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MINI-REVIEW

Epigenetic regulation: another layer in plant nutrition

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ABSTRACT

Uptake, assimilation, and recycling of nutrients are essential for optimal plant growth and development. A large number of studies have contributed significantly to highlight the major features that shape an efficient utilization of nutrients in plants, especially at the transcriptional level. However, only a few examples have explored the epigenetic mechanisms that are intrinsically associated to the transcriptional reprogramming events in response to nutritional fluctuations. In this review, we gather the chromatin-based mechanisms that have been described in response to variations of nutrients availability. At this time of genome and epigenome editing, such mechanisms could potentially represent new targets for crop improvement.

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I. Introduction

In addition to water, light and carbon dioxide, plants require a set of mineral nutrients for their development and reproduction. Macronutrients, such as nitrogen (N), phosphorus (P) and potassium (K) are highly accumulated in plant tissue in contrast to micronutrients, or trace nutrients, such as iron (Fe), zinc (Z) or boron (B).[1] Maintaining the homeostasis of macro and micronutrients is essential for plant growth and development. Mineral nutrient availability can greatly vary depending on several factors such as soil pH, element concentrations, soil horizons, rain events, etc. As sessile organisms, plants have to adapt to these fluctuating environments with fine-tuned responses. Throughout evolution, plants have multiplied and diversified their strategies to cope with these changes.

Regulation of root architecture and adjustment of physiology constitute the main adaptive strategies that plants use in order to face changes in nutritional availability. These adaptive mechanisms most often involve reprogramming of gene expression.[2] In recent years, we greatly improved our knowledge about transcriptional regulation in response to nutrient availability in plants, and about the factors that are responsive to specific nutrient-related stimuli such as excess or starvation.[3,4] However, only a few studies have focused on the importance of epigenetic regulations, and how chromatin environments can affect the response to these environmental constraints.

Chromatin is the combination of nuclear genomic DNA and histone proteins that constitute the genetic content of the nucleus of eukaryotic cells. Nuclear genomic DNA is wrapped up around an octamer of histones composed of 2 histones H2A, 2 H2B, 2 H3 and 2 H4. This basic nucleoprotein complex is called nucleosome, which is the first unit in chromatin organization. Chromatin has been considered for a long time as a simple DNA packaging device, but is now viewed as a highly organized dynamic structure that affects many processes linked with DNA within the nucleus. Indeed, chromatin-based mechanisms superimpose with DNA sequence information to orchestrate genome expression, replication, repair or recombination.

Chromatin organization is highly correlated with changes in gene expression.[5] An open chromatin environment is required for Polymerase II (Pol II) recruitment, and acts in favors to Pol II progression through gene locus. On the other hand, a condensed and closed chromatin environment prevents Pol II action and gene transcription. To switch from one to the other, chromatin organization can be affected by a large range of modifications. (I) Nucleosomes themselves represent an obstacle for Pol II progression and consequently for transcription. ATP-dependent nucleosome remodeling factors are responsible for increasing or decreasing the nucleosome density at specific genomic region to accordingly inhibit or facilitate transcription.[6] In addition to nucleosome remodelers that can process a whole nucleosome, histone chaperones can also facilitate histone exchange, by acting selectively on H3, H4 or H2A/H2B dimers.[7] (II) Specific complexes are also involved in the incorporation of histone variants. Indeed, core histones also display variant versions that, when incorporated, affect nucleosome stability and therefore the accessibility of a specific region to enzymes such as Pol II.[8] (III) Histones can also be submitted to post-translational modifications usually named histone marks. Numerous histones marks have been identified, but several of them have been very well characterized for their effect on gene expression.[9] Acetylation of H3 and H4 lysine (K) residues neutralizes the global basic charge of nucleosome, and thus leads to chromatin unfolding that in turns greatly favors gene transcription. According to this, histone acetylase or deacetylase act positively or negatively on gene expression, respectively. Di- and tri-methylation of H3K4 are also associated with initial steps of gene

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transcription, whereas the presence of H3K36me3 is strongly correlated with transcriptional elongation. On the other hand, H3K27me3 is associated with repression of gene expression. H3K27me3 is established by the Polycomb Repressive Complex 2 (PRC2), which acts to keep thousands of genes silenced. Once established, histone marks can also be landmarks for downstream effectors that will, themselves, further modify chromatin architecture and influence transcription.[10] (IV) DNA itself can be methylated on cytosine residues. When located on repeated sequences, DNA methylation typically leads to transcriptional silencing of loci.[11] The function of gene body DNA methylation is less understood but is also certainly associated to transcriptional processes.[11] (V) Finally, even if they are not strictly part of chromatin, small RNAs (sRNAs) and long non-coding RNAs (lncRNAs) can be deeply associated to transcriptional machineries and processes, and have thus a strong influence on transcript production.[12]

In line with the large amount of knowledge in the regulation of genome expression in response to nutrient availabilities, epigenetic and chromatin-based regulatory mechanisms of nutritional adaptation in plants have started to be elucidated. In this review, we gather data from studies that have linked epigenetic regulations to fluctuating nutrients responses (Table 1). Such work has been mainly produced using the model plant *Arabidopsis thaliana* and for only a few nutrients: P, N, Fe, and B.

II. P starvation response is controlled by multiple chromatin-based mechanisms

The phosphate-starvationresponse (PSR) has been extensively characterized in plants. During PSR, plants adapt by reprogramming the transcription profile of thousands of genes and change their root architecture.[29] PHOSPHATE-STARVATION RESPONSE 1 (PHR1) and its homologue PHR1-LIKE 1 (PHL1) are major transcription factors contributing to PSR by targeting loci with a PHR1 Binding Site (P1BS) which is present at most PSR-related genes.[30] With regards to development, roots of plants undergoing PSR typically decrease their primary root growth to forage the upper part of the soil by increasing lateral root density and root hair formation.[31]

A component of an SWR1-like chromatin-remodeling complex ACTIN RELATED PROTEIN6 (ARP6) has been identified as an actor of PSR through its root phenotype resembling of a P starved-plants in P sufficient medium.[13] ARP6 is a nuclear protein that has been shown to play a role in the incorporation of the histone variant H2A.Z.[32] With a reduced primary root growth and an increase in lateral root and root hair growth, *arp6* mutants harbor constitutively active PSR-related genes such as P transporters. Further analysis showed that transcriptional activation of P transporter genes was due to a lack of histone H2A.Z at these specific loci. Eviction of H2A.Z was also demonstrated necessary for the transcriptional induction observed in response to P starvation in wild-type plants. Another chromatin factor acting on nucleosome composition in response to phosphate starvation was identified using a proteomic approach.[14] Biochemical analysis revealed that NUCLEOSOME ASSEMBLY PROTEIN 1 (NAP1) family proteins were regulated by P supply. NAP1 family proteins have been previously characterized as histone chaperones that can regulate transcription in *Arabidopsis*.[33] Interestingly, they also have been shown to exchange H2A and H2A.Z variants in yeast.[34] In a triple mutant for three NAP1 proteins in

Table 1. Summary of epigenetic mechanisms identified in signaling pathways involved in plant mineral nutrition.

Element	Epigenetic regulation	Epigenetic factors	Type of regulation[a]	Target genes	Phenotype[b]	Reference
P	H2A.Z incorporation	ARP6	-	*AT4, SPX1, BMY1,SRG3, ASK11*	Shorter primary root, enhanced root hair development, reduced Pi content	13
	H2A-H2A.Z exchange	NAP1;1, NAP1;2, NAP1;3	+	*ACP5, RNS1, PHT1*	Reduced Pi content	14
	Reading H3K4me2 and H3K4me3	AL6	+	*NPC4, SQD2, PS2, ETC1*	Impaired root hair development, shorter primary root, reduced Pi content	15
	H3K4me3/ H3K27me3 enrichment	Unknown	a±	*AT4, SPX3*	Shorter primary root, enhanced root hair development	16
	Histone deacetylation	HDA19	+	*SPX3, SPX1*	Impaired root hair development, longer epidermal cells, reduced P content	17
	Histone deacetylation	HDC1	-	*ALMT1, LPR1, LPR2, PT2*	Altered remodeling of root system architecture	18
	Histone acetylation	GCN5	+	*AT4, WRKY6, SBT3.5, RIPK*	Reduced Pi content	19
	DNA methylation	Unknown	a±	*SPX2, SPX1*	Undetermined	20
N	H3K27me3 enrichment	IWS1	-	*NRT2.1*	Increased N uptake	21
	H3K27me3 enrichment	CLF	-	*NRT2.1*	Undetermined	22
	H3K4me3 enrichment	IWS1	-	*Detoxification genes*	Primary root growth, ROS accumulation	23
	lncRNA expression	TAS3	-	*NRT2.4*	Undetermined	24
Fe	H4R3me2 enrichment	SKB1	-	*FRO2, IRT1, BHLH38, BHLH39, BHLH100, BHLH101*	Higher chlorophyll content	25
	H3K27me3 enrichment	CLF	-	*FRO2, IRT1, FIT*	Longer primary root	26
	Histone acetylation/ deacetylation	GCN5/HDA7	a±	*FRD3, EXO70H2, MLP329, CRK25, BOR1*	Impaired translocation from roots to shoots	27
B	Undetermined	BRM	Undetermined	*Undetermined*	Higher tolerance to boron excess	28

[a]Type of regulation refers to a positive or negative effect on the expression of target genes.
[b]Phenotype refers to a specific effect on nutrition-linked defect in plant growth, development or physiological response.

Arabidopsis, PSR-induced genes are strongly compromised to a similar level as a mutant for the major transcription factor PHR1.[14] P content of *nap1* mutant plants was also reduced even under replete P conditions. These studies demonstrate the role of the eviction and incorporation of the histone variant H2A.Z in the transcriptional control of P responsive genes through the action of a positive regulator, NAP1, and a negative regulator, ARP6.

In 2013, Chandrika et al. identified a new PSR regulator by screening T-DNA insertion lines for root hair formation defects under P starvation. They isolated through this screen the *alfin-like 6* (*al6*) mutant, which showed a complete loss of root hair formation even under *P*-depleted conditions.[15] AL6 possess a PHD finger domain that has been previously described as a "reader" of the active marks H3K4me2 and H3K4me3.[35] They identified a subset of 10 PSR-related genes that were poorly induced in *al6* in comparison to wild-type plants and showed that *al6* mutant plants accumulated more iron under P starvation, which is a marker of P depletion. The role of such readers has been further supported by a recent study that demonstrated a differential enrichment in activating and repressive marks in response to P starvation.[16] In response to P starvation, the enrichment in H3K4me3 is increased at genes that are transcriptionally induced such as *SPX-DOMAIN -CONTAINING PROTEIN 3* (*SPX3*) while the enrichment in the repressive marks H3K27me3 is anti-correlated with gene expression. Histone acetylation has also been shown to be involved in the induction of P responsive genes. Through phenotypic analysis of mutant for histone deacetylase, HISTONE DEACETYLASE 19 (HDA19) has been identified as a potential regulator of PSR.[17] Intriguingly, HDA19 was described as a transcriptional activator during PSR while histone deacetylation is usually correlated with transcriptional repression.[36] This suggested an indirect role for HDA19 and histone acetylation on PSR-related genes. However, recently GENERAL CONTROL NONDEREPRESSIBLE 5 (GCN5), a histone acetyltransferase, has been found to target PSR-related genes such as the long-non coding RNA *AT4* and activate their expression via histone acetylation in response to PSR.[19,37] Concomitantly, under P sufficient conditions the HISTONE DEACETYLASE COMPLEX 1 (HDC1) protein directly acts as a repressor of genes involved in P starvation-related remodeling of the root system architecture.[18] When the root system encounters P starvation, HDC1 protein levels are reduced by probable proteasome-mediated degradation, leading to the up-regulation of genes involved in root system architecture remodeling. Altogether, these discoveries show the importance of dynamic histone active and repressive marks enrichment to respond to P starvation.

Finally, changes in DNA methylation patterns have also been investigated in response to P starvation in rice. Secco et al. have performed whole-genome bisulfite sequencing together with RNA sequencing at multiple time points after P starvation and resupply.[20] They could show that the large number of differentially DNA methylated regions (DMRs) they observed occurred after transcriptional activation of nearby PSR-related genes. This demonstrates that, in their model, DNA methylation variations resulted from transcriptional changes, and not the opposite. They also demonstrated that these changes were mainly transient, since the analysis of DNA methylation profile after P resupply could rapidly revert for the very large majority of DMRs. Furthermore, analysis of the progeny of *P*-starved rice plants shows that DMRs were not maintained through generation. In parallel, they did not observe this dynamic DNA methylation pattern in *Arabidopsis thaliana*. This was further confirmed by a recent study on OVARIAN TUMOR DOMAIN-CONTAINING DEUBIQUITINATING ENZYME 5 (OTU5) in which no major changes in DNA methylation pattern have been linked to the response to P starvation.[16]

III. Epigenetic mechanisms in the regulation of expression of nitrate transporter genes

Nitrogen (N) has a major impact on plant nutrition, its availability limits plant growth and has significant repercussions on plant development. For instance, both nitrate perception and nitrate starvation can reprogram a large fraction of genome expression in Arabidopsis.[38,39] Among the genes regulated by nitrate, the nitrate transporters of the *NITRATE TRANSPORTER 2* (*NRT2*) family are high-affinity transporters strongly induced during starvation that are crucial for plant survival under-limited nitrate conditions.[40] The expression of *NRT2* transporters is therefore transcriptionally repressed under nitrate sufficient conditions and activated in response to nitrate starvation.[41]

A forward genetic screen for reactivation of *NRT2.1*, a main nitrate transporter in Arabidopsis roots, under N-sufficient conditions has been conducted to discover new negative regulators of the N starvation response.[21] Through this screen *hni9* (*high nitrogen insensitive 9*) has been identified as a mutant in which *NRT2.1* and other N-starvation related genes are partially expressed even in repressive conditions. *HNI9* encodes INTERACT WITH SPT6 1 (IWS1) which is a nuclear protein that has been described as part of the large polymerase II complex in other eukaryotic organisms. Among other roles, IWS1 has been previously shown to be involved in histone post-translational modification.[42] Interestingly, genome-wide analysis describing the epigenomic profile of Arabidopsis genome (performed under standard N-sufficient conditions) suggest that *NRT2.1* is highly enriched in the repressive mark H3K27me3.[10,43] Indeed, the repression of *NRT2.1* under high N conditions is correlated with an increase in the repressive mark H3K27me3 and this increase is lost in the *hni9* mutant.[21] These results suggested a role for IWS1 in the deposition of H3K27me3 at the *NRT2.1* locus in high N conditions. However, it has been recently showed that H3K27me3 enrichment at the *NRT2.1* locus was actually greater under low nitrate conditions compared to high N conditions.[22] Even though *NRT2.1* is one of the most expressed genes in root under low nitrate conditions, it is still highly enriched in this repressive mark. Mutation in the Polycomb Repressive Complex 2 (PRC2) CURLY LEAF (CLF) subunit, which is responsible for H3K27me3 deposition, alters this enrichment and allows an even higher expression of this transporter under low nitrate conditions. These results suggest that PRC2 could attenuate and control the expression of a significant portion of the most highly expressed genes of the genome. Since PRC2 and

H3K27me3 was so far only described for their role in keeping gene silenced,[44] this unexpected observation deserves to be further characterized.

More recently, it has been demonstrated that HNI9 was indirectly involved in the control of *NRT2.1* expression under high N conditions, independently of H3K27me3 deposition.[23] Indeed, high N conditions lead to an overproduction of reactive oxygen species (ROS), which are eliminated thanks to the HNI9-dependent expression of a set of detoxification genes. Loss of HNI9 function leads to a decrease in H3K4me3 enrichment at these detoxification genes, and to a decrease of their expression. Thus, an accumulation of reactive oxygen species (ROS) content can be observed in *hni9-1* mutant under high N when comparing to WT plants.[23] This ROS increase was proved to be the cause of *NRT2.1* induction in *hni9-1*.

The analysis of long non-coding RNAs (lncRNAs) in response to 12 nutrients deficiency was recently performed in Arabidopsis.[24] New lncRNAs that were only expressed in response to specific nutrient starvation has been identified. Using binding predictions and RNA-seq data, they could find the putative targets of these new lncRNAs, and lncRNAs-RNA regulated pairs were identified for P, K and N starvation-related genes. In particular, a potential role for the lncRNA TRANS-ACTING siRNA 3 (TAS3) in the regulation of *NRT2.4* has been revealed. *NRT2.4* is a high-affinity nitrate transporter that is strongly induced by N starvation.[45] They could show that TAS3-activation tagging line had a lower expression of *NRT2.4*, and moreover, TAS3 binding site on *NRT2.4* correspond to a known siRNA that has been observed in sRNA-seq data.[46] However, these observations could not rule out an indirect role of *TAS3* on *NRT2.4*, since loss of *TAS3* expression also led to an induction of the known *NRT2.4* transcriptional repressor *NITRATE-INDUCIBLE, GARP-TYPE TRANSCRIPTIONAL REPRESSOR 1* (*NIGT1*).[24]

IV. Epigenetic repression of Fe starvation genes under Fe sufficient conditions

Fe is one of the essential micronutrient also called trace nutrient. Excess or deficiency in Fe can limit plant growth and reduce crop yield. Therefore, Fe uptake and distribution are tightly regulated in plants.[47] At the molecular level, the transcription factors FER-LIKE IRON DEFICIENCY INDUCED TRANSCRIPTION FACTOR (FIT) and other BHLH are key regulators of the response to Fe starvation. Among the genes induced in response to Fe deficiency, FERRIC REDUCTION OXIDASE 2 (FRO2) and IRON-REGULATED TRANSPORTER 1 (IRT1) are an essential player that facilitate access to iron and mediates it transport, respectively.[48]

Under iron sufficient conditions two repressive marks, H4R3me2 and H3K27me3, have been shown to repress the expression of genes involved in iron homeostasis.[25,26] H4R3me2 is known to be deposited by SHK1 BINDING PROTEIN 1 (SKB1) which belongs to the protein arginine methyltransferase (PRMTs) family.[49] Microassay analysis performed on the *skb1-1* mutant exhibited a higher expression of BHLH transcription factors involved in iron homeostasis.[25] SKB1 efficiently binds to these loci under iron sufficient conditions and repress their transcription through H4R3me2 deposition. H3K27me3 is a highly repressive marks that is deposited by methyltransferases of the PRC2 complex. Epigenomic studies have associated H3K27me3 enrichment with iron acquisition genes, which led to further investigate the role of CLF in iron homeostasis.[26] CLF was shown to inhibit *IRT1, FRO2* and *FIT* under iron sufficient conditions by H3K27me3 deposition. These marks are removed upon iron starvation allowing the expression of these key genes.

Activating chromatin marks have also been involved in the regulation of iron starvation-related genes. Screening of a set of histone acetylase and deacetylase mutants for iron over-accumulation showed that GCN5 is a positive regulator of the iron starvation response.[27] Indeed, *GCN5* is induced by iron starvation, binds to genes involved in iron homeostasis such as *FERRIC REDUCTASE DEFECTIVE 3 (FRD3)*, and increases their histone acetylation levels. The dynamic of GCN5 enrichment, histone acetylation level and expression of the *FRD3* locus is consistent with the transcriptional induction of the *GCN5* locus upon iron starvation. Interestingly, *gcn5* exhibits the transcriptional profile of nutrient-starved plants with a higher transcription of genes involves in phosphate, nitrate, iron, copper, and zinc starvation responses. This is concomitant with the role of GCN5 described in P homeostasis and we might soon discover that this specific histone acetyltransferase is involved in other nutrient-related stresses.[19] Finally, HISTONE DEACETYLASE 7 (HDA7) and HISTONE DEACETYLASE 14 (HDA14) repress the expression of *FRD3* by reducing its histone acetylation levels, therefore, counteracting the effect of GCN5.[27] Studies linking Fe homeostasis and epigenetic regulations nicely illustrate the duality between active and repressive histone marks but also between “writer” and “eraser”.

V. The chromatin remodeler BRAHMA is a negative regulator of B tolerance

Similarly to Fe, B is a trace element required for optimal plant growth and proper development. Its homeostasis regulation is critical since B excess or deficiency can affect dramatically plant development.[50] A forward genetic screen has led to the identification of mutants that are *hypersensitive to excess boron* (*heb*).[28] *heb3-1, heb6-1*, and *heb7-1* showed a severe defect in root development upon excess B and are corresponding to mutation on two genes that are coding for regulatory particle protein (RP) that are composing a subunit of the 26S proteasome. By studying over-accumulating proteins in these mutants under high B conditions, they could identify the chromatin remodeler BRAHMA (BRM) as regulated by the 26S proteasome. Using phenotypical evidence such as primary root length repression by excessive B, they demonstrated that BRM is a negative regulator of B tolerance in Arabidopsis. Also, high B treatments induce a global hyperacetylation of histone which is prevented under low B conditions by the 26S proteasome. They also suggested a link between histone hyperacetylation and increase in DNA damage in response to high B concentration.

VI. Conclusion

Plant adaptation to fluctuating environments is largely reliant on reprogramming the genome expression.[2] In the last two decades, many studies have been performed to identify transcription factors and signaling pathways controlling the expression of genes in response to fluctuating nutrients. Transcriptional induction or repression at specific loci is tightly correlated with changes in chromatin organization, allowing the DNA to be more or less accessible for transcription-related proteins.[5] Yet, chromatin and epigenetic regulations have been poorly investigated and are missing from the picture. The recent identification of epigenetic factors using unbiased methods, such as forward genetic screenings, demonstrates the importance of these regulators for adaptation to the nutritional environment. The diversity of epigenetic factors involved in nutrient starvation and excess is nicely illustrated by these studies: histone variants have been shown to be involved in P starvation, chromatin remodeler and histone marks in B excess, and long non-coding RNA interference and histone marks in P, N, and Fe starvation. Further studies and forward genetic screenings will certainly uncover new crucial roles for epigenetic regulators in the nutrient starvation transcriptional regulation pathways. Finally, some epigenetic modifications have now been targeted with success by genome-editing technologies.[51] By directly modifying chromatin marks, or by targeting trans- or cis-factors responsible for epigenetic modifications, it is now tempting to speculate that the mechanisms described above could be used in genome-editing crop breeding programs.[52,53]

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