Snapshot of epigenetic regulation in legumes

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Abstract
In the current context of food security and increase in plant protein demand, legumes have an important role in facing challenges of climate change. With the recent improvement of sequencing technologies and the emergence of new knowledge related to plant epigenetic regulation in response to developmental and environmental changes, legume epigenetics is an emerging field with high potential for improving legume crop productivity and adaptability. The objective of this review is to provide a snapshot of epigenetic studies in different legume species. We have summarized the state-of-the-art regarding legume epigenetic regulation controlling or participating in developmental aspects such as nodule, flower, and seed development and related to biotic and abiotic stresses. This extensive view of the different studies on legume epigenetics provides a baseline for identifying common and distinct mechanisms, and key players in epigenetic regulation from those of model species, such as Arabidopsis, and highlights the impact that a better understanding of these mechanisms in legumes could have in order to improve plant productivity and adaptability.

KEYWORDS
DNA methylation, epigenetics, histone marks, legumes

1 | INTRODUCTION

Knowledge in the field of epigenetics has rapidly increased over the past decade. Many epigenetic mechanisms have been identified, although from a very limited number of model species in mammals, insects, or plants such as Arabidopsis. Recently, the rapid increase of genomic technologies has allowed the decryption of many genomes, rendering possible the transfer of this knowledge to non-model organisms.

Since the introduction of the term epigenetic by Conrad Waddington in the 1940s, epigenetic concepts have radically changed, and nowadays, its exact definition is still being debated within the scientific community (Deans & Maggert, 2015). A general and commonly accepted definition refers as epigenetics (that literally means "above genetics"), heritable changes that do not alter the genetic code but could lead to modification of gene expression and phenotypic changes. Indeed, epigenetic changes do not change the DNA sequence, but by modifying the chromatin structure, they will affect how cells transcribe their genes. The two main epigenetic mechanisms are DNA methylation and post-translational histone modifications (PHM). These two mechanisms have been intensively studied in the past years, mainly in Arabidopsis, uncovering some aspects of their function and regulation as well as their influence on each other.

DNA methylation is a conserved epigenetic modification in plant and mammals. It directly impacts DNA by adding a methyl group from S-adenosyl-L-methionine to the fifth carbon position of a cytosine ring to generate a 5-methylcytosine (5mC). While restricted to 5CG sequences in mammals, plant DNA methylation is found in three contexts: CG, CHH, and CHG, in which H can be any base except for a guanine.

In plants, these methylation marks are regulated by DNA methyltransferases such as METHYLTRANSFERASE1 (MET1) for the CG

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context, CHROMOMETHYLASE2, and 3 (CMT2 and CMT3) for the CHG context, DOMAIN REARRANGED METHYLASE2 (DRM2) and CMT2 for the CHH context. These enzymes have a role in DNA methylation maintenance, but some of them have specific role in de novo methylation establishment through the DRM2- and CMT2-dependent pathways (for review Law & Jacobsen, 2010). Indeed, the DRM2-dependent pathway or de novo RNA-directed DNA methylation (RdDM) pathway relies on small RNAs, especially small interfering RNAs (siRNAs) to serve as guides to methylate specific DNA sequences. The RdDM pathway involves two RNA polymerases specific to plants: POL IV, necessary for siRNA production (Herr, 2005; Onodera et al., 2005; Pontier et al., 2005) and POL V needed to guide ARGONAUTE4 (AGO4) to the chromatin (Wierzbicki, Ream, Haag, & Pikaard, 2009) through a well-established process. These 24-nt siRNAs are produced through POL IV, and its associated transcriptional complex including the RNA-DEPENDENT DNA POLYMERASE2 (RDRP2 or RDR2), which generates double stranded RNA (dsRNA), ultimately cleaved by DICER-LIKE PROTEIN3 (DCL3) into siRNAs. These siRNAs are, then, loaded onto ARGONAUTE proteins (mainly AGO4 et AGO6) and paired with scaffold RNA produced by POL V with the help of the DDR protein complex. The DDR complex is composed of DEFECTIVE IN RNA-DIRECTED DNA METHYLATION 1 (DRD1), RNA-DIRECTED DNA METHYLATION 1 (RDM1), and DEFECTIVE IN MERistem SILENCING 3 (DMS3) proteins, which stabilize the POL V chromatin interaction with the help of the MORC protein complex. AGO4, with associated RNAs, interacts with the DNA methyltransferase DRM2 with possible assistance of RNA-DIRECTED DNA METHYLATION3 (RDM3) to methylate targeted regions (for review Matzke & Mosher, 2014; Zhang & Zhu, 2011). Finally, after DNA methylation, another protein complex belonging to the INVOLVED IN DE NOVO2- IDN2 PARALOGUE (IDN-IDP) complex may stabilize the siRNA/scaffold RNA to interact with the SWI/SNF chromatin remodeling complex that will change nucleosome positioning to silence transcription (Finke, Kuhlmann, & Mette, 2012; Zhu, Rowley, Böhmdorfer, & Wierzbicki, 2013). It is still unclear to which extent the RdDM pathway is involved in direct gene methylation and regulation, but it is crucial for targeting specific repetitive sequences and transposable elements (TEs), which may indirectly control nearby gene activation or repression (for review Sigman & Slotkin, 2016). Partially redundant with the RdDM pathway, the CMT2-dependent pathway is involved in de novo CHH methylation of heterochromatin regions and more specifically TEs (Zemach et al., 2013). This pathway, less described than the RdDM pathway, occurs through a siRNA independent manner and relies on DECREASED IN DNA METHYLATION 1 (DDM1) chromatin remodeler.

To counterbalance methylation activity, DNA demethylation occurs either passively due to failure in DNA methylation maintenance following replication or actively by regulation of methylation levels by DNA glycosylases. In Arabidopsis, four 5mC DNA glycosylases are able to excise methyl groups from all three DNA methylation contexts (i.e., DEMETER [DME], DEMETER-LIKE PROTEIN2 [DML2], DEMETER-LIKE PROTEIN3 [DML3], and REPRESSOR OF SILENCING1 [ROS1]; see review Zhang, Lang, & Zhu, 2018). Several studies showed a coordination between DNA methylation and active demethylation by an antagonistic effect of RdDM and ROS1 activity to prevent hypermethylation at specific loci (Tang, Lang, Zhang, & Zhu, 2016). A 39-nt specific regulatory element in the ROS1 promoter, called a DNA monitoring methylation sequence (MEMS), has been identified to serve as a putative sensor of MET1 and RdDM pathway activities. Indeed, high MET1 and RdDM activities lead to hypermethylation of this sensor, which activates ROS1 demethylase expression to regulate the genome-wide DNA methylation (Lei et al., 2015).

DNA methylation is usually described as a repressive modification of heterochromatin and pericentromeric regions, associated with gene and transposon silencing. However, it seems to play different roles depending on methylation locations. Methylation of promoter (or intergenic) regions has been proposed to regulate gene expression by inhibiting the binding of transcriptional activators/repressors, therefore activating or repressing transcription. It was shown to completely repress gene expressions, for tissue-specific genes (Johnson et al., 2007; Zhang et al., 2006). Methylation in promoter regions has been shown to be involved in gene regulation of specific processes such as imprinting during seed development and regulation of some immune-responsive genes (for review Matzke & Mosher, 2014; Zhang, Su, Hu, & Li, 2018). Methylation promoters appeared to be the consequence of the spreading of methylation from closely located TEs. In Arabidopsis, only 5% of promoter regions are methylated, but it does not reflect the situation of plant species with larger genome, such as legume crops, which contain many transposons and repeat elements with possible impacts on nearby gene expression through promoter methylation. Role of DNA methylation within gene bodies is still unclear. In contrast to methylation of promoters, gene body methylation occurs in 30% of Arabidopsis genes but with relatively low methylation levels (Zhang et al., 2006). Some correlations revealed that body-methylated genes were enriched in GC context and that these genes were often associated with high and/or constitutive expression of such housekeeping genes (Zhang et al., 2006). A recent study revealed that gene body methylation levels were not associated with highly expressed genes but rather with long and slowly evolving genes (Kawakatsu et al., 2016). To date, two hypotheses regarding the role of methylation in gene bodies have been proposed: (a) it could mask cryptic transcription sites, and it could help splicing of isoforms (Neri et al., 2017), (b) it could reduce variation of gene expression by excluding H2A.Z from the nucleosome, whose binding to gene bodies is anticorrelated to methylation but correlates to gene responsiveness to the environment (Zilberman, Coleman-Derr, Ballinger, & Henikoff, 2008). The role of methylation in TEs is much clearer; it acts as a repressor of the transposition activity inducing TE silencing. TEs are heavily methylated in all contexts and methylation maintenance involves mainly MET1, CMT3, DRM2 and relies on the RdDM pathway (Zhang et al., 2006). TEs and repetitive elements represent a large proportion of most plant genomes, active TEs could insert within or around protein sequences disrupting normal genome function and threatening genome stability. To prevent
this phenomenon, hypermethylation of TEs will silence and immobilize transposons in order to prevent disruption of normal gene functions and enhance genome stability (Mlura et al., 2001; Suzuki & Bird, 2008; Sekhon & Chopra, 2009; for review Sigman & Slotkin, 2016).

PHM are a conserved epigenetic mechanism controlling recruitment of chromatin remodeling proteins via modification of the nucleosome structure. Indeed, the nucleosome is an important structure controlling access and binding of regulatory factors (Berger, 2007). Eight histone proteins form the nucleosome with two copies of each of H2A, H2B, H3, and H4 proteins, around which is wrapped 147 bp of DNA (Peterson & Laniel, 2004). Amino acids of the N-terminal tails of histones H3 and H4 are easily modified by methylation, acetylation, phosphorylation, ubiquitination, ribosylation, or biotinylation. These modifications will affect inter-nucleosomal interactions and permit recruitment of chromatin remodeling enzymes, leading to chromatin structure change. Histone modifications can activate genes through acetylation, phosphorylation, and ubiquitination and mostly repress genes through methylation, with some exceptions (Table 1). Repressive marks such as H3K27me3, H3K9me3, H4K20me have also been associated with heterochromatin-associated histone modification (Zhao, Zhan, & Jiang, 2019). Acetylation of lysines on H3 and H4 histones is controlled by multiple histone acetyltransferases (HATs) and histone deacetylases (HDACs). Methylation of lysines on H3 and H4 histones is controlled by histone methyltransferases (HMTs) and histone demethylases (HDMs). Regarding methylation, lysine residues can be mono-, di-, or tri-methylated, which confer different transcriptional roles with marks such as H3K4me2 and H3K36me3 acting in gene activation, whereas others such as H3K27me3 and H3K9me2 are repressive (see Table 1).

Table 1: Summary of some major histone modifications with their preferential binding locations and their transcriptional roles

| Histone marks | Transcriptional role | Position          |
|---------------|----------------------|-------------------|
| H3K4me        | Activation/repression| Entire transcribed regions |
| H3K4me2       | Activation/repression| 5’ end of gene body |
| H3K4me3       | Activation           | 5’ end of gene body |
| H3K9me2       | Repression           | Entire transcribed regions |
| H3K9me3       | Repression           | 5’ end of gene body |
| H3K27me3      | Repression           | 5’ end of gene body |
| H3K36me3      | Activation           | 5’ end of gene body |
| H4K20me       | Repression           | -                 |
| H3K9ac        | Activation           | 5’ end of gene body |
| H3K27ac       | Activation           | 5’ end of gene body |
| H3K36ac       | Activation           | 5’ end of gene body |
| H4K5ac        | Activation           | -                 |
| H4K8ac        | Activation           | -                 |
| H4K12ac       | Activation           | -                 |
| H4K16ac       | Activation           | -                 |

Although histones are highly conserved proteins, plants have developed structurally and functionally distinct classes of Histone 2A (i.e., H2A.X, H2A.Z) and H3 (i.e., H3.3) variants, which play important roles in the dynamics of association with DNA (see review Deal & Henikoff, 2011). H2A.Z, for instance, is a variant mainly found in gene bodies and around transcriptional start site of genes, acting with the SWR1 remodeling complex, and highly responsive to heat stress, which induces nucleosome dissociation from DNA, activating gene expression (Kumar & Wigge, 2010; Sura et al., 2017).

Finally, several studies have provided evidence of the interplay between DNA methylation and modification of histone marks to modify chromatin structure. As an example, it was recently shown how DNA demethylase ROS1 is recruited to target specific loci via two bromodomain-containing proteins, essential for recruiting the SWR1 remodeling complex through recognition of histone acetylation, which enhances active demethylation and deposition of H2A.Z histone variants (Nie et al., 2019).

Starting from the state of the art, mainly obtained in Arabidopsis, several recent articles have deciphered and compared epigenetic mechanisms in other plant species. In this review, we intend to provide a snapshot of epigenetic studies in legumes with a specific focus on epigenetic roles in developmental processes such as nodule, flower, pod and seed development, and responses to biotic and abiotic stresses.

2 | DEVELOPMENTAL PROCESSES

Nodule development is mainly controlled by nodule-specific genes including cysteine-rich genes (NCRs), which are specific to legumes producing indeterminate nodules, such as Medicago. In this species, nodule zones represent the temporal developmental stages and are composed of the meristem (or apical meristem, ZI), the invasion zone (ZII), and the nitrogen-fixing zone (ZIII), which display specific ploidy levels ranging from 2C/4C (ZI), 4C/8C (ZII), and up to 32C/64C (ZIII; Vinardell et al., 2003). Moreover, these ploidy levels are correlated with expression of NCR genes in different nodule zones (Nagyimihály et al., 2017). The proportion of these zones will define nodule maturity from immature nodule, when ZI and ZII are predominant, to mature nodule, when ZII is well expanded. The first correlative evidence of the importance of DNA methylation in nodule development was a differential expression of methylases and demethylases between nodule zones, with higher expression of DNA methylase genes such MET1, CMT2, and CMT3 in the nodule apex (ZI) and in contrast, demethylation genes, such as DME, which was more expressed in proximal part of invasion zone (ZIIp; Satgé et al., 2016). To validate the role of DNA methylation in nodule development, DME was silenced by RNA interference. This led to abnormal development of the nitrogen-fixing zone, which was unable to fix nitrogen, indicating that DME control of demethylation is required for forming a functional nodule. DNA capture was performed to detect regions with high gene expression in immature and mature nodules. Four hundred seventy-four of highly expressed regions showed a correlated variation of methylation levels in CG and CHG contexts, whereas the level of methylation in CHH context was stable along nodule development.
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three families were identified with three from the CBP family, nine
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soybean flowering initiation. Interestingly, the majority of these genes
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Dean, 2017).

Several studies also confirmed the role of epigenetics in legume
flower development, highlighting some similarities and differences
with Arabidopsis, despite the fact that in soybean, flower initiation is
known to be induced by short day conditions and does not need ver-
nalization, unlike Arabidopsis. Liew, Singh, and Bhalla (2013) identified
124 histone modifiers and analyzed their expression profiles during
soybean flowering initiation. Interestingly, the majority of these genes
were found to be highly expressed in the shoot apical meristem
(SAM), suggesting an active role of histone modifications in regulating
gene expression in this tissue. Fourteen histone acetylases (HAT) from
three families were identified with three from the CBP family, nine
from the GNAT/MYST family and two from the TAFII250 family. Most
of them displayed higher expression in SAM with a peak of expression
at 1 day after short days, which is coherent with induction of light-
gene expression by two TAFII250 HATs as shown in Arabidopsis
(Benhamed, Bertrand, Servet, & Zhou, 2006). Twenty-four histone
deacetylases (HDACs) were identified, distributed in three classes
(i.e., HD2, SIR2, and HDA with, respectively, 6, 4, and 14 genes).

Among the four SIR2 members, two showed homologies with AtSRT2
and two others with AtSRT1. Interestingly, SRT2 genes in soybean
were more expressed in leaf whereas SRT1 genes were more
expressed in SAM, suggesting different and specific regulations.
Regarding the HD2 class of histone deacetylases, in Arabidopsis, high
levels of ABA repress HD2 expression (Luo et al., 2012). In soybean,
the two HD2 orthologs of AtHD2 showed the same behavior as in
Arabidopsis being highly expressed in the SAM before short-day con-
dition, followed by decreased expression at the onset of short-day
treatment, which induces ABA production (Wong, Singh, &
Bhalla, 2013). Finally, among the HDA class of histone deacetylases,
14 genes were identified in soybean. The most represented, with four
members, was the HDA6 family, which is known to deacetylate at vari-
ous lysine residues (Chen & Wu, 2010; Krogan, Hogan, & Long, 2012;
Zhou, Zhang, Duan, Miki, & Wu, 2005). Interestingly, the functional
analysis of the coding sequence of the HDAC family in soybean
showed that the histone deacetylase domain is highly conserved.
Surprisingly, one soybean HDA member, putative ortholog of AtHDA19,
contained a zf-RVT domain in the HDAC domain, which is typically
present in reverse transcriptase. The combination of HDAC and zf-
RVT domains had not been described in other species and could indi-
cate a specific function which remains to be discovered. Several his-
tone (de)methylases were identified, among them 47 SET proteins
(SDG for set domain group, histone methyltransferases), 15 protein
arginine methyltransferases (PRMTs) and 24 JmjC demethylases in
soybean. These genes were shown to be more expressed in SAM dur-
ing flowering initiation, suggesting their potential role during this tran-
sition. Five classes of SDG genes are defined in Arabidopsis. Two
members of class I, SWINGER (SWN) and CURLY LEAF (CLF), are two
histone methyltransferases implicated in methylation of H3K27 and
involved in the regulation of FT and FLC genes, therefore crucial in
controlling flowering time in Arabidopsis (Jiang, Wang, Wang, &
He, 2008). In soybean, two CLF and two SWN orthologs were identi-
fied but they did not display the same expression patterns. CLFs were
more expressed in SAM and SWNs in leaf, suggesting a specific role
of CLF in flowering. Interestingly, two paralogues of AtREF6, a
H3K27me3 demethylase, were identified in soybean and displayed
opposite expression profiles of CLF, indicating that GmREF6 could
play an antagonistic role to CLF to control FT expression in SAM. The
SDG class III genes composed of ATX1, ATX2, and ATXR7 (known to
methylate H3K4 and H3K36 residues) were shown to prevent
flowering before vernalization by activation of FLC expression in Ara-
bidopsis (Pien et al., 2008; Tamada, Yun, Woo, & Amasino, 2009). In
soybean, the orthologous genes were upregulated in the SAM, even
after vernalization, which suggests a different role for these genes in
the SAM regarding flowering initiation. Interestingly, SDG class V
genes, such as AtSUVR and AtSUVH, constitute the largest group of
histone methyltransferases in Arabidopsis, and the SUVH subgroup
was also highly represented in soybean with 15 genes (compared to
nine in Arabidopsis). However, no ortholog of the SUVH subgroup
was identified in soybean. Three of these PRMTs, including PRMT10,
were shown to regulate FLC in response to vernalization in Arabidopsis. In soybean,
an ortholog of PRMT10 was identified which displayed higher expression in the SAM after 2 days in short-day condition. Because soybean does not need vernalization, GmPRMT10 is probably involved in flowering initiation but could be activated through a different pathway. Regarding JmJc demethylases, 16 (out of a total of 24 in soybean) displayed a peak of expression 1 day after short-day treatment, including two orthologs of **AtEF6** (**EARLY FLOWERING6**), which is implicated in repressing **FT** through demethylation of **H3k4me3** in Arabidopsis (Jeong et al., 2009; Lu, Cui, Zhang, Liu, & Cao, 2010).

Regarding late flower development and pod initiation, Wang et al. (2018) showed differential expression of genes involved in DNA methylation during the three stages of flower development: S1 (ground green gynophores), S2 (white gynophores, 3 days), and S3 (gynophores enlarged, 9 days) in peanuts. Orthologous methylation genes such as **DRM2** and **MET1** DNA methylases and **DMS3** showed higher expression in S2 compared to S1, whereas **DRD1**, **MORC1**, and **IDN2** were more expressed in S3. Almost all genes implicated in the RdDM pathway were transcriptionally stable during all stages of pod development except for **NRPE5**, **HDA6**, **L DL1**, and **DMS3**. Then, authors analyzed the correlation between DNA methylation, expression of transcripts and 24-nucleotide siRNAs or miRNAs. First, only half of transcript expressions was negatively correlated with the level of methylation. Second, a positive correlation was found between abundance of siRNAs and miRNAs and methylation level. These observations suggest a potential role of the RdDM pathway in DNA methylation regulation and regulation of peanut flower/pod development. It is to note that the role of the RdDM pathway in flower development is nonessential as many RdDM mutants displayed proper flower development in other species but could act in flowering time regulation via methylation of the **FWA** promoter region (Chan, Zhang, Bernatavichute, & Jacobsen, 2006).

Regarding seed development, An et al. (2017) analyzed the DNA methylation pattern in cotyledon during three stages of seed matura-
tion in soybean, from early (S2) to middle (S6) and late seed matura-
tion (S8). Global DNA methylation was mainly identified in CG (66%), then CHG (45%) and CHH (9%) contexts. However, the global CG and CHH levels were unchanged during seed maturation, whereas CHH level increased during seed development from 6% in S2 to 9% in S8. Lin et al. (2017) confirmed these previous observations by a more comprehensive analysis of DNA methylation during soybean seed development and within dissected seed tissues from postfertilization to germination. Indeed, global methylation levels in CG and CHH contexts were slightly decreased but changed little during the studied stages, whereas CHH methylation level greatly increased during seed maturation (between early-maturation stage and late-maturation), then dropped drastically at germination. Although the average global CHH methylation level across all samples was globally low (2%) compared to CG (57%) and CHG (37%), it increased more than three-fold during seed maturation then dropped by almost two-fold during germination. The mechanism involved in the variation of CHH methylation during seed development is still unclear because the authors did not observe any changes in **MET1**, CMTs, or DRM expression. To have a better understanding of the role of CHH methylation during seed development, they analyzed the Arabidopsis **ddcc** quadruple mutant (i.e., **drm1dm2cmt2cmt3**), which is deficient in all methyltransferases involved in CHH and CHG methylation. Interestingly, the **ddcc** mutant did not show any major seed developmental defect or major changes in gene expression, suggesting that CHH does not play a fundamental role in proper embryo or seed development. This hypothesis was confirmed by the analysis of methylation levels within or closely related to genes essential in seed development and seed germination such as storage proteins, oil biosynthesis, master regulators of seed development, and germination-enhanced proteins. The authors revealed that almost 50% of these genes were localized in regions poor in methylation, called demethylated valleys (DMVs). The seed DMVs represented 21% of the genome and appeared to be consistent in all tested seed tissues. These DMVs also appeared to be enriched in transcription factors (TFs, with 46% of them), and in genes involved in embryo formation and seed development (e.g., **WOX**, **CUC**, **CLAVATA**, **PIN1** genes). These hypomethylated regions did not show any variation in methylated state during seed development, whereas the genes contained in these regions were highly transcriptionally active and tightly regulated. To explain this gene regulation, they observed that the repressive histone mark **H3K27m3** and the bivalent marks **H3K27me3/H3K4me3** showed some modulation in these regions during seed development that appeared to be correlated with TF gene expression, suggesting a regulation of these TF expressions via histone mark modifications rather than DNA methylation. Finally, in the same study, they revealed that CHH methylation and also the CHG methylation were concentrated upstream and downstream of the coding sequence and within TEs, but very low in gene bodies; in contrast to CG methylation, which was mainly located in gene bodies. Changes in differentially methylated regions between the three developmental stages appeared to be enriched in CHH methylation sites. Indeed, 97% of DMRs were linked to CHH context, and 65% of these CHH-DMRs were found to be differentially methylated between the three stages and located close to transcribed genes. In the **ddcc** mutant, transposases of 106 TEs were upregulated and showed a high density of CHH methylation sites, suggesting that CHH methylation could play a role in repression of TEs during seed development. Although most of these results were obtained in Arabidopsis, the authors mentioned that the overall regulation of methylation during seed development seems highly similar in Arabidopsis and soybean.

### 3 | **STRESS AND ADAPTABILITY**

#### 3.1 | **Biotic stress**

DNA (de)methylation was found to play critical roles in defense responses against a wide variety of pathogens (for review Deleris, Halter, & Navarro, 2016). In plant defense, resistance (R) genes encode Nucleotide binding Leucine rich Repeat (NLR) proteins, which play critical roles in effector perception for triggering immunity.
normal growth conditions, R proteins are maintained at low steady state levels and require a high degree of control to prevent fitness costs (Shirasu, 2009). In common bean, out of 197 CG-methylated NLR genes, 172 (87.3%) showed low to undetectable expression levels, suggesting that DNA methylation could be an alternative way of transcriptionally silencing R proteins under normal growth conditions to avoid fitness cost due to their unnecessary accumulation. NLR proteins are organized in clusters that are often located close to the terminal knobs containing the satellite DNA khipu. Following this observation, Richard et al. (2018) suggested that methylation of NLR genes could result from the spreading of DNA methylation from khipu in common bean. In addition, it was shown that 24 nt siRNAs targeted 24% of NLR genes, which were identified as methylated, validating a potential regulation of NLR expression through RNA-directed DNA methylation (RdDM) pathway (Richard et al., 2018).

RNA silencing mediated by siRNA is employed in plant defense against a variety of pathogens from bacteria, to fungi and viruses. To better understand the importance of this mechanism in plant defense, Garg et al. (2017) analyzed correlations between transcript levels of DICER-LIKE (DCL), ARGONAUTE (AGO), and RNA-dependent RNA polymerase (RDR) gene families in Chickpea infected by Ascochyta Blight (AB, Ascochyta rabiei), pigeon pea infected by Sterility Mosaic Disease (SMD) and groundnut subjected to rust (Puccinia arachidis) and late leaf spot fungus (Phaeoisariopsis personata). A general trend of upregulation of siRNA biogenesis genes in resistant genotypes and downregulation of genes was observed in susceptible genotypes, including DCL2,AGO7 in chickpea, DCL2, DCL4, RDRs genes in pigeon pea, and DCL2 in groundnut, (Garg et al., 2017). A specific focus has been done on these genes as Arabidopsis ago7 and rdr and Tomato dclb2 mutants were found to be more susceptible to fungal and viral pathogens (Ellendorff, Fradin, de Jonge, & Thomma, 2009; Wang et al., 2018).

Several studies also demonstrated that histone methylation and histone acetylation play a role in plant immunity. ChIP-seq experiments of the repressive mark H3K9me2 and active mark H4K12Ac combined with RNA sequencing in common bean at different stages of Uromyces appendiculatus infection revealed key genes related to the bean-rust interaction. Expression profiles of genes such as defense response genes (e.g., low molecular weight cysteine 68, GIGANTEA protein and Dnaj-domain chaperone superfamily), R proteins (e.g., Pleiotropic drug resistance protein 12, MATE efflux family and NB-ARC domain-containing) were correlated with changes of histone methylation and histone acetylation modification (Ayyapann et al., 2015).

Defense priming is an intrinsic protective mechanism, in which plants prime their defense mechanisms after a first attack/infection in order to defend themselves more rapidly in subsequent interactions with pathogens (Mauch-Mani, Baccelli, Luna, & Flors, 2017). It has been shown that this phenomenon is related to the dynamics of chromatin structure. In Common bean, (pre)treatment with salicylic acid analogs such as BABA or INA enhanced resistance against P. syringae pv. Phaselicola, with a protective effect transmitted to the next generation. It has been shown that this effect was due to the induction of pathogen-associated genes such as PRI, PR4, NPR1, and WRKY29, WRKY53, WRKY6, correlated with enrichment of the active histone mark H3K4me3 at the junction between promoter and coding regions in these genes (Martinez-Aguilar, Ramirez-Carrasco, Hernandez-Chavez, Barraza, & Alvarez-Venegas, 2016).

Effectors secreted by pathogens are also known to target the components of HAT or HDAC complexes, thereby manipulating plant immunity. The ADH2 and GCN5 subunits of the SAGA complex (i.e., multi-protein chromatin modifying complex) are essential for HAT activity, which activates gene expression via acetylation of H3K9. Two robust studies in soybean highlighted the action of pathogen effectors in modulating plant immunity. The Phytophthora sojae effector PsAvh23 has been shown to bind to GmGNC5, which disrupts its assembly with ADH2, thereby decreasing H3K9 acetylation and resulting in transcriptional repression of soybean defense genes (Kong et al., 2017). Similarly, PsAvh52, an effector at the early stage of infection, interacts with GmTAP1, an acetyltransferase, regulating histone acetylation and promoting expression of susceptibility genes (Li et al., 2018).

Finally, WRKY TFs are well-documented players in plant defense, regulating transcript levels of many defense-related genes (Birkenbihl, Liu, & Somssich, 2017; Pandey & Somssich, 2009). In chickpea, following Fusarium oxysporum f. sp. Cicero Race 1 infection, high expression of WRKY40 in resistant plants was associated with high enrichment of the active mark H3K9Ac in its promoter region, which could suggest a role of histone activation marks in increasing resistance to this pathogen (Chakraborty, Ghosh, Sen, & Das, 2018).

3.2 | Abiotic stress

Several studies have shown correlations between changes in methylation levels and environmental stresses, suggesting potential involvement of epigenetic mechanisms in plant adaptability. For instance, drought stress in faba bean and water deficit in pea were associated with an overall increase of DNA methylation in both tolerant and sensitive genotypes (Abid et al., 2017; Labra et al., 2002). In contrast, salt stress in pigeon pea induced a global decrease of DNA methylation in shoot (Awana et al., 2019). On a longer term, continuous stress increased global DNA demethylation mainly in a tolerant soybean genotype. This increased demethylation was consistent with increased expression of DNA demethylases such as DML and ROS1. The demethylation analysis revealed that CG and CHG contexts within gene regulatory regions were more critical than CHH in soybean adaptation to stress (Li et al., 2019). In contrast, salinity stress in Medicago truncatula, induced up to 77% of changes in CHH context, with only 9.1% and 13.9% in CHG and CG, respectively. However, no correlation between transcript level and DNA methylation pattern of some key genes known to be involved in salinity stress was reported, implying that these genes might be regulated by other epigenetic mechanisms (Yaish, Al-Lawati, Al-Harrasi, & Patankar, 2018). In contrast, Song et al. (2012) showed that, in soybean, among four TFs induced under salt stress, three were
demethylated in CG and non-CG contexts, preceding enrichments of active histone marks (H3K4me3 and H3K9ac) and decrease of the repressive mark H3K9me2, leading to gene upregulation, suggesting the possible interplay between DNA methylation and histone modification in stress response.

A growing body of evidence assigns crucial roles of histone acetylation and histone methylation in plant responses to external stress. Changes in DNA methylation, histone methylation, and histone acetylation were observed in soybean root meristems growing at different temperatures. Immunostaining patterns indicated that 5-methylcytidine (i.e., a marker of methylated DNA) and H3K9me2, mainly located in the heterochromatin, were more abundant in soybean during chilling stress than during recovery. In contrast, H3K9ac, H4K12ac, and H3K4me, indicators of permissive chromatin, were weakly labeled in the euchromatin of stressed plants, but stronger during the recovery process (Stepinski, 2012). Interestingly, crosstalk between histone methylation and histone acetylation was also reported in soybean subjected to salinity stress. Wu et al. (2011)

![Diagram](image_url)

**FIGURE 1** Summary of (a) developmental processes, (b) biotic, and (c) abiotic stress responses to different legumes species and their corresponding epigenetic mechanisms.
proposed that the salinity stress-inducible plant homeodomain TF, GmPHD5, could bind salt-induced H3K4me2 marks. This binding allowed recruitment of a complex involved in gene activation with non-histone proteins such as GmISWI, a chromatin remodeling factor and GmGNAT1, an acetyl transferase, which can preferentially acetylate H3K14 to further activate expression of salinity-induced genes.

In peanut, another study showed a regulation of gene expression of the AhDREB1 gene. The regulation, by acetylation of H3 enabled this member of the AP2/ERF TF family to positively regulate drought stress related genes, under PEG osmotic stress. Indeed, expression of AhDREB1 was shown to be higher with trichostatin (TSA), an inhibitor of HDAC (histone deacetylase), eventually inducing drought resistance (Zhang, Su, et al., 2018). Salt and drought stresses have also been shown to induce the activation of CaHDZ12, a HD-Zip TF, in chickpea, whose expression was correlated with acetylation of H3K9ac in the promotor region (Sen, Chakraborty, Ghosh, Basu, & Das, 2017).

4 | PERSPECTIVES

From this extensive review of legume epigenetic studies, we can clearly appreciate the importance of epigenetic regulations in developmental and stress-related processes (summarized in Figure 1). Considering legume crops not only with their large genomes containing many TEs and repeat regions but also their genes with high copy number (e.g., as described in this review with histone modifiers), their numerous small RNAs, and their specific legume processes (e.g., nodulation), there is no doubt that we will observed a growing interest in legume epigenetic studies in order to understand specific developmental processes and adaptive responses to environmental constraints in legumes. To conclude, epigenetic studies in legumes are still at an early developing stage and have been predominantly focusing on identification of key epigenetic players in different plant developmental or stress-related processes. This initial descriptive step is essential as most legume genomes are still poorly annotated and contains many genes with high copy number that could have overlapping or distinct functions. Perspectives will be an increase of functional studies of these key epigenetic players that could be enhanced by the rapid development of CRISPR technologies to generate collection of epigenetic mutants in major legume crops. From this perspective, a better understanding of epigenetic mechanisms and the identification of epialleles in legumes will potentially boost plant crop improvement and stress adaptation.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTION

TTD, ZC, DW, and JV wrote, reviewed and approved the final manuscript.

ETHICS STATEMENT

This manuscript does not contain any studies with human or animal subjects.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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