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Transposable Elements and Epigenetic Mechanism: Implications and their Significance in Crop Improvement

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A B S T R A C T

An understanding of the dynamic potential of the genetic material in living organisms is largely a consequence of the discovery and genetic characterization of plant transposable elements. Repeated DNA sequences makes up a large fraction of a typical mammalian genome and some repetitive elements are able to move within the genome *i.e.* transposons and retrotransposons. DNA transposons move from one genomic location to another by either copy- and paste or cut-and-paste mechanism. They are powerful forces of genetic change and have played a significant role in the evolution of many genomes. As a genetic tools, DNA transposons can be used to introduce a piece of foreign DNA into a genome. Indeed, they have been used for transgenesis and insertional mutagenesis in different organisms, since these elements are not generally dependent on host factors to mediate their mobility. Thus, DNA transposons are useful tools to analyze the regulatory genome, study embryonic development, identify genes and pathways implicated in disease or pathogenesis of pathogens and even contribute to gene therapy. To understand the impact of transposable elements (TEs) and their importance in host genome evolution, it is essential to study TE epigenetic variation in natural population. Concurrent with these significant developments, "epigenetics" is the study of heritable changes in the pattern of gene expression resulting from the modification of DNA bases, histone proteins or non-coding-RNA biogenesis without altering the underlying nucleotide sequence. It provides a better understanding of how epigenetic mechanisms regulate plant transposons. One of the common mechanisms involved in epigenetic changes is methylation of 5^{th} carbon in the nitrogenous base by the action of the enzyme DNA methyltransferase enzyme. In addition, histone proteins are post-translationally modified which may affect transcription, DNA replication, chromosome segregation/condensation and DNA repair process. Small-RNA (particularly small-interfering RNAs) plays a crucial role in DNA methylation *via* RNA-directed DNA methylation (RdDM) pathway. The epigenetic changes in plants induced by aforesaid processes can be inherited over the generations in the form of epialleles. A detailed understanding of salient epigenetic mechanisms, such as DNA methylation, paramutation, genomic imprinting and gene silencing, leads to practical solutions and novel strategies for future plant improvement programmes. Therefore, the purpose of this review is to highlight the significance and implications of transposon function and major epigenetic phenomena in relation to genome evolution, gene regulation and crop improvement.

Introduction

Molecular stability is considered as the hallmark of a genetic material. For much of the 20th century, genes were considered to be stable entities arranged in an orderly linear pattern on chromosomes, like beads on a string (Morgan, 1922). In the late 1940s, Barbara McClintock challenged the existing concepts of what genes were capable of when she discovered that some genes could be mobile. Her studies on chromosome breakage in maize led her to discover a chromosome-breaking locus that could change its position within a chromosome. McClintock went on to discover other such mobile elements, now known as transposons. She also found that depending on where they are inserted into a chromosome, these mobile elements could reversibly alter the expression of other genes. She summarized her data on the first discovered transposable element Ac and Ds, in a 1950 PNAS Classic Article, "The origin and behavior of mutable loci in maize" (McClintock, 1950). Eukaryotic genomes contain an abundance of repeated DNA sequence and some of these repeated sequences are capable to move from one location to another in the genome are known as transposable elements. "Transposons are astonishingly abundant, comprising a majority of the DNA in some species. (Fedoroff, 2012). TEs can occupy a high proportion of a species genome. For example, it comprises approximately 10% of several fish species, 12 % of the *C. elegans* genome, 37% of the mouse genome, 45% of the human genome (Pie chart 1)and up to >80% of the plant genomes like in maize. From bacteria to humans, transposable elements have accumulated over time and continue to shape genomes through their mobilization (Lopez *et al*., 2010). A little before McClintock's formal retirement in 1967, mobile genetic elements were discovered in bacteriophages-viruses that infect bacteria (Taylor, 1963). They would soon be discovered in bacteria themselves, and eventually in drosophila as well (Shapiro, 1969 and Preston, 1989). For her contribution McClintock received a number of prestigious awards, including the 1970 National Medal of Science and culminating in an unshared Nobel Prize in Physiology or Medicine in 1983. In the 1950s McClintock described a novel mobile element, Suppressor-Mutator (Spm) and its complex regulation. She discovered that Spm could switch back and forth between an "inactive" form and an active form what she called "changes of phase" now known to be a result of methylation. Some forms of Spm showed specific patterns of expression and were only active in certain plant parts. These pioneering studies foreshadowed later work showing the importance of epigenetics, heritable changes not caused by changes in the DNA sequence, in development.

The mobilization of TEs is termed as transposition or retrotransposition, depending on the nature of the intermediate used for mobilization. There are several ways in which the activity of TEs positively or negatively impact a genome; for example, TE mobilization can promote gene inactivation or alter the expression of genes by insertion within introns, exons or regulatory regions, modulate gene expression or induce illegitimate recombination. Thus, TEs have played a significant role in genome evolution. TEs are also known as selfish DNA or junk DNA and the existence of these elements in a genome represents the fight between selfish DNA (to be perpetuated) and the host DNA sequences (to curtail their spread and its consequences).TEs are able to produce various genetic alterations upon insertion as a consequence of the transposition process (insertions, excisions, duplications or translocations in the site of integration). In addition, TEs can participate in the reorganization of a genome by the mobilization of non-transposon DNA or by acting as recombination substrates. This recombination would occur by homology between two sequences of a transposon located in the same or different chromosomes, which could be the origin for several types of chromosome alterations. Indeed, TEs can participate in the loss of genomic DNA by internal deletions or other mechanisms (Lopez *et al*., 2010).

A transposable element (or jumping gene) sometimes create or reverse mutations and altering

the cell's genetic identity and genome size (Bourque *et al.,* 2018). Transposition often results in duplication of the same genetic material which leads to make up a large fraction of the genome and are responsible for much of the mass of DNA in a eukaryotic cell. Although TEs are selfish genetic elements, many are important in genome function and evolution (Bucher *et al.,* 2012). There is evidence that transposons are not just "selfish genes" intent on replicating themselves or genomic "junk" that provides no benefit to the host.

They may play a creative role in building new functional parts of the genome. Recent research has shown that transposons may help plants respond and adapt to environmental stress by regulating other genes. In bacteria, transposons often carry genes that impart resistance to antibiotic substances, helping the bacteria survive. Transposons are also very useful for researchers as a means to alter DNA inside a living organism.

The epigenetic changes in plants induced by aforesaid processes can be inherited over the generations in the form of epialleles. Epigenetic change in genes caused by DNA methylation or histone modifications during plant development often results in phenotypic changes. It is becoming increasingly evident, that epigenetic changes have important roles to play in acclimatization, stress tolerance, adaptation and evolution processes. With the growing reports on epigenetic changes affecting gene expression, it would be worth investigating the epigenetic machinery of gene regulation in plants and their possible utilization in crop improvement (Kumar *et al.,* 2017).

Mechanism of Transposition

The insertion of a transposon into a new site is known as transposition. It consists of making staggered breaks in the target DNA, joining the transposon to the protruding single-stranded ends and filling in the gaps (Figure 1). The generation and filling of the staggered ends explain the occurrence of the direct repeats of target DNA at the site of insertion. The stagger between the cuts on the two strands determines the length of the direct repeats; So, the target repeat characteristic of each transposon reflects the geometry of the enzyme involved in cutting target DNA (Grindley and Reed, 1985). The use of staggered ends is common to all means of transposition, but it can be distinguished as three different types of mechanism by which a transposon moves:

Replicative Transposition

In replicative transposition, the element is duplicated during the reaction, so that the transposing entity is a copy of the original element. Fig. 2.1 summarizes the results of such a transposition. The transposon is copied as part of its movement. One copy remains at the original site, while the other inserts at the new site. So, transposition is accompanied by an increase in the copy number of the transposon. Replicative transposition involves two types of enzymatic activity: a transposase that acts on the ends of the original transposon and a resolvase that acts on the duplicated copies. A group of transposons related to TnA move only by replicative transposition.

Nonreplicative Transposition

In nonreplicative transposition, the transposing element moves as a physical entity directly from one site to another and is conserved. The insertion sequences and composite transposons Tn10 and Tn5 use this mechanism as shown in Fig. 2.2, which involves the release of the transposon from the flanking donor DNA during transfer.

This type of mechanism requires only a transposase enzyme. Both mechanisms of nonreplicative transposition cause the element to be inserted at the target site and lost from the donor site. What happens to the donor molecule after a nonreplicative transposition? Its survival requires host repair systems which recognize the double strand break and repair it. Another mechanism utilizes the connection of donor and target DNA sequences and shares some steps with replicative transposition.

Conservative Transposition

Conservative transposition describes another sort of nonreplicative event, in which the element is excised from the donor site and inserted into a target site by a series of events in which every nucleotide bond is conserved. Fig. 2.3 summarizes the result of a conservative event. This exactly resembles the mechanism of lambda integration as in 11 Phage strategies and the transposases of such elements are related to the λ integrase family. The elements that use this mechanism are large and can mediate transfer not only of the element itself but also of donor DNA from one bacterium to another. Although originally classified as transposons, such elements may more properly be regarded as episomes (Scott and Churchward, 1995).

Although some transposons use only one type of pathway for transposition, others may be able to use multiple pathways. The elements IS1 and IS903 use both nonreplicated and replicative pathways and the ability of phage Mu to turn to either type of pathway from a common intermediate has been well characterized.

Classification of Transposable elements

Transposable elements represent one of several types of mobile genetic elements. They assigned to one of the two classes according to their mechanism of transposition, which can be described as either copy and paste (Class I TEs) or cut and paste (Class II TEs) mechanism (Kapitonov *et al.*, 2008).

Retrotransposon

Class I TEs are copied in two stages: first, they are transcribed from DNA to RNA and the RNA produced is then reverse transcribed to DNA. This copied DNA is then inserted back into the genome at a new position. The reverse transcription step is catalyzed by a reverse transcriptase enzyme, which is often encoded by the TE itself (Fig 3). The characteristics of retrotransposons are similar to retroviruses, such as HIV.

Retrotransposons are commonly grouped into three main orders:

Retrotransposons, with long terminal repeats (LTRs) which encode reverse transcriptase, similar to retroviruses

Retroposons, with long interspersed nuclear elements (LINEs, LINE-1s, or L1s) which encode reverse transcriptase but lack LTRs and are transcribed by RNA polymerase II

Short interspersed nuclear elements (SINEs), do not encode reverse transcriptase and are transcribed by RNA polymerase III

Retroviruses can also be considered as TEs. For example, after conversion of retroviral RNA into DNA inside a host cell, the newly produced retroviral DNA is integrated into the genome of the host cell. These integrated DNAs are termed proviruses. The provirus is a specialized form of eukaryotic retrotransposon, which can produce RNA intermediates that may leave the host cell and infect other cells. The transposition cycle of retroviruses has similarities to that of prokaryotic TEs, suggesting a distant relationship between the two.

DNA transposons

The cut-and-paste transposition mechanism of class II TEs does not involve an RNA intermediate. The transpositions are catalyzed by several transposase enzymes. Some transposases bind non-specifically to any target site in DNA whereas, others bind to specific target sequences. The transposase makes a staggered cut at the target site producing sticky ends, cuts out the DNA transposon and ligates it into the target site (Fig. 4).

A DNA polymerase fills in the resulting gaps from the sticky ends and DNA ligase closes the sugar-phosphate backbone. This results in target site duplication and the insertion sites of DNA transposons may be identified by short direct repeats (a staggered cut in the target DNA filled by DNA

polymerase) followed by inverted repeats (which are important for the TE excision by transposase).

Cut-and-paste TEs may be duplicated if their transposition takes place during S phase of the cell cycle. When a donor site has already been replicated but a target site has not yet been replicated (Young *et al.*, 2012), such duplications at the target site can result in gene duplication, which plays an important role in genomic evolution (Madigan and Martinko, 2006). Not all DNA transposons transpose through the cut-and-paste mechanism. In some cases, a replicative transposition is observed in which a transposon replicates itself to a new target site (e.g. helitron).

Class II TEs comprise less than 2% of the human genome, making the rest Class I. (Kazazian, and Moran1998).

Autonomous and non-autonomous transposition

Transposition can be classified as either "autonomous" or "non-autonomous" in both Class I and Class II TEs. Autonomous TEs can move by themselves whereas, non-autonomous TEs require the presence of another TE to move. This is often because dependent TEs lack transposase (for Class II) or reverse transcriptase (for Class I).

Activator element (Ac) is an example of an autonomous TE whereas dissociation element (Ds) is an example of a non-autonomous TE. Without Ac, Ds is not able to transpose.

Class II elements types

Ac (Activator) element

Ac is the first element which was isolated from the waxy locus of maize and characterized at the molecular level (Fedoroff *et al.*, 1983). It is of 4563bp long and has 11-bp terminal inverted repeats. It Causes 8-bp target site duplication upon integration. Ac element consists of five exons and four introns.

SPM (Supressor-mutator) element

It is of 8.3-kb long with terminal inverted repeats of 13-bp. It causes 3-bp target site duplication. Primary Spm transcript is alternatively spliced. Four large transcripts identified as TnpA, TnpB, TnpC and TnpD. TnpA – shortest and most abundant trancript and TnpA and TnpB required for transposition.

Miniature Inverted Repeat Transposable Elements (MITEs)

MITEs are found to be associated with genes in several plant species including Maize, Rice, Barley, Green pepper and Arabidopsis (Casa *et al.*, 2000). MITEs are small with high copy number. They prefer to get inserted into A-T rich region and in 2-3 bp targets sequences. Structural features are reminiscent of non-autonomous DNA elements and there is absence of open reading frame. It has the presence of short terminal inverted repeats (11-14bp).

Transposable elements in prokaryotes

Insertion Sequences

Insertion element is a short DNA sequence that acts as a simple transposable element in bacterial chromosomes and plasmids. It has two major characteristics: they are small relative to other transposable elements (generally around 700 to 2500 bp in length) and they code only for proteins implicated in the transposition activity. These proteins are usually the transposase which catalyses the enzymatic reaction allowing the IS to move and also one regulatory protein which either stimulates or inhibits the transposition activity. The coding region in an insertion sequence is usually flanked by inverted repeats (Fig. 5). For example, the well-known IS911 (1250 bp) is flanked by two 36bp inverted repeat extremities and the coding region has two genes partially overlapping orfA and orfAB, coding the transposase (OrfAB) and a regulatory protein (OrfA). A particular insertion sequence may be named according to the form ISn, where n is a

number (e.g. IS1, IS2, IS3, IS10, IS50, IS911, IS26 etc. IS1 first identified in *E. coli* glactose operon is 768 bp long and is present with 4-19 copies in the *E. coli* chromosome. Although, insertion sequences are usually discussed in the context of prokaryotic genomes, certain eukaryotic DNA sequences belonging to the family of Tc1/mariner transposable elements may be considered to have insertion sequences.

Composite Transposons

A composite transposon is similar in function to simple transposons and Insertion Sequence elements. It has protein coding DNA segments flanked by inverted, repeated sequences that can be recognized by transposase enzymes. A composite transposon, however, is flanked by two separates IS elements which may or may not be exact replicas (Fig. 6). Instead of each IS element moving separately, the entire length of DNA spanning from one IS element to the other is transposed as one complete unit. Composite transposons will also often carry one or more genes conferring antibiotic resistance (Zelnick *et al.*, 1987).

Transposable phage (Mu phage)

Mu phage also refers as "Temperate or transposable phage" because at the time of multiplication Mu-phage causes transposition of the genes into the host cell. It mainly attacks the members or species of enterobacteria family and that's why also known as "Enterobacterial phage Mu". An E. coli temperate bacteriophage called Mu. Mu genome is linear duplex DNA of about 39kbp with 20 bp long TIRs flanked by *E. coli* DNA segments. Upon integration causes 5 bp target site duplication. Mu phage served as model for the elucidation of bacterial transposition mechanism at the molecular level.

Tn-3 type or Non-composite transposons

The Tn3 transposon is a 4957 base pair mobile genetic element, found in prokaryotes. It encodes three proteins:

β-lactamase, an enzyme that confers resistance to β-lactam antibiotics (encoded by the gene Bla).

Tn3 transposase (encoded by gene tnpA)

Tn3 resolvase (encoded by gene tnpR)

Initially, it was discovered as a repressor of transposase, resolvase also plays a role in facilitating Tn3 replication (Sherratt, 1989). The transposon is flanked by a pair of 38bp inverted repeats (Fig. 7).

Transposable elements of eukaryotes

Yeast Ty Elements

Yeast carries about 35 copies of a transposable element called Ty in its haploid genome. These transposons are about 5900 nucleotide-pairs long and are bounded at each end by a DNA segment called the σ sequence, which is ~340bp long. Each σ sequence is oriented in the same direction, forming direct long terminal repeats (LTRs). Thus, Ty1 elements in yeast is an example of LTR retrotransposons. Sometimes LTR get detached from a Ty element, creating a so called solo σ. It is thought that these solo σ are generated by recombination between the LTRs of a complete Ty element.

Drosophila Transposons

P elements

P element in Drosophila is one of the best examples for exploiting the properties of transposable elements in eukaryotes. This element, is 2907 bp long and features a 31 bp inverted repeat at each end. DNA sequence analysis of the 2.9 kb element reveals a gene composed of four exons and three introns, that encodes transposase.

Although the transposase is required for transposition, it can be supply by a second element. Therefore, P elements with internal deletions can be mobilized and then remain fixed in the new position

in the absence of the second element. Thus, the P element can serve as a convenient marker. P elements do not utilize an RNA intermediate during transposition and can insert at many different positions in the Drosophila chromosome. Paternal P type mating with maternal M type causes Hybrid Dysgenesis in offspring.

The transposition of a P element is controlled by repressors encoded by the element. P elements has been developed as tools for Drosophila much in the same way as Tn 10 have for bacteria. Namely, P elements can be used to create mutations by insertion, to mark the position of genes and to facilitate the cloning of those genes. P elements can be inserted into genes *in vivo* and different phenotypes can be selected. Then, the interrupted gene can be clone with the use of P element segments as a probe, a method termed transposon tagging.

Copia elements

The copia -like elements constitute at least seven families, ranging in size from 5 to 8.5 kb. Members of each family appear at 10–100 positions in the Drosophila genome. Each member carries a long, direct terminal repeat and a short, imperfect inverted repeat and is structurally similar to a yeast Ty element. *Copia*-like elements also cause a duplication of a characteristic number of base pairs of *Drosophila* DNA on insertion. Certain classic *Drosophila* mutations result from the insertion of *copia*-like and other elements.

For example, the white-apricot (w^a) mutation for eye color is caused by the insertion of an element from the *copia* family into the white locus. Some *copia*-like families have surprising properties. For instance, all the insertion mutations detected so far that result from the *gypsy* family of *copia*-like elements are suppressible by a specific allele at one particular outside locus. That is, the phenotypes resulting from the *gypsy* insertions are affected by unlinked genes. The mechanism of the effect is unknown.

Controlling Elements in Maize: The Ac/Ds Element

In the 1950s, Barbara McClintock during study of corn kernels found that, rather than being purple or white; they exhibited spots of purple pigment on normally white kernels. The explanation for the spotted kernels is that if the corn plant carries a wild type C gene, the kernel will be purple, c (colorless) mutations block purple pigment production, so the kernel is colorless. During kernel development, revertant of the mutation occur, leading to a spot of purple pigment. The genetic nature of the reversion is supported by the fact that descendants of the cell which underwent the reversion can also produce the pigment. McClintock determined that the original c (colorless) mutation resulted from a mobile controlling element, a genetic factor called as Ds (Dissociation). The action of Ds is dependent on the presence of an unlinked gene, Ac (Activator).Ac is required for transposition of Ds into the gene. Ac can also move the Ds out of the C gene, resulting in the wild type revertant, *i.e.* a purple spot. McClintock found it impossible to map Ac. In some plants, it mapped to one position; in other plants of the same line, it mapped to different positions. Moreover, the Ds locus itself was constantly changing position on the chromosome arm, as indicated by the differing phenotypes of the variegated sections of the seeds.

Human: Alu

An Alu element is a short stretch of DNA originally characterized by the action of the *Arthrobacter luteus* (Alu) restriction endonuclease (Schmid *et al.*, 1975). Alu elements are the most abundant transposable elements, containing over one million copies dispersed throughout the human genome (Szmulewicz *et al.,* 1998). They do not contain any coding sequences and contribute about 5% of the human genome. Alu elements were thought to be selfish or parasitic DNA, because their sole known function is self-reproduction. However, they are likely to play a role in evolution and have been used as genetic markers (Kidwell *et al.,* 2001 and Pray *et*

al., 2008). They are derived from the small cytoplasmic 7SL RNA, a component of the signal recognition particle.

Evolutionary implications of Transposable elements

Generation of fine genetic variability

Genome rearrangements-raw material for possible evolution of new genes

Chromosomal shrinkage and expansion

A transposon inserts itself into a functional gene, it will probably damage it. Insertion into exons, introns and even into DNA flanking the genes can destroys or alters the gene activity.

Applications of Transposons and Retrotransposons

Transposon mutagenesis and gene tagging: Facilitated by isolation and characterization of functional transposable elements mainly from Maize (Ac, Spm, Mu), Antirrhinum(Tam3) and Arabidopsis(Tag1).Researchers use them as a means of mutagenesis. In this context, a TE jumps into a gene and produces a mutation. The presence of TE provides a straightforward means for identifying the mutant alleles relative to chemical mutagenesis methods.

TEs are also a widely used tool for mutagenesis of most experimentally tractable organisms. The Sleeping Beauty transposon system has been used extensively as an insertional tag for identifying cancer genes (Carlson and Largaespada, 2005).

Transposons as a genetic tool: The first TE was discovered in maize (*Zea mays*) which was named as dissociator (Ds). Likewise, the first TE to be molecularly isolated was from a plant (snapdragon). Appropriately, TEs have been an especially useful tool in plant molecular biology. Significance in Breeding Programme: Transposons are capable of influencing expression of number of genes involved in different pathways including those that are of breeder's interest. Imprecise excision of plant transposon from the target genes can generate genetic variability that can be further selected upon by breeders.

Sometimes the insertion of a TE into a gene can disrupt that gene's function in a reversible manner, in a process called insertional mutagenesis; transposase-mediated excision of the DNA transposon restores gene function. This produces plants in which neighboring cells have different genotypes. This feature allows researchers to distinguish between genes that must be present inside of a cell in order to function (cell-autonomous) and genes that produce observable effects in cells other than those where the gene is expressed.

The Tc1/mariner-class of TEs Sleeping Beauty transposon system, awarded Molecule of the Year in 2009 (Luft, 2010) is active in mammalian cells and is being investigated for use in human gene therapy. (Ivics and Izsvák, 2006)

Transposons can act as biological mutagen in bacteria.

Retroposons as tools in Molecular Breeding: DNA fingerprinting, Genetic linkage mapping.

Retrotransposons utility in analysis of Biodiversity and Phylogeny: Retrotransposon based markers are suitable for studying phylogenetic relationships and genetic diversity within and between species. Active Retrotransposon family produces new insertions in the genome leading to polymorphism which are exploited in Brassica, Hordeum, Oryza and Pisum.

Was Lamarck Just a Little Bit Right?

A French biologist Jean-Baptist Lamarck (1744-1829) proposed the theory of 'soft inheritance' or 'inheritance of acquired characters' describing that an organism can pass on the characters to their

offspring which they acquire during their lifetime. Although Jean-Baptiste Lamarck is remembered mostly for the discredited theory that acquired traits can be passed down to offspring, new findings in the field of epigenetics, the study of changes in genetic expression that are not linked to alterations in DNA sequences, are returning his name to the scientific literature. Although these new findings do not support Lamarck's overall concept, they raise the possibility that "epimutations," as they are called, could play a role in evolution. Lamarck was a true pioneer of evolutionary theory (Balter, 2000).

Later on, Charles Darwin published his book on the 'Origin of Species' in 1859 wherein he proposed the 'theory of evolution by natural selection' and emphasized on the use and disuse inheritance, but rejected the Lamark's theory of inheritance of acquired characters. Darwin described the natural selection as the process in which struggle for existence and survival of the fittest has a similar effect to that of artificial selection involved in the selective breeding. Later, Gregor Johann Mendel (1822-1884) proposed 'Laws of inheritance' which supplanted the notion of inheritance of acquired traits. Despite this abandonment, interest in Lamarckism continued. Integration of Darwin's theory with the advancing genetic and molecular sciences facilitated the development of a well-supported neo-Darwinian theory of evolution. Recent studies demonstrate that the genetic variations are sufficient for evolution, but genetic theory alone faces difficulty in explaining some features of evolution. The rate of phenotypic variations and genetic mutations are considerably different, which cannot be explained merely based on genetics as the primary molecular mechanism. Additional mechanisms such as epigenetics can help explaining this enigma (Kumar, 2017a). Many traits do not follow normal Mendelian inheritance and are difficult to be explained by the classical genetics. The recently documented molecular mechanisms such as epigenetics can help explaining such genome activity and phenotypic variations (Skinner, 2015). If epigenetics is considered as a complementary molecular mechanism, many of the phenotypic variations (*e.g.* dissimilarity between the clones) can be easily explained. Until the last century, it was thought that isolation of the gene(s) associated with a trait of interest was sufficient to transfer the trait to a crop plant and to achieve the expected phenotype. Recently, definitive evidence has been gathered for the DNA to provide only part of the genetic information for a trait and that chromatin changes also contribute to the expression of the trait. DNA (cytosine) methylation, post-translational modifications (acetylation, methylation, phosphorylation, etc.) of histone proteins and regulatory RNAs (non-coding RNAs or ncRNAs) define distinct chromatin/epigenetic states of the genome (epigenome), which vary with the changing environmental conditions.

Epigenetics: A missing link in genetics

Brink in 1950s noticed interaction between two alleles of b1 (booster 1) locus (B–I: paramutable allele, active; and B': paramutagenic allele, inactive) (Fig. 8). This interaction between the two alleles (possessing the same DNA sequence) of a single locus in maize resulted in a heritable change in one allele that is induced by the other allele (Brink 1956). The b1 locus codes for a transcription factor (bHLH) which activates the genes of anthocyanin biosynthesis pathway in maize.

At that time, Brink could not explain the genetic basis of the observed phenomenon based on the available knowledge in the field of genetics. Therefore, the phenomenon was termed as paramutation. Brink also reported that the influence of paramutagenic allele persists for several generations. Now, the B–I and B' alleles in maize are known to possess variation in DNA methylation in the tandem repeats near the coding region of the gene. Such variation in cytosine methylation has been reported to be the feature of the paramutagenic B' allele and when a paramutable B-I allele gets converted into paramutagenic, it acquires the same DNA methylation pattern. In order to inherit methylation, RNA-dependent RNA polymerases, as well as other components of RNA-silencing

pathways are required, suggesting that paramutation is mediated through the endogenous RNA-silencing pathway (Alleman *et al.,* 2006).

What is epigenetics?

Epigenetics is the exhibition of alternative phenotypes by the same genome because of its different epigenetic states. The term epigenetics was first used by embryologist C. H. Waddington in early 1940swithout having the understanding of its molecular basis of action (Waddington, 1942). He defined epigenetics as ‘‘the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being (Waddington, 1968). The Greek prefix epi (means over, outside of, around) in epigenetics implies that the features are “on top of”, “in addition to” or “from outside of” the classical genetic basis of inheritance. Waddington at that time tried to integrate this new knowledge of genetics in embryology. Epigenetics is defined as the studies of molecular processes in and around DNA that control genome activity independent of the DNA nucleotide sequence which may be inherited through mitosis or meiosis (Kumar and Singh, 2016). These epigenetic mechanisms include DNA methylation, histone protein modifications and biogenesis of ncRNAs (Kumar, 2017a). There is limited evidence for naturally occurring epialleles and yet we know only a little about phenotypic and ecological consequences of the epigenetic variations (Manning *et al.,* 2006). One of the difficulties in correlating phenotypic effects with the epigenetic variations is that epigenetic and phenotypic variations covary in natural systems, which make it difficult to unravel their effects on phenotype (Richards *et al.,* 2010).

Components of epigenetics

Propagation of epigenetic marks in plants takes a much more direct route than that in animals for transmission of cytosine methylation from one generation to the next. DNA methylation, histone modifications and ncRNAs play an important role as epigenetic marks in the expression of genes. Inheritance of epigenetic marks (e.g. natural variation of DNA methylation associated with the environmental changes) over the generation has been reported and may have a genetic (single nucleotide polymorphisms driven gene-body methylation) root cause (Zheng *et al.,* 2017).

Paramutation

Gene expression is tightly regulated. Mechanisms involved in gene regulation include in cis interactions between regulatory sequences and promoters. These interactions are mediated by the binding of regulatory proteins to cis-acting DNA elements. There is increasing evidence that gene regulation by sequences on another chromosome, *i.e.* in trans, is important in higher eukaryotes as well. In addition to in cis and in trans regulation, gene expression is also regulated epigenetically. Epigenetic mechanisms, such as DNA methylation, histone modifications and the incorporation of histone variants are crucial for the regulation of eukaryotic gene transcription and other chromatin-related processes. Epigenetic gene regulation involves the stable propagation of gene activity states through mitotic and sometimes even meiotic, cell divisions without changes in DNA sequence.

These heritable changes are mediated by in trans interactions between homologous DNA sequences on different chromosomes. During these in trans interactions, epigenetic information is transferred from one allele of a gene to another allele of the same gene, resulting in change in the gene expression. Paramutation generally results in transcriptional gene silencing, although gene activation has also been reported. Paramutation has furthermore been linked to processes such as transposition and recombination Although paramutation was initially discovered in plants, it has recently been observed in mammals as well, suggesting that the mechanisms underlying paramutation might be evolutionarily conserved. Recent findings point to a crucial role for small RNAs in the paramutation process. In mice, small RNAs appear sufficient to induce paramutation,

whereas in maize, it seems not to be the only player in the process (Stam, 2009). Paramutation at the b1 locus, for example, occurs between the paramutagenic B' and paramutable B-Intense (B-I) allele (Figure 8). B-I is transcribed at approximately 10–20 times higher levels than B', resulting in high pigment levels in B-I plants and low pigment levels in B' plants (Patterson *et al.,* 1993). The B-I and B' alleles have the same DNA sequence but differ in DNA methylation and chromatin structure and are therefore considered epialleles rather than true alleles (Chandler *et al.*, 2000; Stam *et al.*, 2002a).

Not all alleles of the loci that show paramutation are sensitive to paramutation or able to induce it. In fact, typically, most alleles of such loci follow the classic laws of Mendelian inheritance and are known as neutral alleles.

Genomic Imprinting

Genomic imprinting is the inheritance out of Mendelian borders. Many of inherited diseases and human development violates Mendelian law of inheritance, this way of inheriting is studied by epigenetics. Epigenetics shows that gene expression undergoes changes more complex than modifications in the DNA sequence; it includes the environmental influence on the gametes before conception. When epigenetic changes occur in sperm or egg cells that lead to fertilization, epigenetic changes are inherited by the offspring. It is thus, defined as a reversible modification of DNA that causes differential expression of maternally or paternally inherited genes, although the gene sequence remains the same. In other words, the phenotype elicited from a locus is differentially modified by the sex of the parent contributing that particular allele. This process ultimately results in a functional difference between the genetic information contributed by each parent and the imprinted loci can be thus considered 'functionally hemizygous'. Genomic imprinting is a process of silencing genes through DNA methylation. The repressed allele is methylated, while the active allele is unmethylated. Genomic imprinting occurs when two alleles at a locus are not functionally equivalent and is considered the primary epigenetic phenomenon that can lead to the manifestation of parent-of-origin effects. Genomic imprinting affects both male and female offspring and is therefore a consequence of parental inheritance, not of sex. DNA methylation is a biochemical process crucial for normal development in higher organisms and it is the most thoroughly studied epigenetic mark (Bajrami and Spiroski, 2016).

Molecular epigenetic mechanism

Development of multicellular organisms occurs due to cells differentiation by various programs of gene expression. Cells have their own epigenetic signatures like genotype, developmental history, environmental influences which is ultimately reflected in the phenotype of the cells and the organism (Sandhya, 2011).

Epigenetics act mainly through four different mechanisms:

DNA methylation

Chromosome remodeling

Histone modification

RNA interference/interactions

Modifications at the DNA level

These modifications get cancelled during the process of gametogenesis and embryogenesis. Thus, it is an epigenetic phenomenon but not inherited over the generations.

DNA methylation

DNA methylation in mammals mainly occurs on the cytosine nucleotide in a CpG site. In plants the cytosine can be methylated at CpG, CpHpG, and CpHpH sites, where H represents any nucleotide. MET1 and CMT3: DNA methylases in plants and

CMT3 protein is unique to the plant kingdom.Its role in prokaryotes, as defence mechanism, escape from the restriction enzymes and protection from bacteriophages. In eukaryotes, it controls the mechanism of transposable elements in the genome.

Classes of methyl transferase

De novo class

Enzymes that create new methylation mark on DNA

e.g. DNMT3a and DNMT3b

Maintenance class

Enzymes that recognizes the methylation marks on the parental strand of DNA and transfers new methylation to the daughter strands after DNA replication

e.g. DNMT1

Cytosine methylation

It is the addition of methyl group to the cytosine base of the DNA sequence to form 5' methyl Cytosine (Thymine) (Fig. 9). Any mutation at 5' methyl Cytosine site in the DNA sequence converts it into Uracil and therefore hard to be identified and repair.

Methylation at promoter site

When methylation occurs at the promoter site, the transcription process gets suppressed.

Methylation is important for

Silencing of transcription

Genomic imprinting

X chromosome inactivation

Protecting the genome from transposition

Tissue specific gene suppression and regulation

Heterochromatin

Developmental controls

Cancer therapy

Chromatin remodeling

Chromatin remodeling includes the shifting of nucleosome cores. The process is known as nucleosome sliding. The shift results from disassembling and reassembling the units of nucleosome core. This process is one of the major factors controlling the gene expression by induction and repression.

The remodeling is brought about by SWI/ SNF family of ATPase complexes. There are four types of complexes based on the type of ATPase. These are SWI2/SNF2, initiation switch (ISWI), INO80 and Mi-2 (CHD1).

Histone modifications

Histone: There are several small, basic proteins most commonly found in association with the DNA in the chromatin of eukaryotes are known as histone proteins. Packaging and ordering the DNA into structural unit called nucleosomes. Histone modifications also known as epigenetic modifiers. Biological functions of histone modification include in chromatin organization, gene expression and DNA repair.

Histones are not only packaging factors, but also regulate gene expression like activation and repression. It is a covalent post-translational modification of histone protein.

The post-translational modification made to histones can impact gene expression by altering chromatin structure. There are a lot of histone modifications which are typically conserved over evolutionary processes (Fig. 10).

These include-

Methylation of lysine and arginine residues

Acetylation of lysine

Phosphorylation of serine and threonine residues

proline isomerization

monoubiquitylation

sumoylation

These modifications can occur both in coding as well as non-coding sequences of the genome. Some modifications are specific to either active or inactive regions of transcription. These are influenced by the developmental stage, phase of cell cycle, stress and other environmental factors.

Histone acetylation

It is the process by which the lysine residues within the N-terminal tail protruding from the histone core of the nucleosome is acetylated as part of gene regulation. Acetylated histones are found to open the chromatin and thus enable transcription (Fig. 11). The acetylation of histones is carried out by histone acetylases. These enzymes form part of chromatin remodeling and transcription complexes. The N-terminal lysine residues undergo acetylation and this causes the histone proteins to lose their positive charges. The affinity between DNA and histones get reduces and the promoter regions become easily accessible to the enzymes initiating transposition. When histones are deacetylated, they are less accessible to transcription and are tightly packed. The deacetylation of histones is carried out by the enzyme HDAC or histone deacylase.

Histone methylation

Histone methylation is a process by which methyl groups are transferred to amino acids of histone proteins which make up the nucleosome (Fig. 12). DNA activation or inactivation is largely dependent on the specific tail residue methylated and its degree of methylation.

Histone phosphorylation

It is the addition of phosphate group to histone protein and is catalysed by specific protein kinases and phosphatases which remove the phosphate group (Fig.13). Serine and threonine residues are phosphorylated by histone kinases.

Phosphorylation of histones occurs during mitosis, signal transduction pathways like the ERK pathway.

Histone ribosylation

It is the addition of one or more ADP riboseto histone is known as histone ribosylation (Fig. 14). Source of ADP ribose is NAD+. Cleavage of glycosidic bond between ADP ribose and nicotinamide group is followed by nucleophilic attack of protein side chains.

Deamination

It is the process of removal of an amino group from a molecule (Smith and March, 2013). Enzymes that catalyse this reaction is called deaminases. Spontaneous deamination is the hydrolysis reaction of cytosine into uracil, releasing ammonia in the process.

This can occur in vitro through the use of bisulfite, which deaminates cytosine, but not 5-methylcytosine. This property has allowed researchers to sequence methylated DNA to distinguish non-methylated cytosine (shown up as uracil) and methylated cytosine (unaltered).

Histone ubiquitination

Addition of ubiquitin to a substrate protein is called ubiquitination. Ubiquitination of histones has been found to cause heritable gene silencing and inactivation of X chromosome (Fig. 15).

It involves 3 main steps-

activation

conjugation

ligation

RNA interference

RNA interference also called post transcriptional gene silencing (PTGS) is a biological process in which RNA molecules inhibit gene action. This mechanism of gene silencing was discovered by Andrew Z. Fire and Craig. C. Mello in the nematode worm *Caenorhabditis elegans*. For this discovery they shared the Nobel Prize in Physiology and Medicine in 2006.Epigenetic regulation is influenced by the presence of non-protein coding RNAs.

These RNAs form an essential part of RNA interference. The small double stranded RNA molecules inhibit gene expression by interacting with the nascent RNA molecule, DNA sequence or by other mechanism involving chromatin modifiers. These siRNA molecules are involved in the formation of RISCs (RNA induced silencing Complexes).

These complexes thus formed promote epigenetic silencing by cleavage of RNA molecule or through RNA directed methylation. The process of translation gets temporarily abrupted but doesn't eliminate the gene expression (Fig. 16).

Methods for studying epigenetic modifications

DNA methylation: Bisulfite sequencing, Methylation Sensitive Amplification Polymorphism (MSAP)

Histone modification: Chromatin immunoprecipitation (CHIP)

RNAi: Deep sequencing

Significance and implications of epigenetic mechanism

Epigenetic inheritance and plant breeding

Epigenetic changes in chromosomal proteins and DNA methylation have important phenotypic consequences. Epigenetic phenotypes can result from:

Activation, excision and translocation of transposon elements (McClintock, 1950).

Allelic interactions known as paramutations (Brink, 1956).

Transgene silencing in plants.

Epialleles of endogenous plant genes that control floral induction and morphogenesis, seed development and parental imprinting.

Epigenetic mechanism and genetic variation

Epialleles as a new source of polymorphism may produce novel phenotypes; this could have significant implications in plant breeding. Besides mutation and recombination, epialleles have been found to produce a new source of variation for selection. Epigenetic alleles can result as a genome response to stressful environments and enable plants to tolerate stress.DNA methylation as the generator of epialleles could have important implications for the breeder.

Assessing the importance of methylated epialleles in plant breeding requires the determination of:

The extent of variation in methylation pattern among individuals within a selection population

The degree to which methylation pattern affect phenotypes

The extent to which methylation variants are linked to superior phenotypes are stably inherited

DNA methylation and somaclonal variation

Somaclonal variation is generally attributed to tissue culture induced, heritable genetic changes rather than pre-existing genetic or even epigenetic variation in the somatic cells of the explant.

A somatic cells or group of cells having a unique genetic constitution or epigenetic modification, may produce preferentially in culture. Any plant eventually regenerated from these cells will be a variant.

It is becoming more apparent that somatically acquired epigenetic modifications in plants can be mitotically stable and meiotically heritable, more emphasis is given to variation in DNA methylation as a source of somaclonal variation.

DNA methylation, heterosis and hybrid breeding

Genes controlling protein amounts and enzyme activities directly affect the expression of hybrid vigor.

DNA methylation could be considered as a genome-wide regulatory mechanism that affects the expression of many genes important for the manifestation of heterosis.

DNA methylation analysis techniques results in following inferences-

hybrids in general are less methylated than their parental inbreds.

heterotic hybrids are less methylated than related non-heterotic hybrids.

old, low yielding inbreds are highly methylated.

more modern inbreds, especially those selected for high and stable yield underspacing in the isolation environment, have lower percentage of methylation in comparison with old progenitor lines.

Manipulation of parental imprinting

Development of endosperm can be manipulated through epigenetic mechanism controlling parental imprinting.

Studies in Arabidopsis showed over proliferation of endosperm (desirable trait for seed crops) on removal of parental imprinting.

Exploration of epigenetic mechanism of seed development reveals mysteries about apomixis *i.e*. production of fertile plant progeny without double fertilization.

If this mechanism is applied to commercial crops, hybrids can be regenerated indefinitely.

Interrelationships among DNA Methylation, Transposons, Paramutation and Gene Silencing

DNA methylation play a vital role in regulating transposon activity.

Interaction between homologous transposable elements share some features with paramutation.

Paramutation is more similar to transcriptional gene silencing (TGS) than to post-transcriptional gene silencing (PTGS).

Transposons are genome builders and restructuring agents, which was initially brought about by pioneering discoveries in maize by Barbara McClintock, is now becoming firmly established.

Transposons are inherently mutagenic; but, some of them properties, like imperfect excision (in case of many plant transposable elements) leading to allele and protein variability, and enhanced ectopic recombination, might have had profound effects on genome evolution and evolutionary history.

Transposable elements, particularly retrotransposons, appear to play significant role in genome expansion as well as shrinkage.

Pie chart.1 Human Genome

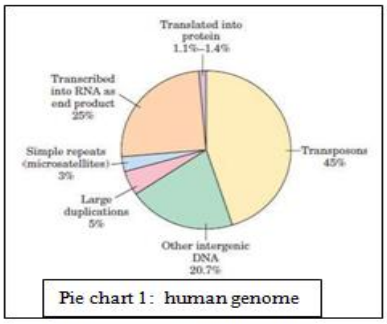


Fig.1 The direct repeats of target DNA flanking a transposon are generated by the introduction of staggered cuts whose protruding ends are linked to the transposon

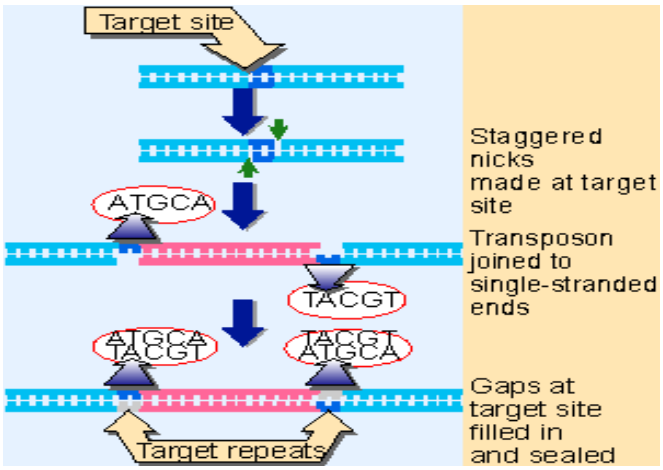


Fig.2.1 Replicative transposition creates a copy of the transposon, which inserts at a recipient site. The donor site remains unchanged, so both donor and recipient have a copy of the transposon.

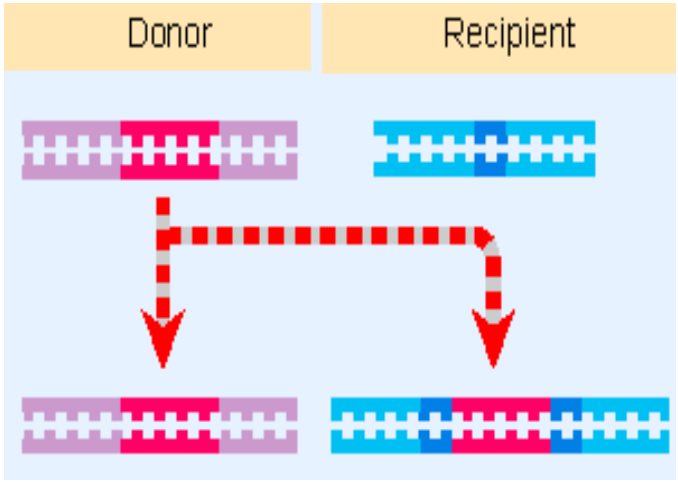


Fig.2.2 Nonreplicated transposition allows a transposon to move as a physical entity from a donor to a recipient site. This leaves a break at the donor site, which is lethal unless it can be repaired.

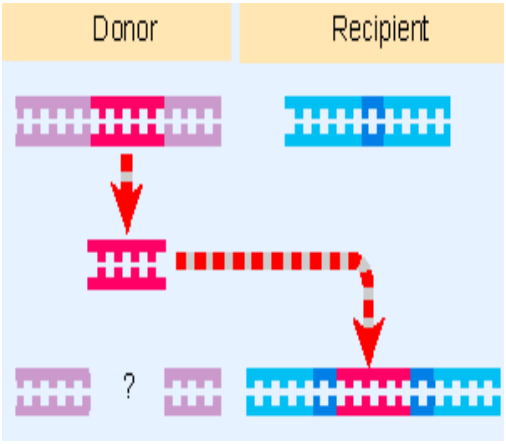


Fig.2.3 Conservative transposition involves direct movement with no loss of nucleotide bonds; compare with lambda integration and excision.

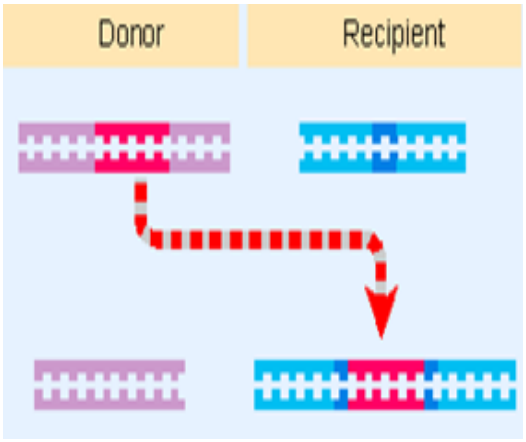


Fig.3 Retrotransposition

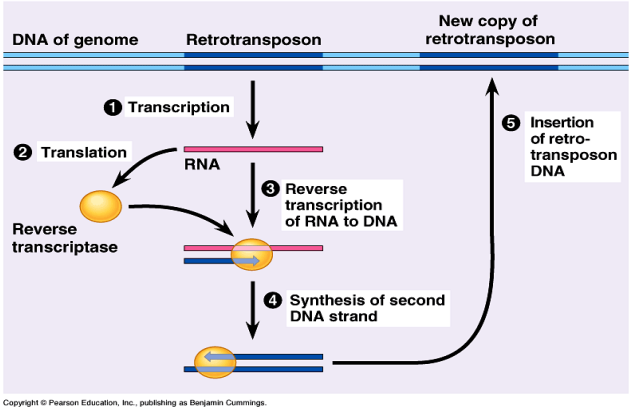


Fig.4 Transposase enzyme activity

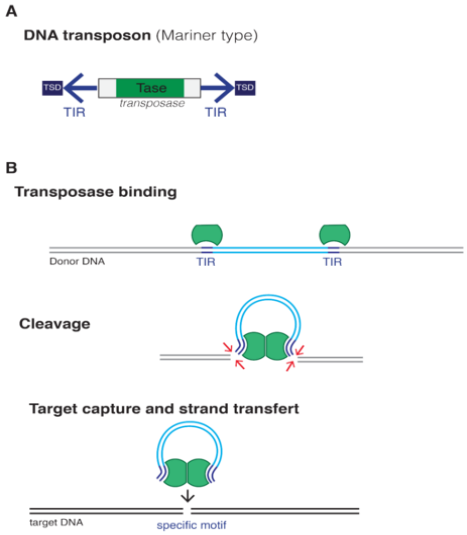


Fig.5 Inverted repeats in Insertion sequence

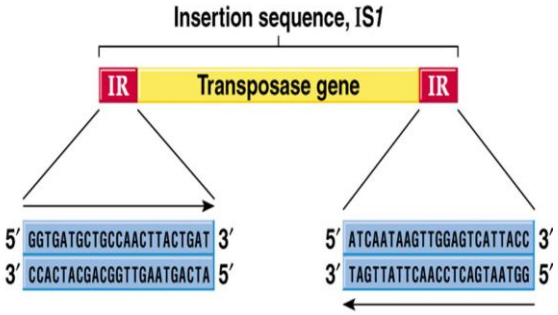


Fig.6 Composite Transposon Sequence

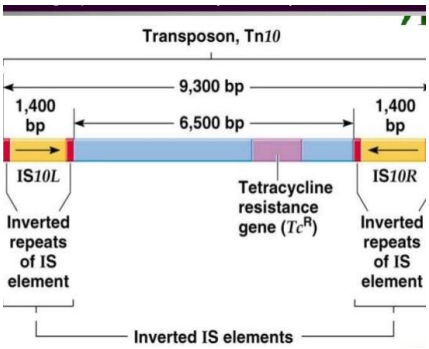


Fig.7 Tn-3 type Sequence

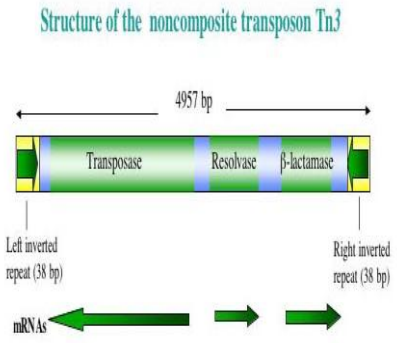


Fig.8 The Principle of Paramutation Illustrated for the Maize b1 Locus. (A) A plant carrying the paramutagenic, inducing B' allele (giving rise to a light pigmented plant) is crossed to a plant containing the paramutable, sensitive B-I allele (giving rise to a dark pigmented plant). When combined in one nucleus, the paramutagenic B' allele interacts intrans (light purple arrow) with the paramutable B-I allele, heritably changing B-I into B'(establishment of paramutation), resulting in light pigmented F1 plants. Seven 853-bp repeats (black triangles), located 100 kb upstream of the b1 coding region, are required for the trans-interaction, and also for enhancing b1expression (green arrow). Once B-I is changed into B, it displays secondary paramutation; it has become paramutagenic itself. Consequently, crosses between the F1 and plants carrying the B-I allele only yield light pigmented progeny.

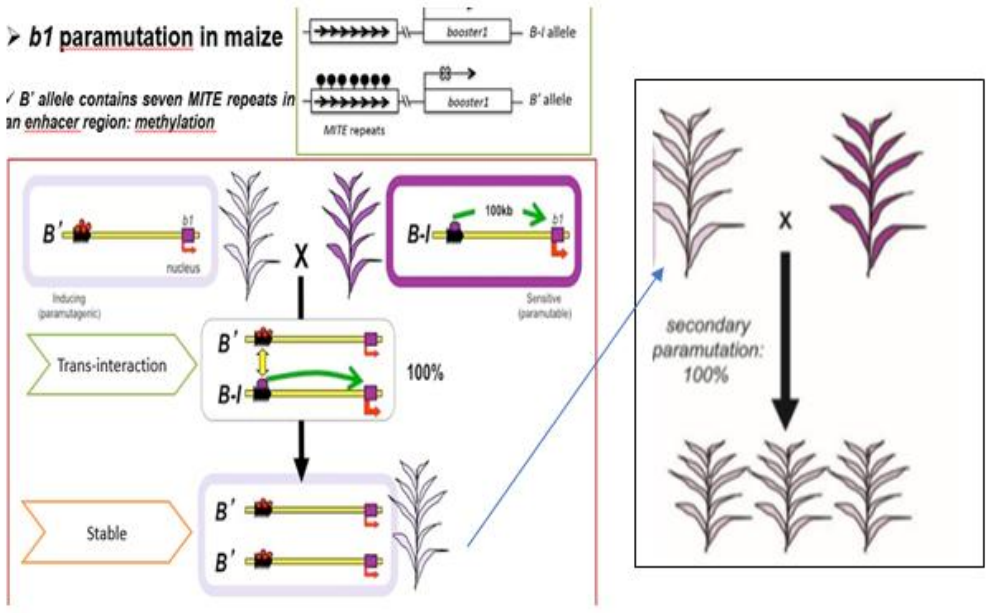


Fig.9 Cytosine methylation

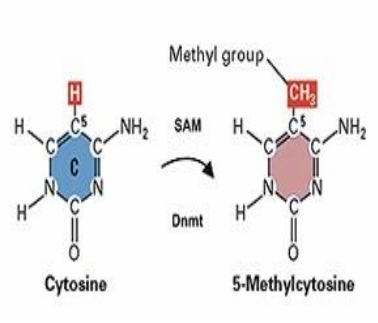


Fig.10 Histone Modifications

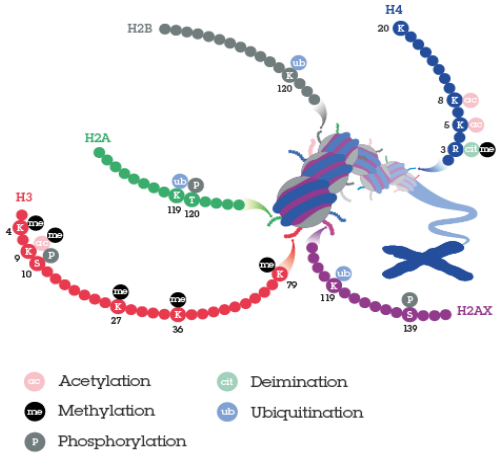


Fig.11 Histone acetylation

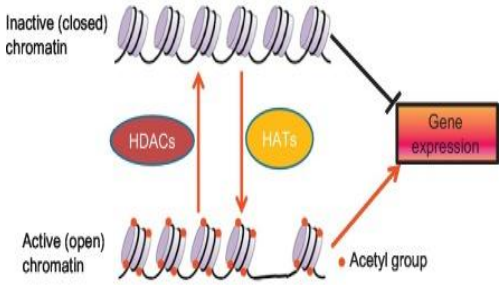


Fig.12 Histone methylation

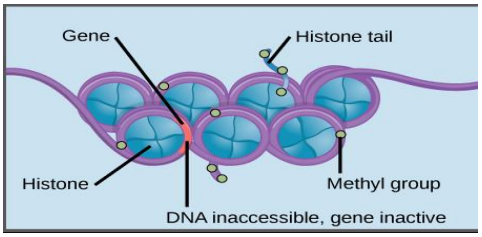


Fig.13 Histone phosphorylation

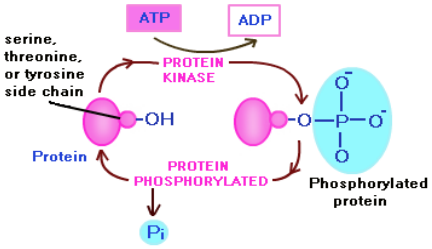


Fig.14 Histone ribosylation

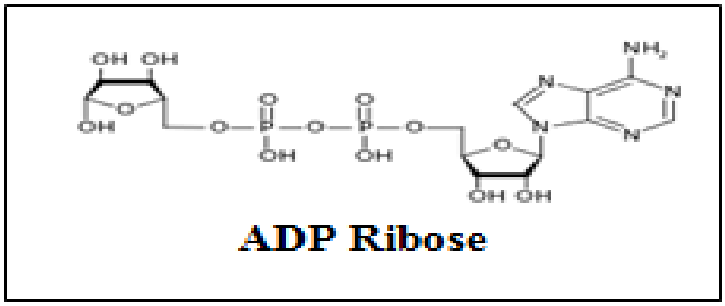


Fig.15 Histone ubiquitination

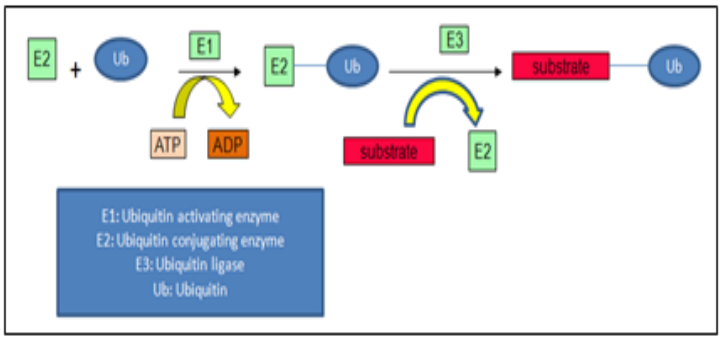
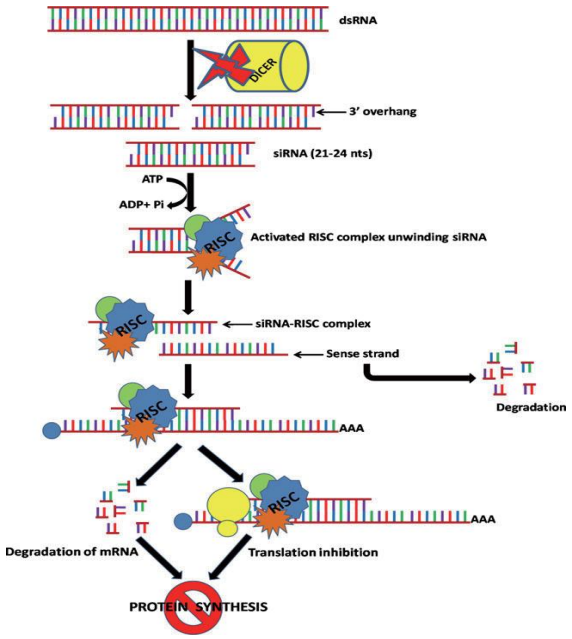


Fig.16 RNA interference



Transposable elements are also now serving as powerful molecular tools for isolation of plant genes, including several genes influencing diverse agronomically important characters in various plant species.

Also, retroelements are now beginning to be utilized as molecular tools for DNA fingerprinting and phylogenetic analysis. With the completion or near-completion of genome sequencing projects in a wide variety of organisms, including bacteria, viruses, plants and animals, the next major challenge shall be to understand how genes function and how they are regulated.

Achieving this goal requires a closer examination of how epigenetic controls are imposed on genes and a better understanding of how such controls are maintained and reset during development and sexual reproduction of a plant. Knowledge of epigenetic controls such as imprinting, DNA methylation and gene silencing is also important from the plant breeding and plant genetic engineering viewpoints and consequently in analyzing stability of performance of both conventionally bred and transgenic cultivars.

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