Epigenetic Signals on Plant Adaptation: a Biotic Stress Perspective

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Abstract: For sessile organisms such as plants, regulatory mechanisms of gene expression are vital, since they remain exposed to climatic and biological threats. Thus, they have to face hazards with instantaneous reorganization of their internal environment. For this purpose, besides the use of transcription factors, the participation of chromatin as an active factor in the regulation of transcription is crucial. Chemical changes in chromatin structure affect the accessibility of the transcriptional machinery and acting in signaling, engaging/inhibiting factors that participate in the transcription processes. Mechanisms in which gene expression undergoes changes without the occurrence of DNA gene mutations in the monomers that make up DNA, are understood as epigenetic phenomena. These include (1) post-translational modifications of histones, which results in stimulation or repression of gene activity and (2) cytosine methylation in the promoter region of individual genes, both preventing access of transcriptional activators as well as signaling the recruitment of repressors. There is evidence that such modifications can pass on to subsequent generations of daughter cells and even generations of individuals. However, reports indicate that they persist only in the presence of a stressor factor (or an inductor of the above-mentioned modifications). In its absence, these modifications weaken or lose heritability, being eliminated in the next few generations. In this review, it is argued how epigenetic signals influence gene regulation, the mechanisms involved and their participation in processes of resistance to biotic stresses, controlling processes of the plant immune system.

Keywords: Chromatin remodeling, histone modifications, inheritance, microRNA, siRNA.

1. PLANT EPIGENETICS: THEME AND CONTEXTUALIZATION

To integrate and survive in a niche in which they are incorporated, plants constantly regulate their internal environment to the external fluctuations, such as soil, climate, and biological interactions. Throughout the evolution, positive selection of physiological adjustment mechanisms took place in organisms. Primarily, they are controlled by transcription modulation of specific genes, in which orchestration of the gene expression occurs by protein effectors (transcription factors), chemical changes in DNA (for both eukaryotes and prokaryotes) and chromatin topological properties (for eukaryotes).

Historically, transcription factors in gene regulation process was first observed by Jacob and Monod [1], in the lactose metabolism of *Escherichia coli*. They showed that *E. coli* use glucose as a primary energy source and that, in specific situations, they could utilize lactose. In this way, different DNA binding-proteins may alter the transcription rates of the three essential genes for metabolizing lactose either by activating or repressing them, according the relative amounts of glucose and lactose presented in the environment. This dual mechanism of gene expression (induction/suppression) adjusts the bacterial cell´s enzymatic complexes for these metabolic pathways.

Studies relating genetics to developmental processes established new perceptions to the identified mechanisms of gene regulation. To this context, Conrad Hal Waddington [2] adjusted the Greek word "epigenesis" that defines one of the theories of development. This theory proposes that early embryo cells are undifferentiated. He adapted this notion to these new observed perspectives calling it “epigenetics”. This newly referred word represents a developmental concept in which a single genome originates many epigenomes and consequently, a variety of cell types. Waddington [2] defined it as “the branch of biology, which studies the causal interactions between genes and their products, which bring the phenotype into being".

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The contemporary conception of epigenetics is a different one. Actually, the combination of the epithet “epi” with the word “genetics", where “epi” is a Greek prefix meaning “over" "above” or “in addition", is defined as "the study of mitotically and/or meiotically inheritable changes in gene function (expression) that cannot be explained by changes in DNA sequence [3]". This modified status of gene expression may be passed to daughter cells or to a progeny of individuals. Additionally, recent adjustments of this word, suggests epigenetics as “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states [4]”. The lack of consensus or concrete definition of the word was reinforced by Richards *et al.* [5], in 2010.

Two independent groups, Holliday and Pugh [6] and Riggs [7], were the first to report data associated to the modern definition of epigenetics. Both studies suggested that chemical changes in DNA (adenine methylation) acted in gene expression regulation in bacteria. Then, these changes were passed on to the progeny. Today, there are several recognized chemical changes in eukaryotic DNA and also histones able to remodel chromatin structure, making it more permissive (or not) for gene activities and/or also acting by signaling to specific protein complexes (inducers/suppressors) to regulate target gene expressions [8]. In some organisms, processes were associated to different epigenetics effects. The following may be cited, among others:

- Paramutation in maize: the ability of particular DNA sequences to communicate in trans establishing meiotically inheritable expression states [9];
- Position effect variegation in the fruit fly *Drosophila melanogaster*: the change in phenotype due to the change of a gene’s position in the genome [10];
- The imprinting of particular paternal or maternal loci in mammals: phenomenon wherein allele-specific differences in transcription occur depending on whether they are inherited from the mother or the father [11, 12].

Studies of several phenomena show that not only developmental processes are associated to epigenetic regulation of gene expression. Signals' interpretation resulting from different epigenetic changes can also affect the transcriptome of a determined tissue under stress. Both plants [13] and animals [14] display this response. In plants, a fraction of the mechanisms associated to tolerance/resistance to stress, such as specific gene expression changes [15] and hormonal signaling [16] can be controlled by enzymes, whose modifications reverberate epigenetic signals. The influence of these epigenetic signs during a stress response is spread not only among cell generations but also to the offspring [17]. This inheritance could mediate the transmission of environmental memories from ancestral plants to their progeny, thereby preparing them for new growth conditions.

Due to the relevant aspects of epigenetics' signals, involved in plant physiology, this report aims to present an overview of inductors’ mechanisms of those phenomena. It also highlights the triggering processes of the enzymes participating in plant gene signaling and orchestration under biotic stresses, potentially influencing plant immunity. This review considers the epigenetic definition presented by Russo *et al.* [3] together with the transgenerational epigenetic inheritance from parents to progeny, but excluding transmission within the cell linage, or within the individual body. It also discusses epigenetic processes, regardless of their heritability, according to Bird’s epigenetic definition [4].

2. EPIGENETIC MODIFICATIONS

The accessibility of the eukaryotic transcription machinery to specific genes when altered by signals or modifications in DNA/chromatin originate epigenetic changes. These modifications, relating to epigenetic phenomena, start with processes such as RNA-directed chemical modifications of DNA´s nitrogen base; post-translational modifications; chromatin remodeling complexes.

2.1. RNA-directed chemical modification of DNA´s nitrogen base

In the earlier studies of molecular genetics, after the presentation of the Central Dogma of Molecular Biology [18], only three RNA functions were known: RNAs functioning as intermediate of DNA´s informational content (mRNA); RNAs working in amino acids' transport (tRNA); and RNAs composing ribosomes (rRNA). This set of functions was already known as being related to protein synthesis.

New research found that RNA molecules that work as enzyme (ribozymes) can catalyze particular biochemical reactions [19]. Thereafter, RNA came to be recognized as both genetic material and enzyme, once it became also known as a catalyzer. Additionally, studies of the molecular mechanisms involved in plant-virus interactions and the advent of plant transformation technology set innovative directions for scientists, suggesting the involvement of RNAs in gene expression silencing processes. The analysis done by Lindbo *et al.* [20] and Wassenegger *et al.* [21] both working with transgenesis of viral genes and plant-virus interaction in tobacco are worth mentioning in this aspect, as well as the one by Napoli *et al.* [22] working with transgenesis of the chalcone synthase gene in petunia.

Currently, it is widely accepted that RNAs take part on this process by two ways. One of them is post-transcriptional gene silencing (PTGS, in plants), also known as RNA interference (RNAi, in animals). It participates in sequence-specific labeling of target RNAs and their degradation [23]. The other is called transcriptional gene silencing (TGS), in which RNA directs cytosine methylation of the promoter regions causing a decrease in RNA synthesis [24]. Processes such as these, in which RNAs modulate the expression of target genes, are nominated RNA silencing [25]. Despite its use as a defense mechanism against non-self-sequences [26], it has been reported that RNA silencing is an integral part of endogenous gene expression control [27]. Additionally, these mechanisms suppress transposition of mobile elements, besides taking part in activities that make them analytically essential to sustain genome stability [28].

Fundamentally, PTGS/RNAi and TGS mechanisms are associated to two basic principles: double strand RNA formation (dsRNA) and subsequent production of small RNAs (sRNAs). The latter regards molecules consisting of about 20 to 30 nucleotides, actively responsible for the process of di-

recting transcriptional silencing [29]. According to Eamens *et al.* [30], Szittya *et al.* [31] and Vazquez *et al.* [32], based on the sRNAs' biogenesis, there are at least four transcriptional silencing mechanisms. One of them associated with microRNAs (miRNA), and the others related to small interfering (si) RNAs [trans-acting siRNA (tasiRNA), natural-antisense siRNA (natsiRNA), viral siRNA (vsiRNA) and RNA-directed DNA methylation (RdDM)]. Castel and Martienssen [33] further presented an additional mechanism, including PIWI-interacting RNA (piRNA) expressed only in animals (originally P-element induced wimpy testis in Drosophila). The present review provides details about miRNAs and siRNA (RdDM), once they can trigger methylation processes of cytosines in eukaryotic DNA. Information about the different types of RNAi mechanisms is available in Eamens *et al.* [30] and Wilson and Doudna [34] articles.

In eukaryotes, *de novo* methylation demands siRNAs or miRNAs synthesis, besides requiring the activity of DRMs (Domains Rearranged Methyltransferases) enzyme family and other protein groups. Such RNAs differ by both their origin, once genome derives miRNAs whereas siRNAs may be endogenous or arise via viral infection or other exogenous sources. They also differ in the respect on their associations with distinct subsets of effector proteins that take part in their synthesis [35].

The canonical view of RNA-directed methylation (RdDM; TGS) encompasses the participation of both different types of RNA polymerases (IV and V) and the PTGS/RNAi processing machinery. In summary, the process of siRNAs biogenesis consists in: transcripts formed through RNA Pol IV activity at its target loci (Fig. **1**, step 1) working as precursors to the RNA-dependent RNA polymerase (RDR2) activity (Fig. **1**, step 2). Their action yields dsRNAs [36], which are substrates digested by the enzyme DICER-LIKE 3 (DLC3; Fig. **1,** step 3). This digestion produces shorter fragments of 24 nucleotides [37], the siRNAs. These structures present a 2-nt overhang at each 3' terminus and a phosphate group at each recessed 5' terminus (Fig. **1**, step 3). Afterward, these siRNAs (guide and passenger strands) are exported to the cytoplasm where they interact with the ARGONAUTE4 (AGO4) protein (Fig. **1**, step 4). Together with DICERs and other enzymes, AGO4 forms the RNA-induced silencing complex (RISC). This complex compels the silencing of a target mRNA through degradation (PTGS/RNAi), transcriptional repression (TGS) or even both. RISC cleaves passenger RNA, exposing the guide RNA. Thereafter, such complex is forwarded to the nucleus where researchers suggests that RISC containing AGO4 binding siRNA connects the guide strand with a nascent RNA Pol V transcript, through base-pairing during RNA Pol V-mediated transcription (Fig. **1**, step 5; [38, 39, 40]). Then, the new complex recruits DRM2 to catalyze the *novo* methylation at the homologous genomic sites (Fig. **1**, step 6; [41, 42, 43]).

The mentioned process recruits a DNA methyltransferase to mediate *de novo* methylation of cytosines in all classes of sequences contexts: 5'-CpG-3' and 5'-CpHpG-3', which are known as symmetric contexts, once these sequences are self-complementary with methylatable cytosines in pairs on opposite strands; and 5'-CpHpH-3,' with H = A, C or T, which is known as asymmetric context [44]. The term CpG represents a cytosine (C) bonded to a guanine (G) through a phosphate (p) in a chain of nucleotides in DNA. In plant genomes, there are many regions called CpG/CpHpG islands, which contain high frequencies of CpG or CpHpG relative to their occurrence in the genome. These areas are important because of their strong correlation with gene regulation due to methylation processes [45, 46].

Regarding miRNAs, they were only associated to processes of marking and degrading target mRNAs (PTGS), by the activity of canonical miRNAs. In plants, the sequential activity of type III endoribonuclease DICER-LIKE 1 (DCL1) originates mature miRNAs (20-22 nucleotides; [47]). However, several studies have identified a non-canonical population of miRNAs (ncmiRNAs; 23-27 nucleotides) in model species such as *Physcomitrella patens* [48], *Arabidopsis thaliana* [49] and *Oryza sativa* (rice) [50]. Besides, those ncmiRNA can guide cytosine DNA methylation not only at their gene loci in *cis* [50], but also at their target gene loci in *trans* [49], resulting in TGS.

Another important aspect to observe is the maintenance or heritability of the cytosines' methylation process after DNA replication. There are reports of two different pathways involved in the referred process: the first, involving the MET1 family of methyltransferases, for 5′-CpG-3′ [51] and other involving the CMT3 class of methyltransferases, for 5'-CpHpG-3' [52, 53]. Such enzyme families recognize hemimethylated substrates (e.g., those methylated on one strand but not the other) to copy the modifications to the other strand. CpHpH methylation is not maintained; hence, it depends on *de novo* methylation. To this sequence context, the process must be carried out in every DNA replication cycle, once there is no complementary sequence to serve as a guide for re-methylation of a particular cytosine [54, 55].

The cytosines' methylation mechanism in DNA has two functions: (a) it protects the genome from selfish DNA elements and (b) regulates gene expression [56]. There are reports of two mechanisms regarding gene expression regulation. The first one is the transcription repression, which works through the linkage blocking of transcriptional activators to their cognate sequences [57]. Moreover, the other one serves as signaling to proteins that can recruit transcription repressors, causing gene expression silencing [58].

Additionally, regarding the methylation process, it is significant to highlight that the methyl groups added to DNA, despite being chemically stable, can be removed by demethylation. In plants, a family of DNA glycosylase domain-containing proteins, carries out this action. DEMETER (DME) and REPRESSOR OF SILENCING 1 (ROS1) are examples of these enzymes in *Arabidopsis thaliana*. Such enzymes probably act associated with the base excision repair (BER) pathway [59, 60].

Regarding the specificities in methylation patterns of distinct plant groups (monocotyledons and dicotyledons), Feng *et al.* [61] observed that these groups were highly similar to each other, including rice (monocot), *Arabidopsis thaliana* and poplar (both dicots). In relation to the different methylation contexts in the analyzed organisms, they noted that the methylation occurred in the following way: CpG sites at the highest level, CpHpG sites at an intermediate level, and

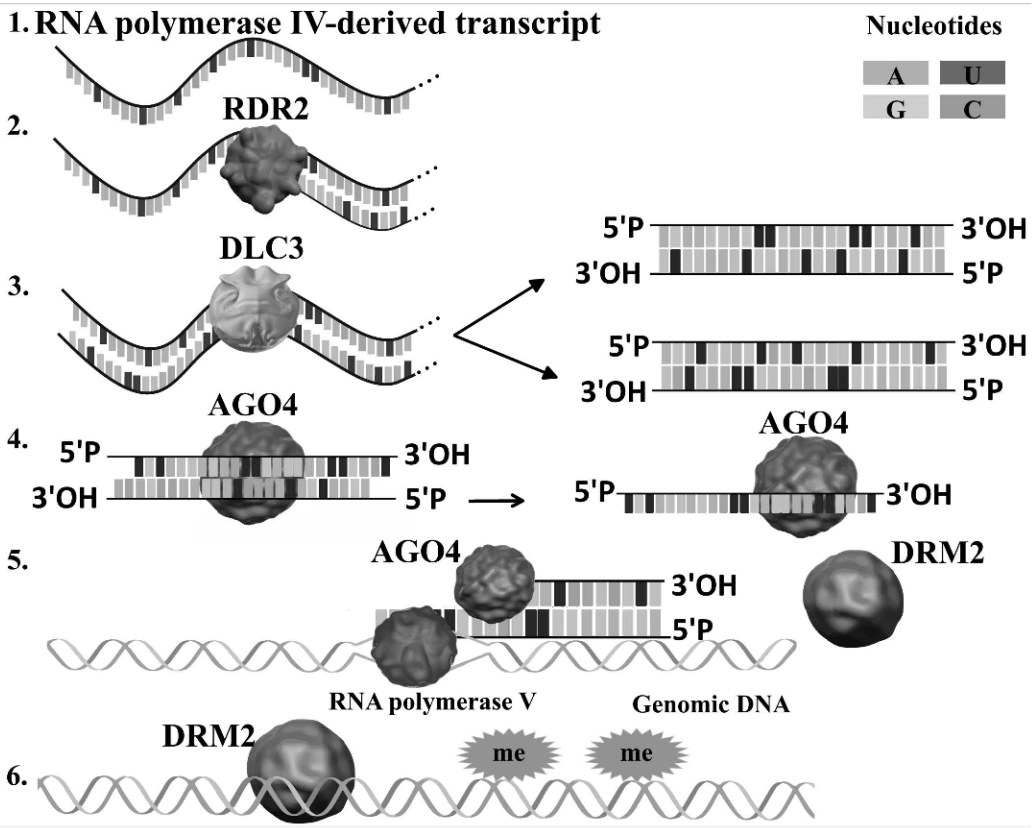

Fig. (1). Cytosine methylation process directed by siRNAs (siRdDM) in plant DNA. (1) RNA polymerase IV originates a transcript; (2) RNA-dependent RNA polymerase (RDR2) recognizes and copies the transcript; (3) The DICER3 (DLC3) enzyme cleaves dsRNA originated from the activity of RDR2, yielding 24 bp siRNAs; (4) The protein ARGONAUTE4 (AGO4) reads the siRNAs and degrades the passenger strand, keeping the guide strand; (5) The guide strand physically interacts with the transcript produced by RNA polymerase V, marking the locus to be methylated (me); and (6) in order to do so it recruits domains rearranged methyltransferase (DRM2).

CpHpH sites at the lowest level. Furthermore, they found out that the hotspots distribution of cytosine methylation does not occur randomly in plant genomes. The three types of methylation were highly enriched in repetitive DNA and transposons. Functionally, the lack of DNA methylation in plants is associated to gene activity induction. Several analyzes using the "methylation filtration" technique have confirmed this proposition. This methodology results in the isolation of genome non-methylated regions and these are greatly enriched in transcribed sequences [62, 63]. In plants, methylation of promoter sequences commonly inhibits transcription. On the other hand, gene body (coding regions) methylation, usually, either has no impact in gene expression or shows only modest effects [64-68].

2.2. Post-Translational Modifications

Post-translational modification processes and epigenetics' phenomena involve proteins called histones. These small basic proteins together with DNA are the main constituents of chromatin. In this structure, DNA is wrapped around the histones, forming units called nucleosomes. Each nucleosome consists of 147 DNA base pairs connected to an octameric core of histone proteins, composed by 2 H3-H4 histone dimers enclosed by 2 H2A-H2B dimers [69].

Initially, chromatin was believed to be only associated with DNA´s compaction in the nucleus. However, its topological state (tridimensional structure) represents an important mechanism of transcriptional control. Functional studies on nucleosomes or regarding their anatomy revealed that N-terminal histone tails protrude out of the nucleosomes. There are about 30 amino acids in these protrude tails which are not inert structures. They act as substrates for post-translational covalent modifications. Moreover, to a lesser extent, residues anchored in the histones' central domain, preserving the structural organization of nucleosomes, were also subjected to post-transductional modifications [69].

Despite some variation in the amino acid composition that makes up a histone (102 to 135), these proteins are highly conserved, when comparing different taxa [70]. Post-translational modifications within the referred monomers are associated with activation or repression of gene activity, what depends on the type and position of the amino acid in the histone [71]. These modifications can either alter (strengthening or relaxing) the interaction of these proteins with DNA or they represent signals that recruit protein complexes that regulate the target genes' expression [72]. A number of different enzymes accomplish these modifications, mainly by (de)acetylation, (de)methylation, and (de)phosphorylation. Additionally, there are protein modifications such as ADP-ribosylation, ubiquitination, small ubiquitin-related modifier (SUMO), histone tail clipping, histone proline isomerization, deamination, β -N-acetylglucosamine, biotinylation that are less addressed when compared to the main ones (more information is avail-

able in Bannister and Kouzarides, [73], and Chinnusamy and Zhu, [74]). The before mentioned biochemical processes and their combinations make up the so-called histone code [72, 75], which is active in cell signaling.

2.2.1. Acetylation/ Deacetylation

Lysines (K) work as backbones to the addition / subtraction of acetyl groups in histones. It is a highly regulated mechanism carried out by two families of enzymes with antagonistic action (addition: histone acetyltransferases (HATs); subtraction: histone deacetylases (HDACs); Bannister and Kouzarides, [73]). The addition of acetyl residues to Ks neutralizes the positive charge of this amino acid, modifying the interaction between DNA and histones [76]. It may also signal a conformational change [77] or modify nucleosome-nucleosome interactions or both [69]. Initially, data indicated that the change of charge would destabilize the nucleosome structure or arrangement. This fact would give more access to a given locus by the nuclear factors involved in the transcription machinery [78, 79]. Nonetheless, there are reports also relating the function of HDACs with transcriptional activation of specific loci [80, 81]. In *Arabidopsis thaliana*, acetylation modifications regulate histone H3 lysines K9, K14, K18, K23 and K27 in addition to histone H4 lysines K5, K8, K12, K16 and K20 [81, 82] (Fig. **2**).

2.2.2. Phosphorylation/Dephosphorylation

Kinases and phosphatases, respectively, control the adding and removing of histone phosphate groups. These processes occur in the hydroxyl groups of serine (S), and threonine (T) residues, found in H2A, H2B, H3 and H4 histones [74]. The kinases' activity significantly increases DNA´s negative charge, affecting chromatin structure by decompressing it [74]. There are reports showing that this process may regulate both gene activation and repression. Sun *et al.* [83] observed that the phosphorylation of H3T28 is associated with labile nucleosomes in chicken. This modified histone is highly enriched in the active/competent chromatin gene fractions, suggesting that it helps in the dynamic disassembly-assembly of nucleosomes in active promoters. Burkhart *et al.* [84], on the other hand, while investigating the response of the mouse mammary tumor virus (MMTV) promoter in human UL3 cells under hypertonic osmotic stress (0.2–0.3 M sorbitol for 1–24 h), reported that phosphorylation might act as a transcription suppressor factor. These scientists observed that there is an inverse correlation between H3S10 and H3S28 phosphorylation of the MMTV promoter and the binding of the glucocorticoid receptor (GR). This receptor is a transcription factor that controls target genes, both directly by interaction with DNA regulatory elements, and indirectly by cross-talking with other transcription factors [85, 86]. It was suggested that, in this case, the increase of these modifications regulates the displacement of GR and represses transcription. Thus, phosphorylation and repression were correlated.

Besides, phosphorylation and acetylation may act synergistically as observed by Cheung *et al.* [87] in mammalian cells. The stimulation of epidermal growth factor (EGF) resulted in a fast and sequential phosphorylation and acetylation of H3, and these di-modified H3 molecules were better related with the EGF-activated *c-fos* promoter in a MAP kinase-dependent way.

Still few data are available in relation to plants regarding phosphatases and their influence on gene regulation. Based on mammalian (mice) brain data, Koshibu *et al.* [88] reported the PROTEIN PHOSPHATASE 1 (PP1) as an important regulator of chromatin remodeling. PP1 controls histone post-transcriptional modifications and gene transcription associated with long-term memory. A selective inhibition of the nuclear PP1 in forebrain neurons in transgenic mice induced several histone post-transcriptional modifications, not only related to phosphorylation but also acetylation and methylation. Based on Bannister and Kouzarides [73], given the fast turnover of specific histone phosphorylation, phosphatase should be highly active within the eukaryotic nucleus. These kinase-phosphatase complexes can modulate cellular signals. The Aurora kinase–PP1 complex acts as negative regulators of kinase activation. In this case, PP1 phosphatase works in a opposite way to Aurora B kinase, that is crucial in mitosis (attachment of the mitotic spindle to the centromere by phosphorylation of H3S10 and H3S28).

2.2.3. Methylation / Demethylation

Histone's methylation takes place through the action of methyltransferases. It is one of the best-studied epigenetic mechanisms. This process arises in lysines (K), which can be mono-, di- or tri-methylated, and arginine (R), which can be mono- and symmetrically or asymmetrically di-methylated [73]. It is worth mentioning that this process does not change the overall charge of the histone tails. Meanwhile, different methylation signatures may be more related to the activation or repression of the site where they are anchored. This occurs through the signaling process that recruits activators / repressors of gene activity [89] or changes the chemical properties of histones reflecting in their interaction with DNA [90].

In *A. thaliana,* covalent binding of one (me1), two (me2) or three methyl groups (me3) primarily occur on H3K9, H3K27 and H3K36 (Fig. **2**) [91]. H3K27me3 is considered one of the major repressor epigenetic marks, also called epigenetic signals [92]. Their correlation with more than 4,000 repressed genes in *A. thaliana* genome confirm their status in this species [93]. H3K9me3 is another mark associated with repression in *A. thaliana* [94], together with H3K9me2 [95]. Otherwise, reports show that H3K4 methylation participates in gene activation as observed in *Arabidopsis thaliana* [96] and soybean [97]. As mentioned above, methylation by itself does not modify chromatin structure. In fact, it flags for chromatin-associated proteins to mediate alterations in higher-order chromatin structure [90]. Additional data indicated that H3K4me2 and H3K4me3 (Fig. **2**) facilitate transcription by recruiting transcription factors [98] and cofactors [99] and by inhibiting repressors from binding to chromatin [100].

The histone methylation process is also dynamic, once demethylases can remove the methyl groups on histone lysine and arginine residues. Eukaryotes have two types of known histone demethylases: the JUMONJI C (JmjC) domain family proteins [101], and the other is the LYSINE SPECIFIC DEMETHYLASE1 (LSD1) type [102]. Researches indicate that these enzymes have important regula-

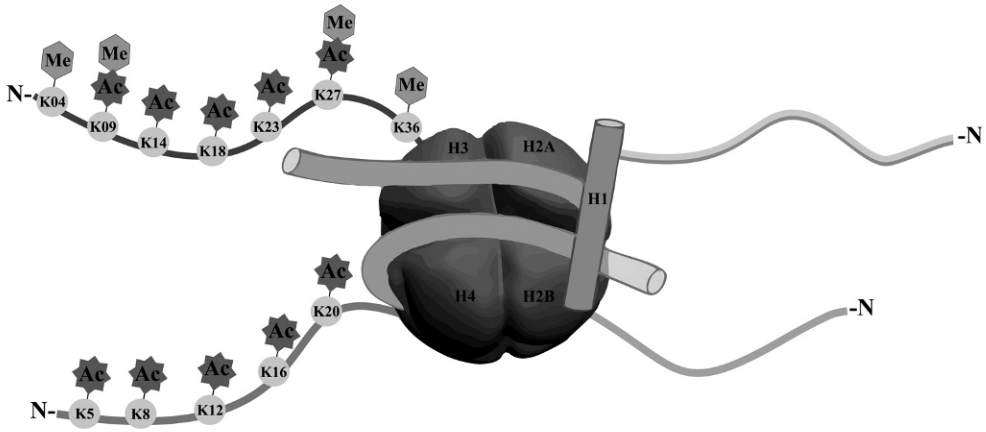

Fig. (2). Nucleosome scheme highlighting the H1 histone and the histone octamer (two H3-H4 histone dimers enclosed by two H2A-H2B dimers), in addition to the terminal N tails presenting some modifications. Abbreviations: Me (methyl group); Ac (acetyl group); K (lysine residue).

tory roles in plant physiology, and that they take part in developmental processes such as floral development in rice [103] and the circadian regulation in plants and also human [104]. For more information about these enzymes and their functions in plants, see Luo *et al.* [105].

3. CHROMATIN REMODELING COMPLEXES

In eukaryotes, factors determining gene activity status of a given locus are influenced by the balance between local genomic packaging and transcriptional machinery access, in addition to the methylation degree of their promoters' cytosines. Besides the above mentioned histone covalent modifications, it is worth to emphasize the importance of ATP-dependent chromatin remodeling complexes as a second alteration mechanism of the chromatin´s topology, since they may connect to each other as observed by Ito *et al.* [106] and Verbsky and Richards [107]. Furthermore, Phillips *et al.* [27] reported that these complexes provided the mechanism to modify chromatin allowing transcription signals to achieve their purposes on the DNA strand. They do not play a role directly in the issuance of molecular signals. However, according to Erdel *et al.* [108] these complexes can read chromatin signals like DNA methylation profiles or histone modifications, and they can interact with chromatin-associated proteins such as transcription factors to identify precise target nucleosomes in the nucleus. Additionally, ATP-dependent chromatin remodeling complexes can regulate specific pathways within the biotic stress signaling networks [109].

Chromatin remodeling factors, also called ATP-dependent chromatin remodeling factors or even nucleosome remodeling factors, are enzymes that constitute the chromatin remodeling complexes. They can work as activators or repressors of gene activity. They also may have roles outside of transcriptional regulation such as DNA repair [110, 111]. Among the various complexes identified in different species, four structurally related families have been described [112]: inositol requiring 80 (INO80), chromodomain, helicase, DNA binding (CHD), switching defective / sucrose non-fermenting (SWI / SNF) and imitation switch (ISWI). These protein complexes and histone chaperones can alter chromatin by histones or entire nucleosomes displacement [113]. All remodeling families contain the SWI2 / SnF2-family ATPase subunit recognized by an ATPase domain split into two parts: DExx and HELICc. The unique domains residing within, or next to, the ATPase domain underlie the differentiation of each family [112].

4. EPIGENETIC MARKS (SIGNALS) AND PLANT RESPONSES TO BIOTIC STRESSES

Plants have several defense mechanisms that protect them against harmful biological factors' attacks, both herbivores, and pathogens. Some of these mechanisms are constitutive while others function through specific regulation. The primary plant immune response is mainly based on the ability to recognize the characteristic configurations of invading organisms. Immune receptors, able to detect nonself-molecules or altered host cellular states, identify these arrangements. Receptors known as pattern recognition receptors (PRRs) distinguish preserved characteristic structures of invader biological factors, interacting with plants. These molecular signatures are called microbe-associated molecular patterns (MAMPs), including bacterial flagella, the elongation factor thermo unstable (EF-Tu) lipopolysaccharides (LPS), peptidoglycans, and components of fungal cell walls such as chitin fragments (N-acetyl-chitooligosaccharide oligomers) [114]. The activation of PRRs leads to MAMP-triggered immunity (MTI), which provides a first line of inducible basal defense against pathogens [114]. As an "aggression" strategy, invading pathogens try to circumvent this first defensive barrier, avoiding/suppressing MTI through the introduction of pathogen virulence molecules called effectors, which promote virulence in the absence of their immune recognition. As a defense strategy, plants activate a second line of protection called effector-triggered immunity (ETI). Interactions of high specificity of pathogen effectors [encoded by avirulence (*avr*) genes] and the products of plant R genes (R proteins, which constitute the second class of receptors; [114]) are the base for ETI. This last approach is qualitatively stronger and faster than MTI, comprising the targeted, and the hypersensitive response (HR), which is a form of localized programmed cell death [115].

Additionally, the presence of pathogens, besides initiating MTI and ETI, induces the production of signals related to

the synthesis of the hormone salicylic acid (SA) and methyl salicylic acid (MeSA), which leads to systematic expression of pathogenesis-related (PR) genes in places not yet attacked by them. This expression aims to protect the rest of the plant from secondary infection, known as systemic acquired resistance (SAR; [116]). Massive transcriptional rearrangements and metabolomics, in which there is involvement of epigenetic mechanisms, elaborate the above-mentioned molecular changes.

The use of model species such as *A. thaliana* and tobacco is a widely accepted tool for evaluation of epigenetic processes in response to stress, both biotic and abiotic. Nevertheless, there are also reports on cultivated species, since the manipulation of biotic and abiotic stress resistance/tolerance mechanisms in crops represents vital biotechnological tools. The methylation of specific target sequences of pathogenic organisms aims its transcriptional silencing (TGS mechanism). In plants, cytosines' methylation in DNA sequences has a crucial function in the processes of resistance to pathogens. In this way, Yadav and Chattopadhyay [117] analyzed contrasting soybean varieties (resistant and susceptible) under biotic stress, suggesting a distinct epigenetic mechanism in both. The authors compared the distribution of siRNAs derived from the bipartite geminivirus MYMIV (Mungbean Yellow Mosaic India Virus) along with the viral genome incorporated to the host. They also related the methylation level of the compatible sequences to these siRNAs in resistant (line PK416) and susceptible (line JS335) plants, after few days following pathogen inoculation. In PK416, most siRNAs were complementary to the intergenic region (IR), which anchors the promoters of geminivirus genes. In JS335, most siRNAs anchored in the coding regions of the virus genome. Considering that: (1) siRNAs can act in the cytosine methylation process; (2) promoter regions methylation usually inhibits transcription; and (3) coding regions methylation usually does has a moderate effect or none in gene expression; the exposed data indicates that the transcriptional gene silencing is more effective in the resistant variety. The higher frequency of IR DNA methylation in the resistant variety corroborated this observation.

Additionally, Dowen *et al.* [118] also reported the involvement of DNA methylation in plant protection to biotic stress. They exposed mutant *Arabidopsis thaliana* plants, globally defective in maintaining CG methylation (*met1-3*) or non-CG methylation (*ddc*, which is*drm1-2, drm2-2, cmt3-11),* to the Pst bacterial pathogen. In their study, they observed that these plants showed increased resistance to this pathogen and some defense genes were modulated through DNA methylation, once those mutants lacking CG, or non-CG, methylation showed constitutive and inducible misexpression of pathogen-responsive genes. The authors also observed that methylation levels within transposable elements may actively drive the expression of transposon and, sometimes, also of the proximal gene in response to stress.

In turn, histone modifications were reported in plant defense responses against phytopathogens. Wang *et al.* [119] showed in *Arabidopsis thaliana* that the Elongator complex subunit2 (ELP2), a subunit of the multitasking protein complex named Elongator, which serves in several cellular processes, participates in the response to *Pseudomonas syringae* pv *tomato* (*Pst*) DC3000/avrRpt2 infection, through multiple changes of epigenetic marks. It was found that ELP2 acts on some major defense genes, including *NON-EXPRESSOR OF PATHOGENESIS-RELATED GENES1* (NPR1; a transcription co-activator of plant immunity), to regulate plant immune responses. Once the Elongator complex has HAT activity, the authors analyzed the acetylation of target genes (in elp2 mutant) and found that, except for *NPR1*, the PR genes *PR1*, *PR2*, *PR5*, besides *EDS1* and *PAD4* genes showed a decrease in histone H3 acetylation at K9 and K14. This fact suggests that ELP2 regulates histone acetylation levels in several defense genes, and since histone acetylation relates with transcriptional activation (with exceptions as mentioned in subsection 2.2.1), lower levels of histone acetylation may benefit the setback or the reduction, or both, of defense genes' induction in *elp2*. Additionally, another epigenetic role for ELP2 was reported, including the regulation of *NPR1* by modulating the degree of methylation of cytosine anchored in its promoter. On the other hand, Ding *et al.* [120] analyzed the role of histone deacetylase 701 (HDT701) in the modulation of innate immunity, in rice (*Oryza sativa*) undergoing infection by *Magnaporthe oryzae* and *Xanthomonas oryzae* pv *oryzae* (*Xoo*). The HDT701 is a member of the plant-specific HD2 subfamily of HDACs, and the mentioned pathogens are, respectively, the causal agents of blast and bacterial blight diseases. Transgenic plants overexpressing HDT701 showed greater susceptibility to both pathogens studied. The silencing of this gene via RNAi in transgenic lines resulted in higher levels of acetylation on histone H4 (H4K5Ac and H4K16Ac residues). Likewise, it raises transcription of PRR and defense-related genes. It also expands formation of free active oxygen species after MAMP elicitor treatment. Finally, it improves resistance to both phytopathogens. The authors concluded that HDT701 negatively controls innate immunity by balancing the amounts of histone H4 acetylation of PRR and genes associated to defense in rice.

Recently, the involvement of histone ubiquitination was reported in processes of plant defense against fungal pathogens. This mechanism presents less information than other epigenetic modifications. In relation to the protein ubiquitination mechanisms, multiubiquitination is associated with the pathways of protein degradation [121], whereas monoubiquitination is involved in regulatory roles and modifying histones, as described by Hu *et al.* [122]. The authors studied wild-type and H2Bub mutants (H2B monoubiquitination loss-of-function mutations) of *A. thaliana* to elucidate mechanisms involved in the defense response to the fungus *Verticillium dahliae* (*Vd*) toxin. Divergent responses among these individuals were observed in response to the toxin analyzed involving the depolymerization of the cortical microtubules, a process that plays a functional role in the signaling pathway that mediates the expression of defense genes. The loss-of-function alleles of *HISTONE MONOUBIQUITINATION1* and *HISTONE MONOUBIQUITINATION2* mutations presented a weaker depolymerization of the microtubules, structures necessary for plants to block fungal penetration. Additionally, it was observed that H2Bub is a positive regulator of the gene expression of tyrosine phosphatase proteins and that they play a crucial role in the regulation of the referred structures' dynamics. Through the compilation of

these results, the authors [122] demonstrated that H2Bub is involved in modulating the microtubules dynamics, more likely via the protein tyrosine phosphatase-mediated signaling pathway.

5. EPIGENETIC INVOLVEMENT IN PLANT HORMONE SIGNALING UNDER BIOTIC STRESSES

According to Glazebrook [123], based on the feeding strategy, the phytopathogens may be classified as necrotrophic, biotrophic and hemibiotrophic. The necrotrophic phytopathogens are those that cause the immediate death of the host cells as they pass through them, feeding on the dead material. On the other hand, biotrophic phytopathogens correspond to those with a long-lasting relationship with the host. The biotrophs feeds on living host tissues, without killing them. Finally, hemibiotrophic phytopathogens are those with the ability to change their feeding strategy throughout the life cycle, incorporating aspects of both biotrophs and necrotrophs. As mentioned before (subsection 4), phytohormones participate in response of plants to pathogens, whereas systemic plant signals, mediated by these compounds, influence the resistance levels.

To biotrophic and hemibiotrophic phytopathogens, resistance processes can be triggered by the action of *R* genes and signaled by SA, which acts on the stimulation of different *R* genes, assisting in prompting the HR and depriving pathogens of the food source [123, 124]. To necrotrophic pathogens, the action of the same pathway - triggering a hypersensitivity reaction and consequent cell death - only facilitate their activities. Differences in plant response to these types of phytopathogens can be seen in Thomma *et al.* [125]. These authors demonstrated that mutations in genes that block SA signaling result in loss of resistance to the biotrophic oomycete *Peronospora parasitica*, but have no effect on resistance to the necrotrophic fungus *Alternaria brassicicola*. Conversely, mutations in genes that blocks jasmonic acid (JA) signaling compromised the resistance to the necrotrophic fungus *A. brassicicola*, probably by affecting the camalexin synthesis, a phytoalexin involved in antifungal resistance. These mutations have no effect on resistance to biotrophic oomycete *P. parasitica*, which is triggered by the action of *R* genes and SA signaling [123]. Additional findings indicate JA as an inducer of basic PR genes, and also as an inhibitor for acidic PR genes, while SA does the opposite [126]. Plant resistance activation against necrotrophic pathogens correlated with JA and ethylene (ET) signaling was demonstrated by McDowell and Dangl [127].

Under biotic stresses, the action of the JA and ET phytohormones is related to the state of epigenetic marks in target genes, which trigger processes of response and resistance. Zhou *et al.* [128] studied in *A. thaliana* the expression and function of a yeast *REDUCED POTASSIUM DEPENDENCY3* (*RPD3*) homolog, denominated *HISTONE DEACETYLASE19* (*HDA19*; AtRPD3A) under hormonal stimulation and abiotic/biotic stresses. In their study, the expression of the reporter gene *HDA19*: beta-glucuronidase (GUS) was induced by wounding, JA, ET, and *Alternaria brassicicola* (necrotrophic pathogen). Previous reports presented by the authors showed that both JA and ET act synergistically inducing defense genes as *CHI-B* (Basic Chitinase) and *BGL* (β-1.3-glucanase). In transgenic *Arabidopsis thaliana* plants overexpressing *HDA19* they reported induction of these genes. In contrast, the expression of *CHI-B* and *BGL* was decreased in *HDA19*-RNAi plants. Additionally, the authors observed that the *HDA19* overexpression in *Arabidopsis thaliana* did not increase the SA-regulated *PR* gene expression, whereas the set of results supports a role for *HDA19* in ethylene and JA-mediated defense response.

Latzel *et al.* [129] presented other data associating the epigenetics with hormonal regulation. They used different epigenetic recombinant inbred lines, epiRILs, of *A. thaliana*. These lines diverge only in the extent to which their genomes were methylated, and not in their nucleotide sequences. The authors aimed to analyze the epigenetic influence in several ecologically important traits, including the reaction to JA and SA, and found significant epigenetic variation in plant responding to these phytohormones. According to the authors, the variation in response to analyzed phytohormones is usually associated with variation in the strength of induced defense, or with different defense strategies, and the results suggested that instigated plant defense could vary depending upon the epigenetic context. Furthermore, a positive epigenetic correlation was observed between plant responses to JA and SA, which indicates that plant responses to herbivore and pathogen attack may have a similar molecular epigenetic basis. As a conclusion, it was suggested that part of the variation of plant defenses noted in natural populations may be due to underlying epigenetic, instead of entirely genetic, variation.

In the same way, Stokes *et al.* [130] presented a heritable, but metastable (i.e., that presents epigenetically modified loci in a variable and reversible manner), *Arabidopsis thaliana* variant denominated *bal*, that is a dwarfing variant generated in an inbred *ddm1* mutant line (strain Columbia). *ddm1* mutations lead to a reduction in cytosine methylation throughout the genome. It also causes inherited epigenetic changes, including hypermethylated *SUPERMAN* (*sup*) and *AGAMOUS* (*ag*) epialleles and hypomethylated *FWA* epialleles. Several tests show that *bal* contains an epigenetic alteration (probably hypomethylation), mapping to a cluster of NBS-LRR-class disease-resistance genes. Overexpression of one gene (*At4g16890*) of this cluster stimulates the disease response pathway and causes dwarfing and elevated disease-resistance, wherein the full phenotypic expression of the *bal* variant is dependent on SA signaling, once the SA-dependent defense response pathway displayed constitutive activation.

Other examples associated with epigenetic mechanisms regulating phytohormones and plant physiology face to biotic stress conditions are shown in Table **1** that comprises a summary of a variety of processes (histone modification and chromatin remodeling complexes) with activating or repressing influencing processes of pathogens' resistance.

6. EPIGENETICS AND BIOTIC STRESSES: MAINTENANCE OF GENOME STABILITY AND HERITABILITY

Some of the previously mentioned studies show a reduction in the level of cytosine methylation of specific genes during unfavorable periods, such as pathogen infection. Primarily, the immediate effect of this process is related to the

Table 1. Proteins involved in epigenetic modifications and their participation in hormonal signaling process in Arabidopsis mutant or plants under biotic stresses.

Protein	Epigenetics mechanisms	Hormonal involvement	Function	Stress	References
SNI1	chromatin remodeling	salicylic acid signaling pathway	Repression	*Pseudomonas syringae* infection	Durrant *et al*. [131]
SNI1	chromatin remodeling	salicylic acid signaling pathway	Repression	–	Mosher *et al*. [132]
SYD	chromatin remodeling	jasmonate and ethylene signaling pathways	Induction	*Botrytis cinerea* infection	Walley *et al*. [109]
EMF 1 and 2	histone methylation	ethylene signaling pathway	Repression	*Pseudomonas syringae* infection	Kim *et al*. [133]
SDG8	histone methylation	jasmonate and ethylene signaling pathways	Induction	*A. brassicicola* and *B. cinerea* infections	Berr *et al*. [134]
HDA19	histone deacetylation	salicylic acid signaling pathway	Repression	*Pseudomonas syringae*	Choi *et al*. [135]

Abbreviations: SNI1 (SUPRESSOR OF NPR1, INDUCIBLE); SYD (SPLAYED; an SWI/SNF class chromatin remodeling ATPase); EMF 1 and 2 (EMBRYONIC FLOWER 1 and 2); SDG8: histone methyltransferase SET DOMAIN GROUP8; HDA19 (RPD3/HDA1-class histone deacetylase HDA19); - (analysis of the mutant plant).

transcriptional activation of loci triggering an adaptive response to a new condition. An extensive analysis including the global behavior of the genome, the methylation level of it and the biotic stresses, indicate other effects derived from the cytosines methylation/demethylation processes in the DNA. They are: (1) its participation on the diversity generation influenced by stress conditions, as observed it from recombination rates of hypomethylated target loci, which are more pronounced in relation to hypermethylated loci; (2) supporting the maintenance of the genome stability, since there is an overall increase in the degree of methylation of the genome, thus reducing unspecific recombination.

Boyko *et al.* [136] presented an elegant experiment to analyze the inheritance of epigenetic marks and stability of the tobacco genome under stress by *Tobacco mosaic virus* (TMV) infection. They paralleled the recombination rate of loci carrying the homology to LRR region of the gene of resistance to TMV (*N-GENE-LIKE R-GENE*) from progeny with TMV infected parental (PI) and the control progeny (mock; PC). Concerning PI, changes in the stability (increase in recombination frequency) of LRR-containing loci, as the result of loci-specific hypomethylation was seen while the PC did not show the same, exhibiting no variation in methylation. Thus, it was suggested that hypomethylation could be a mechanism to facilitate the rearrangement of individual loci since the recombination rates showed no change for LRR-containing loci in PC and hypermethylated housekeeping genes in PI. The authors suggested that the LRR-containing loci studied could potentially function as 'building blocks' of (un)successful rearrangements aiming at the 'creation' of active *R*-gene(s), trying to improve the adaptability of the resulting progeny. Still, an increase in the global methylation of the PI genome line was observed, as compared with PC lines, considered as a defensive response that limits the occurrence of non-specific genome rearrangements under stress conditions. Moreover, analyzes in *Arabidopsis thaliana* [137] and *Pinus silvestris* [138] collected from areas with different levels of contamination around the Chernobyl nuclear power plant also suggested that increased global methylation of the genome is correlated with genome stability and stress tolerance in response to irradiation.

Another important question when dealing with epigenetics is the heritability of the changes. Interpreting an epigenetic modification as inherited, according to Skinner [139], deserves careful analysis. The exposure of a gestating female (F_0 generation) to a particular condition, results in the F_1 generation embryo and F_2 generation germ-line being directly exposed. Thus, only the F_3 generation is the first not directly exposed to the environmental compound. In contrast, postnatal or adult exposure (F_0 generation), results in the F_1 generation germ-line being exposed, such that the F_2 generation is the first to not be directly exposed to the environmental compound [139]. According to Sano and Kim [140], this argument might be extended to plants. They concluded that at least insightful analyzes up to the F_3 generation are necessary for claiming the "transgenerational inheritance" epithet.

A number of reports establish that plants use epigenetic mechanisms to adapt to stressful conditions (biotic and abiotic). These conditions increase the frequency of transgenerational epigenetic effects in unstressed progeny of stressed plants. However, in some situations the only representative of F_1 progeny is analyzed (see Boyko *et al.*, [141]; Hauser *et al.*, [142]); while, in other studies, the transgenerational inheritance given is contradictory. This is the case presented by Molinier *et al.* [143] and Pecinka *et al.* [144]. The first group after exposed *Arabidopsis thaliana* plants to UV-C radiation and the bacterial elicitor flagellin reported an increase in somatic homologous recombination, which has been observed in up to four generations after the stresses application. However, the second group reported that such transgenerational stress memory is not a general response in

Arabidopsis thaliana. Pecinka *et al*. [144] analyzed two ecotypes subjected to ten types of stresses. They checked the frequency of recombination within two generations after stresses application. As a result, they detected an increase in the recombination rate for most of the treatments. However, two subsequent non-treated generations only showed low and stochastic increase in somatic homologous recombination that did not correlate with the degree of stimulation in the parental plants. A similar effect was also observed by Boyko *et al.* [136], from the exposure of parental *Arabidopsis thaliana* plants to diverse stresses (high salinity, UVC, cold, heat, and flood). The results showed a higher homologous recombination frequency, increased global genome methylation, and higher tolerance to stress in the untreated progeny. However, under control conditions, such effect did not persist, and the resulting progeny showed no high recombination rate.

Sano and Kim [140] performed an extensive review on the subject of "Transgenerational Epigenetic Inheritance" (TEI). At the time, they found some cases associated with the level of stringency of what they regarded as TEI, considering cases in which:

1) the “acquired traits” to the characters were beneficial or at least not detrimental for the organism, so changes could ultimately contribute to the evolution;
2) the heritability of the "acquired trait" went through at least until F_3;
3) the altered phenotype clearly correlates with altered expression of the corresponding gene.

Of the 12 documented cases, five were in plants: flax [145] *Arabidopsis thaliana* [143], maize [146], snapdragon [147] and pea [148]. As transgenerational inheritance examples are few, and the vast majority of epigenetic modifications do not persist in the absence of an inducing factor (e.g. stressor factor), some authors [142, 149] have associated the transfer of epigenetic marks to subsequent generations to the "soft inheritance" mechanism, proposed by Ernst Mayr [150, 151]. Such mechanism proclaims – despite the classical view that only random changes in DNA sequences affect inheritance – that the environment can have an impact on inherited information content, allowing for directed transmission of environmental effects into subsequent generations. It should be emphasized that although it looks like a Lamarckian tendency, due to its component of environmental influence passed on to the next generation, the mechanisms presented here are short-term adaptations that add possibilities to the evolutionary processes based on the Mendelian and Darwinian thoughts. Thus, these examples did not corroborate the Lamarck’s ideas of the evolutionary model, based on the inheritance of acquired characters.

In turn, Saijo and Reimer-Michalski [152] suggested six steps, covering regulation of epigenetic signals associated with transcriptional orchestration of defense-related genes (DRGs) during an immune response in plants (Fig. **3**):

1) under normal conditions (absence of pathogen), DRGs are inactive or transcriptionally maintained at baseline, which is ensured by transcription-repressive or partially permissive chromatin configuration, respectively;
2) “after MAMP recognition, a change in chromatin conformation occurs, from the state of transcriptional repression to a permissive state, which prevents the spreading of repressive histone marks (signals) or allows a rapid access and action of transcriptional activators, or both”;
3) “increase the strength of the immune signaling beyond the threshold of activation leads to a massive activation of gene transcription, which in turn recruit defense-induced transcription factors and histone modifications that facilitate and/or enhance the transcription of DRGs”;
4) “following initial transcriptional changes, the persistence of active MAMP-triggered signaling or a distinct mode of signaling upon pathogen recognition (e.g., ETI signaling) leads to robust activation of gene transcription, which can be established by further spreading or acquisition of transcription-associated histone modifications".
5) “upon sustained activation of gene expression (including individual post-transcriptional steps), transcription-coupled active histone and other epigenetic marks are firmly established and/or widely spread, which allows their persistence even after the removal of defense triggers”;
6) “such long-lasting epigenetic states keep the altered activation threshold, thereby providing a basis for a chromatin-level memory of the immune response”. However, according to the authors, the lack of power of stimulations (stressor factor) turn off gene transcription, which may lead to restoration of the initial state of transcription through restoration of transcription-repressive (or basal, less permissive) patterns of histone modifications.

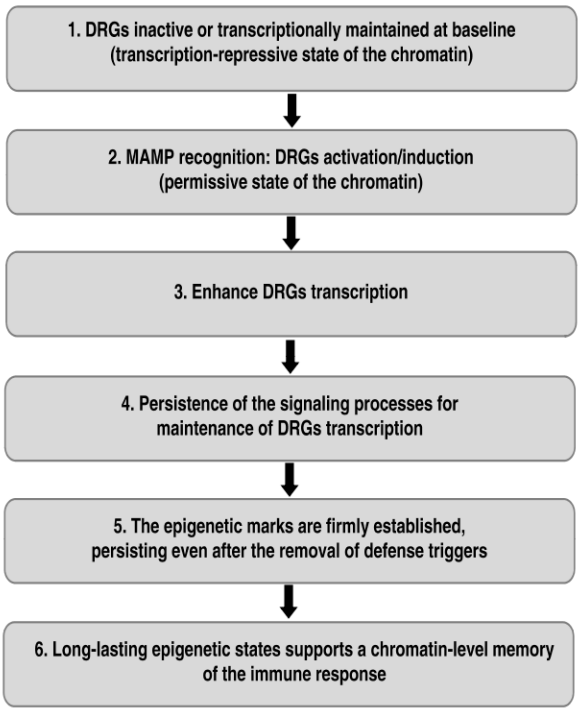

Fig. (3). The stepwise regulation of epigenetic processes associated with transcriptional activation/ attenuation of defense-related genes during plant immune response, as proposed by Saijo and Reimer-Michalski [152]. Abbreviations: “DRGs” (defense-related genes); MAMP (Pathogen-associated molecular patterns).

7. FINAL CONSIDERATIONS AND PERSPECTIVES

Epigenetic signals in regulating gene activity have been studied traditionally in the developmental context and controlling the activity of transposons. However, an increasing number of scientific articles have addressed the flexibility of chromatin organization and the variation in the degree of cytosine methylation in particular regions of the genome, both in response to biotic or abiotic changes. To date, the biological significance of epigenetic phenomena is not yet fully understood. Although some post-translational modifications of histones (e.g. methylation and acetylation) are well described in terms of its reversible dynamics, enzymes and signaling purposes in the recruitment of activators and repressors of gene activity, understanding other as ADP-ribosylation, ubiquitination and SUMO is still incipient. However, it is known that under stressful conditions, epigenetic phenomena in plants have plural action. Besides working in transcriptional regulation of specific genes, they take part in plant defense by silencing the expression of exogenous sequences incorporated to the host [117]. Likewise, they assist in the genome stability maintenance, due to the overall increase in the cytosine methylation [136, 137, 138]. Moreover, they contribute, indirectly, to generate genetic diversity, since specific loci hypomethylated during stress periods are subject to higher genetic recombination rates [136], assisting in achieving a more diverse offspring, better able to support the selective pressures of the environment in which they live. It has been reported [144], in addition, that the length of epigenetic signals is proportional to the presence of a stressor factor (or inductor of epigenetic modifications); in their absence, the signs persist only a few generations. Due to these facts, these changes have been considered as a short-term adaptive role, with little or no relevance to natural selection and evolution. Few studies addressing epigenetic phenomena in non-model cultivated plants are available, but almost all the information is on species considered model. Based on these organisms, the influence of epigenetic mechanisms in the plant immune system has been reported, including its role in the regulation of important phytohormones closely related to defense responses. Thus, understanding the genetic and epigenetic influences on important characters is essential to determine whether the variation and / or the observed phenotypes can effectively be fixed / captured by or seem unstable for practical use in traditional breeding programs.

Another context also reported is the use of biotechnology and machinery related to epigenetic phenomena to act for the improvement of important crops. In this regard, Wang *et al*. [153], applied PTGS / RNAi procedures to develop resistant barley lines to barley yellow dwarf virus. Hu *et al*. [154] in turn, applying similar principles, obtained tobacco with high levels of resistance to *Tobacco mosaic virus* and *Cucumber mosaic virus*. Both groups have used inverted repeated sequences of partial cDNA from these plant viruses and introduced into host plants for dsRNA expression and induction of RNA silencing. Other example involving virus resistance induction, PTGS / RNAi, and transgenic plants can be seen in Tabassum *et al*. [155]. Researchers are also taking advantage of these processes to improve the nutritional quality of crops, which is an important aspect of plant breeding. Liu *et al.* [156] genetically modified the fatty acid composition of cotton seed oil, using PTGS/RNAi gene silencing to repress the seed expression of two key fatty acid desaturase genes (*ghSAD-1*-encoding stearoyl-acyl-carrier protein Δ9-desaturase and *ghFAD2-1*-encoding oleoyl-phosphatidylcholine ω6-desaturase). The down-regulation of the *ghSAD-1* gene substantially increased stearic acid from the normal levels (2-3%) up to as high as 40%; and the silencing of the *ghFAD2-1* gene resulted in significantly elevated oleic acid content, up to 77%, compared with about 15% found in seeds of untransformed plants. In addition, palmitic acid (which is nutritionally undesirable because of their low-density lipoprotein cholesterol-raising properties) was significantly lowered in both high-stearic and high-oleic lines. Assays involving PTGS/RNAi and improved nutritional content have been reported in *Brassica napus* [157], tomato [158], corn [159], among others. From the foregoing, it is observed that genetic engineering associated with epigenetic is becoming more popular among the strategies applied to plant breeding, complementing existing methodologies and allowing the development of new elite materials from breeding programs.

LIST OF ABBREVIATIONS

Ag	=	AGAMOUS
AGO4	=	ARGONAUTE4
avr genes	=	avirulence genes
CHD	=	chromodomain, helicase, DNA binding
CMT3	=	DNA (cytosine-5)-methyltransferase CMT3
DCL1	=	DICER-LIKE 1
DLC3	=	DICER-LIKE 3
DME	=	DEMETER
DRGs	=	defense-related genes
DRMs	=	Domains Rearranged Methylases
EGF	=	epidermal growth factor
ELP2	=	Elongator complex subunit2
epiRILs	=	recombinant inbred lines
ETI	=	effector-triggered immunity
GR	=	glucocorticoid receptor
H3K27	=	lysine 27 on histone 3
H3K36	=	lysine 36 on histone 3
H3K9	=	lysine 9 on histone 3
H3S10	=	Serine 10 on histone 3
H3S28	=	Serine 28 on histone 3
H4K16Ac	=	lysine 16 acetylation on histone 4
H4K5Ac	=	lysine 5 acetylation on histone 4
HATs	=	histone acetyltransferases
HDA19	=	HISTONE DEACETYLASE19
HDACs	=	histone deacetylases
HDT701	=	HISTONE DEACETYLASE 701

HR = hypersensitive response

INO80 = inositol requiring 80

IR = intergenic region

ISWI = imitation switch

JA = Jasmonic acid

JmjC = JUMONJI C

KDMs = histone lysine demethylases

LRR = leucine-rich repeat

LSD1 = lysine specific demethylase1

MAMPs = microbe-associated molecular patterns

MeSA = methyl salicylic acid

MET1 = DNA METHYLTRANSFERASE 1

miRNA = microRNAs

MMTV = mouse mammary tumor virus

mRNA = messenger RNA

MTI = MAMP-triggered immunity

MYMIV = Mungbean Yellow Mosaic India Virus

natsiRNA = natural-antisense small interfering RNA

NBS-LRR = nucleotide-binding site leucine-rich repeat

ncmiRNA = non-canonical miRNAs

NPR1 = NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1

piRNA = PIWI-interacting RNA

PP1 = PROTEIN PHOSPHATASE 1

PR genes = pathogenesis-related genes

PRRs = pattern recognition receptors

PSTVd = potato spindle tuber viroid

PTGS = post-transcriptional gene silencing

RdDM = RNA-directed DNA methylation

RISC = RNA-induced silencing complex

RNAi = RNA interference

ROS1 = REPRESSOR OF SILENCING 1

RPD3 = REDUCED POTASSIUM DEPENDENCY3

rRNA = ribosomal RNA

SA = hormone salicylic acid

SAR = systemic acquired resistance

siRNAs = small interfering RNA

sRNAs = small RNAs

SUMO = small ubiquitin-related modifier

Sup = SUPERMAN

SWI / SNF = switching defective / sucrose non-fermenting

tasiRNA = trans-acting small interfering RNA

TGS = transcriptional gene silencing

tRNA = transfer RNA

vsiRNA = viral small interfering RNA

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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