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The ability of plants to appropriately respond to the soil nutrient availability is of primary importance for their development and to complete their life cycle. Deciphering these multifaceted adaptive mechanisms remains a major challenge for scientists to date. Recent technological breakthroughs now enable to assess the dynamism and complexity of these processes at unprecedented resolution. In this review, we present some of the most recent findings on the involvement of histone modifications, histone variants and DNA methylation in response to nutrient stresses as well as discussing the potential roles these chromatin changes could serve as priming or as trans-generational stress memory mechanisms.

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## Introduction

Because of their sessile nature, plants can adjust their growth and development in response to a multitude of environmental cues such as light quality, temperature, photoperiod and nutrient availability. This plasticity allows them to adapt to their local and changing environment, providing the optimum responses to acclimate to these challenges. Nutrient availability, like other environmental cues, is perceived and transmitted by a multitude of signalling pathways, ultimately enabling plants to better cope with dynamic and challenging environments. In recent years, numerous studies ranging from phenotypic to molecular analyses have greatly improved our understanding of the complex regulatory networks involved in these mechanisms [1–8]. Among these, sophisticated dynamic changes in chromatin structure have been observed in response to numerous environmental conditions, often associated with concomitant changes in gene expression (reviewed in Refs. [9–14]). The basic chromatin unit is constituted of 147 base pairs of DNA wrapped around the eight core histones and forms the nucleosome. Chromatin remodelling involves the rearrangement of chromatin between condensed and transcriptionally quiescent and accessible and transcriptionally permissive states, modulating the ability of transcription factors or other DNA binding proteins to access DNA and control gene expression. Biochemical changes in chromatin state include histone modifications and histone variants as well as DNA methylation, which can be dynamically changed to maintain gene and genome activities. The capacity of some of these modifications to be stably transmitted through mitosis as well as meiosis led to the hypothesis that changes in chromatin state could serve as stress priming and/or memory mechanisms to prepare future generations to efficiently cope with biotic and abiotic stresses (for review see Refs. [14–17]). However, to date very few experimentally validated cases of mitotic or meiotic transmission of stress induced changes in chromatin structure have been reported in plants. Thus it is important to clearly distinguish chromatin changes from epigenetic changes. Indeed both terms are frequently used to designate any changes in chromatin structure, independently of any notion of heritability [9]. In this review, the term epigenetics refers to heritable patterns of phenotypic variation, that is, stable transmission of information through mitosis or meiosis that are not solely attributable to differences in DNA sequence. Indeed, stress-induced changes in chromatin structure may play critical roles in the plant response to this condition without necessarily leading to mitotic or meiotic heritable changes. The field of chromatin research has greatly benefited from high-throughput next generation sequencing technologies, the availability of quality antibodies for modified DNA or histone residues, as well as improved genome sequences and annotations, enabling assessment of chromatin changes at the whole genome level and at unprecedented resolution. As a result, changes in chromatin structure have been observed in response to a multitude of conditions, including abiotic stresses, such as drought, salt stress, and temperature (for review see Refs. [12,13,18–20]). To date, vernalization likely represents the best-understood example of environmentally induced chromatin changes (for a detailed review, see

Ref. [21]). These modifications in chromatin state are heritable and are hence considered epigenetic. While chromatin modifications are integral to some epigenetic phenomena, some cases of chromatin changes are likely not heritable and are thus not considered as epigenetic [22]. To date, only a small number of studies have focused on the role of chromatin regulation in response to changes in nutrient availability, and thus its potential role in regulating nutrient homeostasis (Tables 1 and 2). In this article, we will provide a review of the current state of the field as well as discussing potential limitations and future directions.

## Histone modifications

Histones are the protein components of the nucleosomes that form the basic architecture of eukaryotic chromatin. Each nucleosome is comprised of an octameric complex containing two copies each of the histones H3, H2A, H2B and H4, and is typically enfolded by 147 bp of DNA [23]. Each histone has both a C-terminal histone-fold and a N-terminal tail, with the N-terminal tails being preferentially subject to a variety of post-translational modifications, such as acetylation, phosphorylation, methylation, ubiquitination, and ADP-ribosylation, as well as other poorly studied or yet unknown modifications [24]. These modifications are reversible and maintained by the action of a variety of histone modifying enzymes, influencing chromatin structure and hence playing an important regulatory role in processes such as transcription, DNA repair, and replication. To date, most of the investigation of histone modifications dynamics in response to nutrient stresses have focused upon histone methylation. In 2011, Widiez *et al.* characterized the *high nitrogen-insensitive 9-1* (*hni9*) mutant that is impaired in the systemic feedback repression of the root nitrate transporter NRT2.1 by high N supply, revealing that HNI9/AtIWS1 was a key factor in the deposition of trimethylated lysine 27 of histone H3 (H3K27me3) at the *NRT2.1* locus in response to high N supply [25]. More recently, it has been shown that symmetric dimethylation of histone H4R3 (H4R3sme2) was involved in iron homeostasis [26•]. Indeed, mutation in the *Arabidopsis* Protein Arginine MethylTransferase 5 (*PRMT5*, also referred to as *SKB1*), involved in catalyzing histone H4R3 symmetric dimethylation, resulted in mutant plants having higher iron accumulation in shoots and greater tolerance to iron deficiency than wild type plants. Mutation in *PRMT5* also affected the expression of several Ib subgroup bHLH genes [26•], which are required for the regulation of iron uptake and homeostasis in *Arabidopsis* [27] and iron-uptake processes [26•]. The involvement of trimethylated lysine 4 of histone H3 (H3K4me3) in response to nutrient stress was also reported in a study aimed at identifying genes involved in root hair elongation in *Arabidopsis* specifically under phosphate starvation, revealing the *alfin-like 6* (*AL6*) gene [28,29]. AL6 contains a Plant Homeo Domain (PHD) finger that can bind to H3K4me3 [30], thus qualifying AL6 as a *bona fide* histone reader. *AL6* is non-transcriptionally responsive to Pi starvation and the *al6* mutant plants displayed a pleiotropic phenotype including reduced anthocyanin accumulation and altered root architecture in response to low Pi, namely very short root hairs. Since H3K4me3 is thought to be a binding platform for transcriptional activators and for factors that mediate transcript elongation and mRNA maturation, the authors suggested that AL6 could affect transcript maturation and stability of critical genes involved in root hair elongation [28,29]. A recent study from the same group revealed that histone acetylation was involved in Pi homeostasis, through the investigation of the *Arabidopsis* histone

**Table 1**

**Summary of chromatin changes affecting histones in response to nutrient availability**

| Chromatin change | Stress | Gene | Function | References |
|---|---|---|---|---|
| Histone modifications | | | | |
| H3K27me3 | N | *AtHNI9* | Involved in the deposition of H3K27me3 at the *NRT2.1* locus in response to high N supply | [25] |
| H4R3sme2 | Fe | *AtPRMT5* | Negatively regulates iron homeostasis, via regulation of Ib subgroup bHLH genes | [26•] |
| H3K4me3 | P | *AtAL6* | Affects transcript maturation and stability of critical genes involved in root hair elongation | [28,29] |
| Acetylation | P | *AtHD19* | Involved in controlling in both Pi deficient and sufficient conditions as well as being involved in regulating a subset of key phosphate starvation | [31] |
| H3K9ac, H3K14ac | Fe | *AtGCN5* | Major role in FRD3-mediated iron homeostasis | [32••] |
| Histone variants | | | | |
| H2A.Z | P | *ARP6* | Required for proper deposition of H2A.Z at numerous key Pi starvation-induced genes in response to Pi starvation | [34] |
| H2A.Z | P | *IPK1* | Involved in the transcriptional regulation of some Pi starvation-responsive genes | [38] |

**Table 2**

**Summary of nutrient stress related changes in DNA methylation**

| Stress | Method | Organism | Role | References |
|---|---|---|---|---|
| N | MSAP | Rice | Changes in DNA methylation that could be transmitted to offspring and provide enhanced tolerance to stress | [40] |
| P | WGBS | Rice | Mainly transient changes in DNA methylation of TEs in the vicinity of Pi-stressed induced genes<br>No transgenerational transmission<br>Causality between changes in DNA methylation and gene expression | [42••] |
| P | WGBS | *Arabidopsis* | Limited changes in DNA methylation observed, associated with Pi starvation-inducible genes | [42••] |
| P | WGBS | *Arabidopsis* | Extensive changes in DNA methylation associated with changes in gene expression<br>Differential methylation nearby Pi responsive motif proposed to regulate TF binding and gene expression | [43••,44] |
| S | WGBS | *Arabidopsis* | Mutation of *MSA1* affects genome-wide DNA methylation including the methylation of S deficiency responsive genes<br>Differential methylation nearby S responsive motif proposed to regulate TF binding and S deficiency responsive gene expression | [47••] |

deacetylase 19 (HD19) [31]. Indeed, characterization of the *Arabidopsis HD19* mutant and over-expressing plants revealed a key role of HD19 in controlling root cell elongation in both Pi deficient and sufficient conditions as well as being involved in regulating a subset of key phosphate starvation induced genes, including some of the *SPX* genes involved in Pi sensing and signalling [31]. An additional case of histone acetylation-regulated nutrient homeostasis was recently discovered with the observation that mutation of the histone acetyltransferase General Control Non-repressed 5 (*GCN5*) gene resulted in impaired iron translocation from the root to the shoot in *Arabidopsis* [32••]. In this study, the authors revealed that GCN5 could directly bind to the promoters of five iron-related genes, including *Ferric Reductase Defective 3* (*FRD3*), a key factor involved in iron nutrition modulate their acetylation levels of histone 3 lysine 9 (H3K9ac) and histone 3 lysine (H3K14ac) levels, and in turn regulates their transcript expression [32••].

## Histone variants

Histone variants are non-canonical (non-allelic) variants of histones that possess one or several amino-acid differences, and that have specific expression, localization and species-distribution patterns. The incorporation of histone variants in the nucleosome can confer novel structural and functional properties on the nucleosome, ultimately affecting chromatin remodelling and gene expression [33]. Among the core histones, the H2A family is the most diverse, and the SWR1 chromatin-remodelling complex is involved in replacing the canonical histone H2A with the H2A.Z variant at specific chromatin regions. In 2010, Smith *et al.* [34], demonstrated that the *Arabidopsis* nuclear actin-related protein 6 (ARP6), a key component of SWR1 [35,36], was required for proper H2A.Z deposition at numerous key Pi starvation-induced genes in response to Pi starvation. Indeed, mutation of *ARP6* resulted in the loss of H2A.Z at many phosphate starvation induced genes and resulted in depression of these genes under Pi replete conditions [34]. Similar observations were also seen in yeast, where the SWR1 complex has been implicated in controlling the expression levels of numerous Pi responsive genes, such as the PHO genes [37]. The involvement of H2A.Z in regulating Pi homeostasis in plants has recently been strengthened through the study of the role of the *Arabidopsis* inositol pentakisphosphate 2-kinase coding gene (*AtIPK1*) that is involved in the biosynthesis of phytic acid, the main source of P in the seed [38]. Indeed, mutation of *IPK1* resulted in numerous phosphate starvation-induced genes being induced, and correlated with a reduction of histone variant H2A.Z occupation in the chromatin at these loci [38].

## DNA methylation

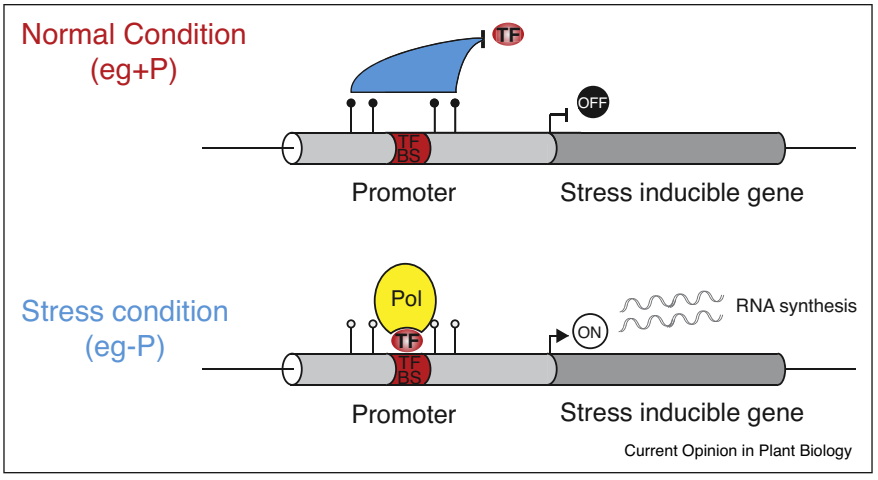
DNA methylation is a covalent and stable modification of cytosine in genomic DNA that can influence gene expression and transposon activity [39]. In plants, it refers to the formation of 5-methylcytosine from cytosine through the action of a DNA methyltransferase, and can occur in all three DNA sequence contexts: CG, CHG and CHH, where H is any nucleotide except guanine. Since DNA methylation is often mitotically and meiotically heritable [39], it has been hypothesized that it could serve as a stress memory mechanism, with stress-induced DNA methylation changes being maintained through mitotic and/or meiotic cellular division and thus acting as a priming mechanism to prepare future generations to efficiently cope with biotic and abiotic stresses. In 2011, Kou *et al.* used methyl-sensitive AFLP (MSAP) to identify changes in DNA methylation in rice plants growing under different nitrogen limiting conditions [40]. Despite identifying changes in DNA methylation that could be transmitted to the next generation of plants, the

approach used has limitations in quantifying DNA methylation changes and is often inconsistent [41]. Using whole genome bisulphite sequencing to generate base-resolution maps of DNA methylation throughout the genome, two recent studies revealed that phosphate starvation could induce numerous changes in DNA methylation [42••,43••]. In the first study, Secco *et al.* showed that phosphate starvation in rice resulted in widespread transient changes in DNA methylation, mainly through hypermethylation of transposable elements (TEs) in the vicinity of Pi-stressed induced genes. While it is often assumed that changes in DNA methylation drive changes in genes expression, this study clearly established the causality in this relationship, whereby changes in transcript abundance preceded local changes in DNA methylation [42••]. In addition, this study assessed the potential stress-memory mechanism, revealing limited stability of such induced DNA methylation events through mitosis, and the absence of their transmission through meiosis [42••]. Surprisingly, using a similar experimental design in *Arabidopsis* revealed a limited number of Pi starvation induced changes in DNA methylation, proposed to be a consequence of a lower transposable element (TE) content compared to rice [42••]. Yong-Villalobos *et al.* recently reported that Pi starvation in *Arabidopsis* resulted in extensive remodelling of global DNA methylation that often correlated with changes in a transcript abundance of key phosphate starvation induced genes and that the expression of genes encoding DNA methyltransferases appeared to be directly controlled by the key regulator PHOSPHATE RESPONSE 1 (PHR1) [43••]. The discrepancies observed between the two studies could potentially be attributed to differences in the experimental design such as the length and extent of the Pi starvation treatment, but are most likely the result of differences in identifying and calling the changes in DNA methylation. Indeed, to date, there is no consensus on what constitutes a differentially methylated region (DMR), that is what is the minimum number of differentially methylated cytosines (DMC) a DMR should contain, the maximum distance between neighbouring DMCs, the fold change for each DMC and for the DMR? In addition, very little information exists on the effect of DMRs on nearby gene expression, that is, is there a minimum number of DMCs required to regulate gene expression or a minimum fold change in DNA methylation, as well as the distance of the DMRs to the nearby gene? All these criteria will have dramatic consequences on the number and robustness of DMRs that are identified, as well as the identification of DMR-associated genes and thus on the interpretation on the results. In a complementary study, Yong-Villalobos *et al.* reported that differential methylation near Pi-responsive motif sequences in the genome correlates with gene expression modulation, suggesting that the methylation status of some regulatory elements could affect the binding capacity of the cognate transcription factors and hence control transcription [44]. Such a mechanism has been reported in tomato fruit development, where the binding sites for RIN (Ripening Inhibitor), one the main transcription factors involved in fruit ripening, were frequently demethylated during ripening, thus enabling the induction of ripening genes [45]. Using a high-throughput approach, it has recently been shown that >75% of the 327 *Arabidopsis* TFs surveyed were methylation sensitive [46], highlighting the importance of DNA methylation in modulating transcription factor binding. Recently, an additional study reported the involvement of DNA methylation in controlling nutrient homeostasis, with the identification of the more sulphur accumulation1 (*msa1*) mutant, characterized by high sulphur levels in the shoots [47••]. MSA1 is required for the biosynthesis of *S*-adenosylmethionine (SAM), which is a universal methyl donor for many methylation reactions, including DNA methylation. As a consequence, mutation in *MSA1* resulted in a global reduction of DNA methylation levels, including localized changes at key sulphate responsive genes, such as the two high-affinity sulphate transporter genes *SULTR1;1* and *SULTR1;2* [47••]. Further analysis revealed that the flanking sequence of the S responsive element (SURE) of the *SULTR1;1* promoter sequence, which is essential for the S deficiency response, was hypomethylated in *msa1-1* roots. Such an observation [47••], with that of Yong-Villalobos *et al.* [44], points towards a key role of DNA methylation in modulating transcription factor binding and/or occupancy to control the expression of key nutrient stress-responsive genes under specific stress conditions (Figure 1).

## Conclusions and perspectives

To date, multiple lines of evidence indicate that chromatin remodelling is involved in controlling responses of plant to nutritional stresses and environmental cues in general. However, we are still far from understanding the underlying molecular mechanisms and significance of such modifications. Integrative studies assessing multiple chromatin marks are still often missing, despite potentially providing key information on the complex regulatory mechanisms involved in these processes. In addition, the relationship between transcriptional activity and chromatin modifications is often based on correlative studies, and more efforts are still required to reliably establish the causality of these processes. Similarly, to date, only seldom studies have assessed the stability of these stress-induced changes in chromatin and how these marks would potentially contribute to priming or trans-generational stress memory. The reduction in the price of DNA sequencing technologies will hopefully circumvent these current limitations. Furthermore, recent technological developments now enable the generation of cell type-specific or single cell data that will greatly facilitate the interpretation of these changes in chromatin marks and their role in transcriptional regulation in response to nutritional stresses. The increase in the generation of

**Figure 1**




Potential model of the regulatory role of stress-induced changes in DNA methylation in modulating transcription factor (TF) binding. Schematic of a stress inducible gene (dark grey) and its promoter region (light grey) containing a binding site for a specific transcription factor (in red, TFBS). Under normal conditions, the cytosines near the transcription factor binding site (TFBS) are methylated (black lollipops), preventing the TF to bind to its binding site and to induce transcription of the gene. Under stress conditions, the cytosines near the TFBS are actively demethylated (white lollipops), allowing the TF to bind to the promoter and for the gene to be transcribed by RNA Polymerase II (in yellow). The number and extent of changes in cytosine DNA methylation represented is purely schematic.

large chromatin marks datasets, such as DNA methylation profiles, also raises the crucial need to define a consensus for defining DMRs, DMCs and other parameters associated to DNA methylation profiling analysis that can affect data interpretation. It is also important to keep in mind that most of the studies performed in this field have been undertaken in *Arabidopsis*, characterized by its small genome and relatively small population of transposable elements compared to other plants, which could affect our current knowledge when transferred to agronomically important crops. Notably, one of the biggest challenges for (epi)-genomics research in crops plants resides in generating and assembling accurate and representative genomes, often complicated by their large genome sizes, high proportion of related repeat sequences, and the closely related homeologous genes in polyploid crops. It is thus crucial that genomic and bioinformatic applications are further developed to enable high-throughput identification of nutrient-stress induced changes in chromatin structure in crops. Understanding the underlying mechanisms would potentially allow generation of stress-resilient plants using the recently discovered techniques for precision epigenome engineering.

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In this study, the authors identified MSA1 as being required for proper DNA methylation and for the production of *S*-adenosylmethionine which is a universal methyl donor for many methylation reactions, including DNA methylation. The *msa1* mutant plants displayed elevated sulphur accumulation as well as genome-wide changes in DNA methylation, including the methylation of S-deficiency responsive genes. This study also revealed that the flanking sequence of the S responsive element (SURE) of the sulphate transporter SULTR1;1 promoter sequence was hypo-methylated.