammals also has been described another kind of RNA editing consisting in a change of cytosine to uridine [100]. This unexpected epigenetic mechanism

that occurs only in eukaryotes, changes the function of mutations at DNA level and their importance in the evolution of prokaryotes and eukaryotes. Thus the epimutations in ncRNAs also are very important in the adaptation of eukaryotes, specially in reaction norm and phenotypic plasticity.

9. The post-transcriptional nc RNAs epimutations and their role in the norm of reaction and phenotypic plasticity

Until recently it was thought that in eukaryotes the mutations important for the organism were located into the areas of DNA that code for proteins. Under this framework, protein were the only molecules that regulate the action of genes and, a mutation into the a structural gene could cause a change in the primary structure of proteins. A single amino acid change could cause a serious disease. With the advances in molecular genetics and the discovery of ncRNAs, now we know that In the ncRNAs also occurs epimutations that can also cause phenotypic changes and diseases. These epimutations are more difficult to interpret at a molecular level because they do not affect the protein sequence. Generally the epimutation in ncRNAs alter the RNA structural ensamble between ncRNAs and mRNAs and, alter the message of genetic information in the cells [101,102]. Similar to proteins, the epimutations produced in the ncRNAs into cells that belonging to differents organs and tissues within the body in eukaryotes can cause a great variety of illness.

The non-coding region of DNA previously thought was garbage, we now know it is not. An exception to this rule is the contribution of by the transposable elements described in maize by Barbara McClintock in 1947, dubbed as controlling elements. The merit of her discovery was the realization that the genome is not static and there are genes that are unstable in terms of location in the genome and could promote its own transposition. Now we know that these transposable elements are found in unicellular and multicellular organisms and have a viral origin [31]. Also the discovery of transposable elements and horizontal transferences of genes had led to the understanding that the genome is a "fluid mosaic of genetic information" from different origins, where the horizontal transfer mediated by virus, tramposons and viruses play an important role in the genic flow between the organisms, not necessarily related genetically [31]. Reciently, in prokaryotes and eukaryotes there are many evidences in that another class of molecular interaction occurs in the regulation of gene action and cellular processes, principally manifested by small ncRNAs that base pairs with mRNAs and regulate the gene expression postranscriptional [101,103]. NcRNAs are a very good tool for the inactivation of specific messages, for example some classes of these ncRNAs such as siRNAs and miRNAs have been found in the regulation of of development and cell death. The nc RNAs act also in prokaryotes, in the replication and maintenance of extrachromosomal elements they have an epistatic effect to any transcriptional signals for their specific mRNAs. Thus, a single ncRNA can regulate multiple genes and have profound effects on cell physiology[104].

10. Conclusions

The mutations not only occur in the structural genes but also in those areas that code for ncRNAs, in the mRNA messenger (RNA editing) and also in the introns and in both ends of mRNA, specifically in the 3'UTR and 5'UTR regions where as well are located ncRNAs. Thus mRNA is not only an intermediary between DNA and protein, as is expressed in the classic Crick's Central Dogma of Molecular Biology, but also correspond to a relevant producer of miRNAs and siRNAs. In addition the transcription of all eukaryotic genome generates a large amount of different ncRNAs which together with proteins regulating the expression of genes. The experimental evidences show that ncRNAs do not occur randomly in all cells but there are an enrichment of a particular ncRNAs depending of their function and cell where they act. There is now evidences that the environmental and developmental influences have effects on the phenotype. The epigenetic changes at DNA and RNA level such as DNA methylation, acetylation of histones, epimutation and RNA editing have an importance in the Darwinian fitness and could be adaptative [105]. Also many of these changes are inherited in a different way that the classic Mendelian model of heredity. One of the assumptions of population genetics is that genes are vertically transmitted to the progeny according to the laws of Mendelian inheritance. In this context, and based on Weissmann's barriers between somatic and germinal cells, only genetic changes that take place within gametes are inherited by the next generation. However at present there are evidences about a non-Mendelian model of heredity which has a close proximity to a neo-Lamackian inheritance model.

This model is based on epigenetic changes induced by the environment, in the epimutations at ncRNAs level, in the mRNA editing and also in horizontal gene transfers. Thus epimutations could be heritable. In this type of heredity there must be no barriers that prevent the changes in somatic cells could be integrated into the genomic information that resides in the nucleus of germ cells. The transposable elements, viruses and ncRNAs can be vectors incorporating somatic mutations within the genome and epigenome of the germ cells. Thus could be evade the Weissman's barriers between somatic and germ cells through retrovirus [106]. Also a mutation in piRNAs which block the action of a virus or transposable element of somatic origin could facilitate the negative impact of mobile elements in germ cells and this change may be inherited.

In humans has been postulated that cardiovascular and metabolic function and that elements of the heritable or familial component of susceptibility to cardiovascular disease, obesity and other non-communicable diseases (NCD) can be transmitted across generations by non-genomic means. Placenta's inaccurate nutritional cues, increases the risk of NCD. Endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by unbalanced maternal diet during pregnancy. Elucidation of epigenetic processes may permit perinatal identification of individuals most at risk of later NCD and enable early intervention strategies to reduce such risk [105].

Unlike prokaryotes, the eukaryote genome expresses numerous types of ncRNAs that play a fundamental role in the regulation and gene expression. Those small molecules have the possibility of interact with different kinds of proteins generating a homeostatic system that can respond quickly to environmental changes. Both class of molecules, protein and ncRNAs, are the manifestation of a great amount of information accumulated within the genetic and epigenetic programs. The epigenetic plasticity protects individuals from environmental changes and explain the classic concepts of reaction norm and phenotypic plasticity that previously had been poorly explained on its genetic basis. But now we know that if there is an epigenetic control for these phenotypic changes. Also, these ncRNAs contribute to the processing of information in at least two form: a) Saving a lot of information on their small molecules with a minimal of energy cost. b) Rapid acquisition of information from environmental with a rapid response and adaptation. Further ncRNAs appear to facilitates the acceleration of the evolution of an organism's information contained and functional computational system. This new picture provides a new dimensions about information processing in the brain [70] and in other cells belonging to other tissues where the ncRNAs can mitigate the negative effects of the environment, increasing adaptability and acceleration in the organic evolution.

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Acknowledgements

Financed by the project code B-12-1, Direction of Extension of the Metropolitan University of Educational Sciences, Santiago, Chile

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