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REVIEW ARTICLE

EPIGENOMICS: ROLE, APPROACHES AND APPLICATIONS IN PLANTS

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ABSTRACT

Epigenetic changes are caused due to change/activation of certain genes in DNA microstructure and not in DNA sequences. With continuous growth in existing knowledge about the mechanisms and potential role of epigenomics in plants, there is a lot of enthusiasm and eagerness about the prospective for three epigenetic information systems (EIS) *viz.* DNA methylation, Histone modification and RNA interference. The various genetic and biochemical approaches along with epigenomics will broaden our understanding of plant genomes and metabolic pathways. Insight into epigenomics can also help in improving strategies for better control over the transgene expression during development of transgenics. Although there were many studies about epigenetic modifications in previous decades, it is only through high-performing approaches and developments in bioinformatics technology that made possible to analyse this globally. Epigenomic information is important in understanding gene regulation during early stages of plant development, plants' responses to the external stimulants and in natural variation for crop improvement. Therefore, the present review aims at discussing the role of epigenomics, the combination of approaches used and the applications of epigenomics in context to plants.

Key words: Epigenomics, *Arabidopsis*, DNA methylation, siRNA, histone.

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INTRODUCTION

The standard paradigm of genetics requires that all heritable variation between members of a population should correspond to their DNA sequence. Although the major phenotypic changes have the genetic bases yet there is some part of heritability which can relate to epigenetic modifications of DNA (Jablonka and Lamb 2005; Weigel and Colot, 2012; Fedoroff, 2012; Park and Lehner, 2013). In 1942, British developmental biologist Conrad H. Waddington combined "epigenesis" and "genetics" and introduced the term "epigenetics" which is the interplay between genes and their products that are responsible for phenotype (Waddington, 1942). The changes in nucleotide sequences are not solely responsible for hereditary variations. There are certain other mechanisms that modulate gene expression resulting into a changed phenotype. These changes, like other changes in DNA sequences, are heritable and modify the gene expression. The study of complete sets of these heritable alterations is called epigenomics. This field of omics studies the epigenomes of the cell. Heritable information is not monitored only in the nucleus in the form of DNA sequences but some part of this is also regulated by an epigenetic network. Three-dimensional structure of DNA, methylation state of DNA and histone proteins (H2A, H2B, H3 and H4) are part of this network (Margueron and Reinberg 2010). It is well known that acetylation and methylation of histone proteins of chromatin at a peculiar amino acid regulate gene activity (Bannister and Kouzarides, 2011). In DNA, the addition of methyl group to the cytosine have the capacity to affect the transcriptional activity of a gene (Phillips, 2008). The sum of these epigenetic changes impacts the transcriptional state of that gene. Histone modifications occur mainly by the binding of protein complexes with chromatin (Bannister and Kouzarides, 2011). DNA methylation is also caused by small RNAs which directly influence the transcriptional state (Majo and Calore 2018). Small RNAs can also regulate assembly and breaking up of full-length RNA molecules from gene (Deng *et al.,* 2018). These chromatin changes play a part in epigenetic regulations of gene pursuit.

Epigenomics has common features in terms of its methodology with genomics and proteomics (Han and Garcia 2013). It identifies and characterizes epigenetic modifications on a genomic level. The present approaches in microarray and high-performing next generation sequencing techniques bring into existence the feasibility to develop the side views of epigenetic details genome-wide in plants (He *et al*., 2011 and Robert *et al*., 2011). DNA methylation profiling methods (bisulfite sequencing or amalgamation of chromatin immunoprecipitation (ChIP) technique with microarray) and high-performing sequencing techniques are being used in obtaining high-resolution epigenomic maps in

different plant species (Yong *et al.,* 2016). These technologies have been used to observe the upshots of epigenetic moderations and status of chemically addition of methyl group to DNA variations in *Zea mays, Oryza sativa* and *Arabidopsis* (Vaughn *et al*., 2007; He *et al*., 2010; Eichten *et al*. 2011; Fujimoto *et al*., 2012; Greaves *et al*., 2012 and Shen *et al*., 2012).

In plants being sessile autotrophs, the epigenetic gene expression is more important in responding to various environmental stimuli in a quick and reversible manner in order to protect the plants from deleterious effects of certain DNA sequences like transposable elements (Magdy, 2010). However, this defence mechanism may result in an unfavourable effect by affecting the genetic engineering process through silencing the transgene (Rajeevkumar *et al.,* 2015). There are different approaches for epigenomics which include DNA methylation, phosphorylation, acetylation, histone and chromatin modifications, change in gene expression using siRNA (small interfering RNA) and miRNA (micro RNA). The various development mechanisms in plants like shoot elongation and leaf formation, flower initiation and seed growth have both genetic as well as epigenetic aspect. Various plant biological phenomena like stress, paramutations, genome imprinting, silencing of introduced foreign gene, gene silencing induced through viruses, transposable elements, involve epigenetic phenomenon (Pikaard and Scheid 2014).

There are multiple epigenomics inferences in modern era of genetic engineering and conventional plant breeding techniques. These include improving plant stress tolerance, viruses and other pest resistance, parental imprinting, role in yield and heterosis, role in improving transgene stability, etc. which will be described in the present review. Insight into epigenomics can help in improving plant breeding strategies including the selection of desirable physiological states that have expression of favorable epialleles, and better control over the transgene expression during development of transgenics (Gallusci *et al.,* 2017). Hence, various epigenomic approaches along with other methods of cell specific studies will deliver a lot in future. The present review highlights the role of epigenomics in plant biotechnology, high-throughput approaches used in this area and the applications of epigenomics in crop improvement.

Approaches for Epigenomics: In order to know about the various systems and role of epigenomic bypath at genomic level, many researchers have combined microarray and high-performing DNA sequencing approaches with biochemical techniques (Han and Garcia 2013). Many epigenomic approaches those linked with DNA methylation and genome-wide profiling of sRNAs have revolutionized the plant epigenomic research (Cokus *et al* 2008). These approaches are discussed here.

Method for profiling histone modifications: Histone modifications are also called as epigenetic modifiers. Histone modifications distributed on the heterochromatin are generally linked with addition or removal of methyl group to cytosine (Grewal and Jia 2007), while the euchromatins are evident with histones hyperacetylation and addition of more than one methyl groups to H3 histone in contrast to transcriptionally inactive heterochromatin regions (Vaquero *et al*., 2003 and Dou *et al*., 2005).

Chromatin immunoprecipitation coupled with DNA microarray (ChIP-Chip): This is the most commonly used technique for describing moderations in histone, as well as proteins binding sites that recognize these histones or DNA moderations (Lippman *et al*., 2004, Elling and Deng 2009 and Robert *et al*., 2011). In this method, the chromatin is broken down into small fragments either using vibrations or digestion enzymes. ChIP having corresponding specific antibodies are used to isolate chromatin fragments having histone modifications. Since, histone proteins are maintained throughout eukaryotes therefore, antibodies once came into being can be applied for wide range of organisms including animals and plants. In addition to this, genomic locations of these modifications are fixed on DNA by microarray and sequencing techniques (Elling and Deng 2009, Egelhofer *et al*., 2010 and Robert *et al*., 2011). In eukaryotes, like yeast ChIP-chip has been used extensively (Barski *et al*., 2007) wherein, the high-performing DNA sequencing techniques have been linked with chromatin immunoprecipitation. The ChIP sequencing technique adopts the similar procedure of immunoprecipitation but as an alternative DNA fragments are sequenced and not purified and hybridized on chip. This method is more suitable for studying patterns of histone moderations at genomic level, providing higher resolution than earlier method (Gibson and Spencer 2009).

Profiling of DNA methylation: DNA methylation involves methylation of cytosine ring and is observed in both the uniformity of CG as well as in CHG or CHH (H may be A, C, or T) sequence contexts in plants (Law and Jacobsen, 2010; Fujimoto *et al*., 2012; Kurdyukov and Bullock 2016). This change (i.e. addition of methyl to cytosine) is vital for gene silencing through transposons and other epigenetic controls (Zhang *et al*., 2006). The heterochromatin is more sensitive to be methylated where centromere and its adjacent portion have more transposons (Law and Jacobsen, 2010 and Fujimoto *et al*., 2012). Most of the transposons are silenced via DNA methylation to protect genome integrity. DNA methylation profiling is based on three methods which are well described here.

Restriction enzyme based method: The genomic DNA can be digested by applying molecular scissors which are sensitive to methylation. These may include restriction by Msp I and Hpa II enzymes (McClelland and Nelson 1988). The intrinsic properties of the restriction enzyme (like suitability of specific sites) limit the effectiveness of this method. These restriction enzymes can be used to distinguish the methylated and normal state of DNA in the transposons and other genes. Moreover, the methylation in the RNA sequence of plant genes can also be differentiated by this method (Tran *et al*., 2005 and Lippman *et al*., 2004).

Antibody based method: The proteins or antibodies (anti-mC) that specifically attach to DNA with methylated cytosine can be used to isolate methylated compared to non-methylated genomic DNA(Cross *et al*., 1994). Further, high-performing sequencing is applied to separate methylated fragments (Zilberman *et al*., 2007) and has been successfully applied in *Arabidopsis*.

Sequencing based method: This approach involves the treatment of genomic DNA with sodium bisulfite that converts unmethylated cytosines to uracils, followed by PCR amplification and sequencing of bisulfite-treated DNA. The methylated cytosines are distinguished from unmethylated cytosines as the later appear as thymines while the methylated remains as cytosine (Henderson *et al*., 2010). This approach also includes the cytosines which are incompletely converted to uracil, that acts as false positives, which is a limitation of this method. Further, bisulfite should be removed from the reaction which otherwise may result into degradation of DNA (Laird, 2010). Therefore, the advanced sequencing method, next-generation sequencing (NGS) can suitably replace the bisulfite sequencing in genome-wide methylation analysis (Kurdyukov and Bullock 2016). The method can reveal the methylation patterns at the maximum resolution i.e. on the level of single nucleotide. Due to bisulfite treatment of DNA, the sequence complexity is reduced which make the assembly step challengeable. The whole genome shotgun bisulphite sequencing (WGBS) can remove these drawbacks to some extent which has been done in *Arabidopsis* (Laird, 2010).

Profiling of RNA: Profiling of RNA includes characterization of cellular RNA pools which will uncover more RNAs present between genes, RNAs that do not code (ncRNAs), isoforms of RNAs which occur during splicing (Lister *et al*., 2008; Robert *et al*., 2011). The various sRNAs (siRNAs, miRNAs, tasiRNAs and nat-siRNAs) which are present in the cells in large amount controls gene expression, silencing of heterochromatin and defence against viruses (Lu *et al*., 2006; Zhai, *et al*., 2008). High-performing RNA sequencing is also being used on large scale along with microarray technique for RNA profiling. Strand-specific RNA libraries and cDNA libraries are prerequisite for RNA sequencing methods (Lister *et al*., 2008).

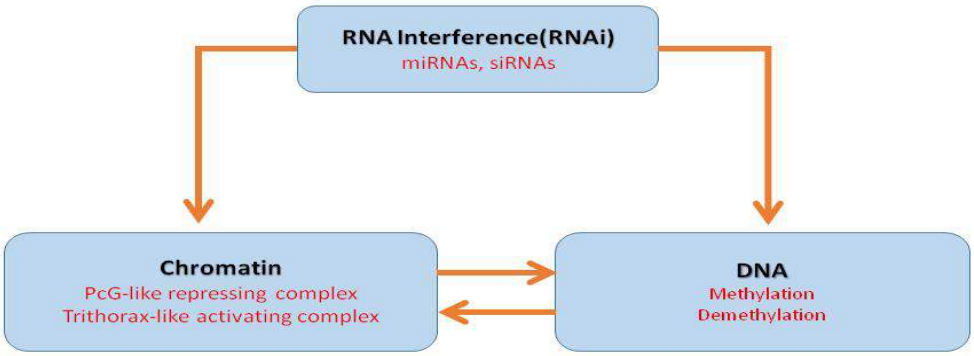

Fig. 1. The interplay between epigenetic information systems (EIS) (Tsaftaris *et al.* 2008). RNA interference controls the both (Chromatin moderations DNA methylation, which are important for one another)

Detection method: Using single molecule real-time method (SMRT), direct detection of DNA methylation is possible without using bisulfite treatment (Flusberg *et al.,*2010). This method is based on DNA polymerase kinetics in which the nucleotides which are marked with fluorescent dye are incorporated into newly synthesised strands by DNA polymerases. In SMRT the modified nucleotides are detected in DNA template by moment of their arrival and time taken to give rise fluorescence pulses that is due to kinetics of polymerase (Flusberg *et al*., 2010). Studies have been demonstrated to collect genome-wide epigenetic data in prokaryotes (Korlach *et al*., 2008).

Applications of epigenomics in crop improvement: Epigenetics can contribute in crop improvement significantly as it can help plant breeder in selecting positive epigenes, regulation of transgene expression and creation of new epialleles. A fine knowledge of epigenetic part of quantitative trait loci (QTLs) may make better about the prophecy of physical make-up of a plant

and may result in obtaining steady improvements through selection (Springer, 2013).

Improving Plant Stress Tolerance: The accumulation of oxygen free radicals under stress conditions of growth can be disruptive for different macromolecules like DNA, RNA and proteins. Repair mechanisms at genomic level in plant could result into making many differences at genetic and/or epigenetic level in the adversed zone. Abiotic stress conditions result in quick and desirable build up of reactive oxygen species (ROS) in plant cells (Polle and Rennenberg, 1993). In *Arabidopsis* recognition of miR398 that act as suppressor of Cu/Zn superoxide dismutases CSD1 and CSD2 gene results into identification of governing position of miRNAs in various stress reactions in plants. The plant response to stress was improved by over expression of miR398-resistant version of CSD2 (Sunkar *et al*., 2006 and Tsaftaris *et al*., 2008).

Epigenetic moderations have been described as a consequence of water deficit conditions in plants. Excessive methylation of heterochromatin in case of *Nicotiana* was reported as a result of osmotic stress (Kovarik *et al*., 1997), while in case of *Pisum sativum* hypermethylation at a peculiar site of chromatin in root tip has been reported following to water deficit (Labra *et al*., 2002).

In natural population of flax, LS-1 (an insertion of a nucleotide at particular locus) was described in the genotypes (Chen, 2005) which was absent in the flax progenitors supporting the fact that some other inheritance mechanism is involved for the better adaptation of plant.

The changes in the developmental mechanisms of plants under nutritional (P and Fe) stress were to specify the part of environmental states on growth of plants (Guimil and Dunand 2006). Root hairs grow longer under the state of limiting iron and phosphate nutrients in case of *Arabidopsis* (Lopez-Bucio *et al*., 2003 and Muller and Schmidt 2004).

Enhancing Viruses and Other Parasites Resistance in Plants: The environmental elements are known to effect progeny phenotypes (Roach and Wulff 1987). Roberts (1983) studied the transgenerational effects of damage caused by animals (herbivores) and insect-pests in a systematic manner. He observed an induced resistance against TMV virus in the offspring of diseased plant (*Nicotiana tabacum*) as measured against the offspring of normal plants. In some more studies on *Brassica* and oilseed rape it was revealed that seeds set on plants damaged by animals or insect-pests possess greater extent of phenolics (related to defence amalgam) as measured against normal plants (Lammerink, *et al*., 1984, Shattuck 1993). Further, the infection of tobacco plants with tobacco mosaic virus (TMV) not only enhanced resistance against TMV in the offspring, but also anticipated other pests like oomycete (*Phytophthora nicotianae*) and bacteria (*Pseudomonas syringae*) (Kathiria *et al*., 2010). Similar observations were made in *Arabidopsis*, where bacterial (*P. Syringae)* infestation resulted into enhanced resistance against bacteria and an oomycete (*Hyaloperonospora arabidopsidis)* (Slaughter *et al*., 2012). These experiments support initiation of transgenerational resistance due to damage in the offspring plants. The salicylate and jasmonate signaling pathways were initiated resulting broad spectrum resistance. In plants where resistance was initiated with bacterial (*P. Syringae)* infestation, the acetylation of histone (H3K9) protein at promoter (salicylate-receptive) resulted in higher concentration of transcript whereas; histone (H3K27) at promoter (jasmonate receptive) were hypermethylated resulting into decreased transcript production. The DNA was overall hypomethylated that resulted into increased resistance to bacteria in *Arabidopsis* (Holeski *et al*., 2012 and Luna *et al*., 2012).

Parental Imprinting: Maize was the first plant where parental imprinting was first reported (Kermicle, 1970). The term parental imprinting,is mostly used to distinguish the parental genomes in hybrids based on their peculiar effects and are contemplated as "imprints" (Surani *et al*., 1984; De la Casa‐Esperon and Sapienza, 2003). The study has got importance in model plant species i.e., *Arabidopsis*, where imprinting for specific traits at DNA level was developed (Scott and Spielman 2006; Gehring *et al.,* 2004; Kohler and Grossniklaus, 2005). Interploidy cross experiment in *Arabidopsis* had shown that genomic ratio of both parents is accountable for seed characters including size and viability (Scott *et al.,* 1998). There are different genes responsible for imprinting and has been demonstrated in Zea mays and in *Arabidopsis thaliana* (Garnier *et al*., 2008) (Table 1). Epigenetic mechanisms that control parental imprinting for development of endosperm in seed are potential research areas. Similarly secret of apomixis can be solved by knowing about epigenetic control of seed growth (Koltunow and Grossniklaus 2003). If the apomixes can be put in application to agronomically important crops, then hybrid vigor can be maintained for more than one single generation in commercial hybrids (Tsaftaris *et al* 2003).

Role in Yield and Hetrosis: Several researchers have investigated that the DNA methylation occur in hybrids following hybridization (Zhao *et al*., 2007, Jin *et al*., 2008, Banaei *et al*., 2010). He *et al*. (2010) reported that in hybrids, the expression of gene was altered due to addition of methyl group to the DNA. Greaves *et al.,* (2012) revealed that methylation at CG complex was higher and methylation at CHH was reduced as compared to the parents in hybrids of Arabidopsis and found that changes in DNA methylation occurred most frequently at loci where parental methylation levels were different. Shen *et al*. (2012) also repeated the methylation study in

similar *Arabidopsis* F_1s and found the same in both reciprocal hybrids, especially in transposable elements. It was found that the addition of methyl group to cytosine was increased throughout the genomes and differential methylation status of parents was responsible for addition of higher methyl groups to cytosine in hybrids. It is important to mention that in hybrids the decrease in cytosine methylation have made a settlement with increase in size and robustness, which provided the direct confirmation about the possible part of methylation of cytosine in hybrid vigor in plants. There are also reports for large scale changes in small RNA of hybrids as reported in *Arabidopsis* (Li *et al.*, 2012 and Shen *et al.*, 2012), *Oryza sativa* (He *et al.*, 2010 and Chodavarapu *et al.*, 2012), *Zea mays* (Barber *et al.*, 2012 and Ding *et al.*, 2012), and *Triticum aestivum* (Kenan-Eichler *et al.*, 2011). Several workers have used mutated HEN1 and MOP1 genes (responsible for biogenesis of plant small RNAs) for developing hybrids in *Arabidopsis* and maize but got different results. Comparisons of epigenomic outlines between parents used and hybrids developed have shown that their epigenetic elements showed changes which were specific to a locus and at whole genome level. They were also associated with alterations in chromatin conditions and activity of genes in F_1s (Fig. 2). Much work needed to be done to demonstrate the part of small RNAs in hybrid vigor.

Table 1. Parental imprinting genes known in plants.

Name of Gene	Allele Expressed	Plant	References
MEDEA	Maternal	*Arabidopsis thaliana*	Verona *et al*., 2003, Guitton and Berger, 2005
FWA	Maternal	*Arabidopsis thaliana*	Kakutani *et al*., 2004
PHE1	Paternal	*Arabidopsis thaliana*	Kohler *et al.,* 2003
FIS2	Maternal	*Arabidopsis thaliana*	Gehring *et al.,* 2006
fie1 and fie2	Maternal	*Zea mays*	Makarevich *et al.,* 2006
meg1	Maternal	*Zea mays*	Danilevskaya *et al.,* 2003
Nrp	Maternal	*Zea mays*	Gutierrez-Marcos *et al.,* 2004
peg1	Paternal	*Zea mays*	Guo *et al.,* 2003
Mez1	Maternal	*Zea mays*	Gutierrez-Marcos *et al.,* 2003

Hetreosis in plants is associated with histone modification. This was first revealed by Ni *et al*.. (2009). Other workers (like Li *et al*. 2011 and He *et al*., 2010) revealed that in hybrids the histone alterations take part in distinctive gene articulations. These studies revealed that stable inheritance of histone modifications effected both additive and non-additive expressions of many genes. These reports provided hints for perceptions of molecular apparatus acting during distinctive gene articulations in hybrids, and inspire the scientists to discover more direct confirmations for the participation of histone alterations in making a hybrid's superiority over its parents (He *et al*., 2013). A full perception of molecular apparatus working for superiority of hybrids in plants is dependent on investigation of all elements responsible for genetic and epigenetic control of differences operative during gene articulations in hybrids (Fig. 3).

Role of plant tissue culture to induce epigenetic variations: Epigenetic changes are considered to trigger a variety of familiar tissue culture events like habituation, rejuvenation and morphological alterations such as bushiness, flower abnormalities and tumor outgrowths in oil palm, gerbera, Zantedeschia and rhododendron (Smulders and Klerk 2011). Tissue culture has been method of choice in improving plant varieties. Although tissue cultured derived plants are expected to have identical genetic information as that of the parent yet there are instances of variation in their genome which may be attributed to epigenetics (Han *et al.,* 2018). Experiments studying tissue culture plant regeneration showed consistent alterations in genome-wide methylation patterns which are heritable in multiple generations (Stroud *et al*., 2013). Such studies hold importance due to the essential role tissue culture has in the crop breeding industry (Ji *et al*., 2015). Numerous studies involving tissue culture and regeneration show alterations in DNA methylation via different mechanisms (Stroud *et al*., 2013; Ong-Abdullah *et al*., 2015). Tissue culture may diminish DNA methylation or demethylation. (Han *et al*., 2018). DNA methylation can be heritable meiotically and mitotically (Calarco *et al*., 2012) and is among the most largely studied chromatin modifications in plants (Niederhuth and Schmitz, 2014). It acts as a bridge between DNA sequence and morphological variation (Ji *et al*., 2015). Although, DNA methylation patterns are stably inherited y*et al*terations in DNA methylation pattern may happen at some loci as a consequence of tissue culture leading to somaclonal variation (Han *et al*., 2018). The heritable epigenetic changes due to tissue culture have been studied in maize genome by sequence-capture bisulfite sequencing approach where the plants regenerated from tissue culture demonstrated that some loci are either targeted or act as hotspots for epigenetic variation (Han *et al*., 2018). An inhibitor of DNA methylation, 5-Azacytidine, has been

used in the regulation of DNA methylation as low levels of DNA methylation are associated to elevated embryogenic potential in explants during the somatic embryogenesis induction (Osorio-Montalvo *et al*., 2018).

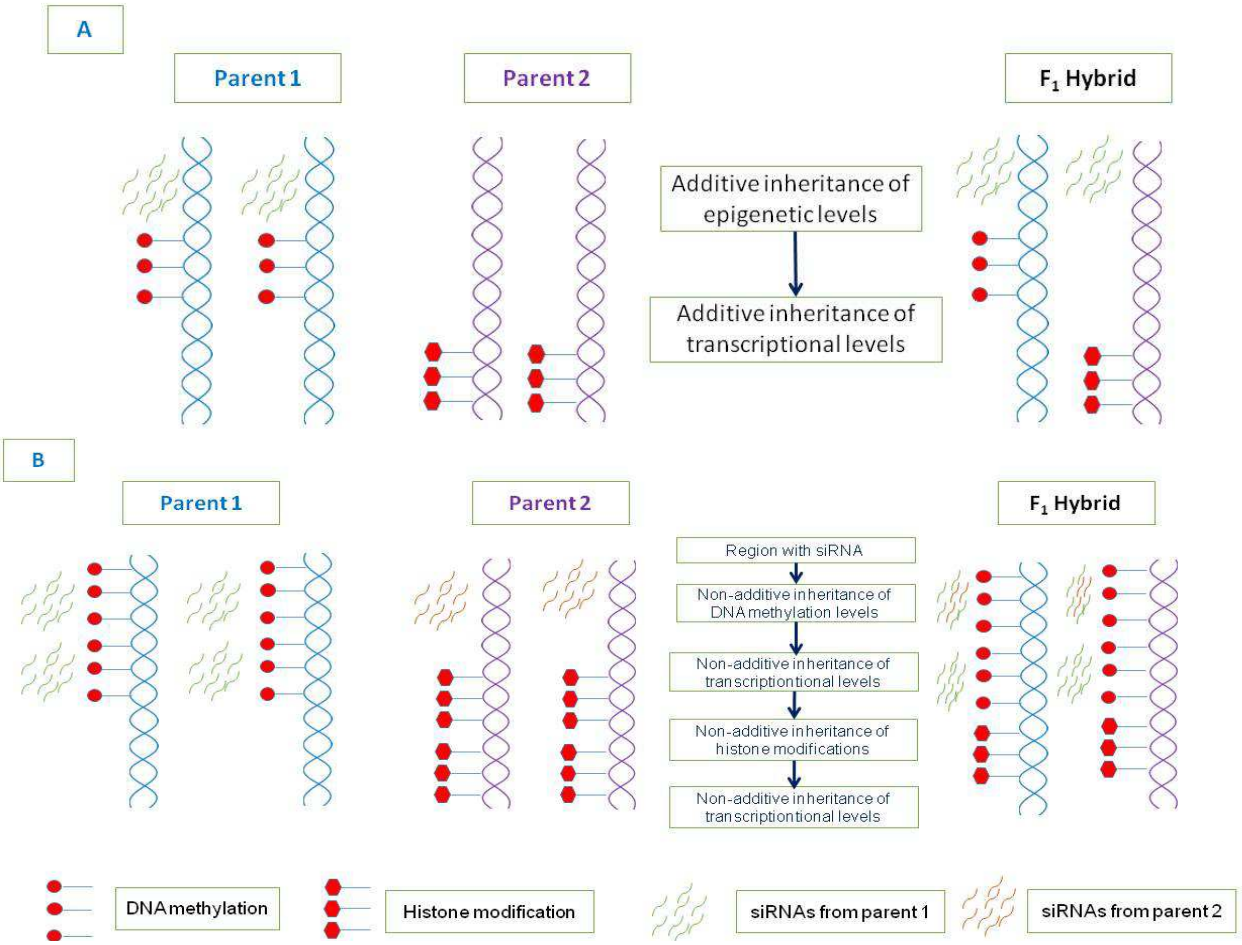

Fig. 2. Model for inheritances of epigenetic marks in F1 (He *et al*., 2013)

A: Additive model for epigenetic inheritance. Here there is cis-regulation between three EIS elements and have middle values in hybrids than parents B: Non-additive model for epigenetic inheritance. Here the three EIS elements have higher or lower values in hybrids than parents.

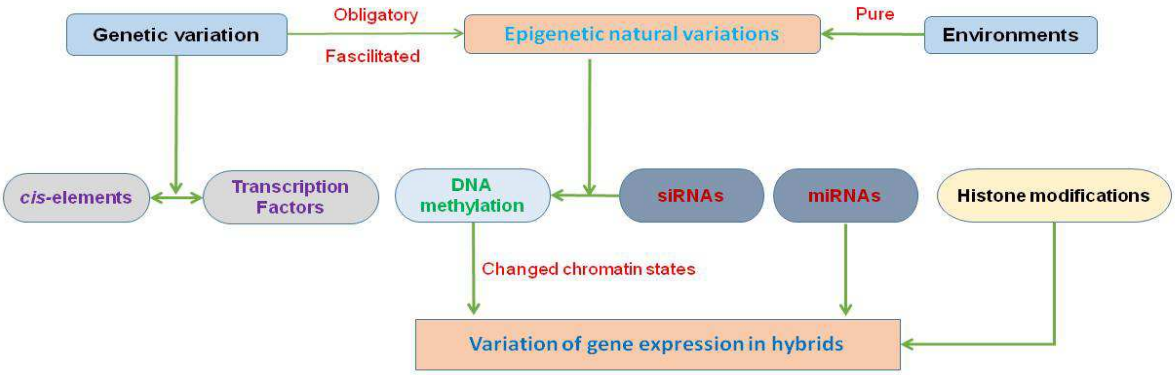

Fig. 3. Gene articulation in hybrids controlled by Genetic and epigenetic elements.

Genetic (cis and trans-acting elements) and epigenetic components are responsible for different gene articulations in hybrids (He *et al*., 2013).

Role in improving transgene stability: The unpredictable silencing or variable expression of transgenes is a ubiquitous phenomenon in plant systems. The silencing of transgene either due to multiple copies of transgene or due to endogenous genes is based on homology and is called as transcriptional gene silencing (TGS) or post-transcriptional gene silencing (PTGS). In RNA-directed DNA methylation (RdDM), both TGS and PTGS are linked with DNA methylation which is induced by siRNAs (small interfering RNAs). RdDM inactivates transcription by promoter methylation during transcriptional gene silencing (Huettel *et al*., 2007). It has been observed that the cytosines of the transcribed region are methylated during post-transcriptional gene silencing due to which the transcript stability and/or translation rate are affected (Dalmay *et al*. 2000 and Chawla *et al*., 2007).

In addition to this, histone amino acid modifications are the other epigenetic changes that are more associated with transgene silencing at transcription level. Hypo and hyper methylation of H3 histone (H3K4 and H3K9) are the oppressive histone moderations linked with transgene silencing (Meyer, 2011). Further, acetylation of H3 and H4 has been linked with dynamic promoter conditions. Cytogenetically, hypomethylation (H3K4) is linked with euchromatin while hypermethylation (H3K9) is with heterochromatin (Fuchs *et al*., 2006).

Conclusions: The latest DNA sequencing technologies have helped exploring the complex field of epigenomics. DNA methylation, histone modification and RNA-interference are the three interacting systems that can regulate the expression or silencing of genes. Resolving the relationships between these epigenetic components would lead to surprising and rapidly evolving new concepts. Epigenomic information can play central role in understanding plant's developmental gene regulation, its response to the environmental stimuli and in better exploitation of natural variation for crop improvement. The epigenomic has a direct role in rectifying the transgene silencing which is a common problem in developing transgenics. The peculiar association of EIS in plant's genetic reactions to various biotic and abiotic stresses and in maintaining heterosis, stable yield of cultivars and better exploitation of resources should be explored extensively.

Conflict of interest: The authors declare that they have no conflict of interest.

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