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The plant epigenome governed by nutrients and metabolism

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Nutrients are essential regulators of growth and development across all life forms, serving not only as energetic resources and structural building blocks but also as dynamic signals that govern cell proliferation, metabolism, growth and development. Nutrients and metabolic processes orchestrate plant developmental programs and plasticity via the coordination with dynamic changes in the epigenomic landscape, which is fundamental for governing gene expression programs and developmental transitions in multicellular organisms. In this review, we explore the interplay between nutrition, metabolism, and epigenetic reprogramming in plants, with a particular focus on the novel mechanisms, including nuclear localized metabolic enzymes, moonlighting functions of metabolic enzymes, epigenetic regulators as metabolic sensors, and nutrient sensing and signaling pathways. Elucidating these mechanisms holds significant implications for understanding plant growth and development and improving crop yield and quality.

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Introduction

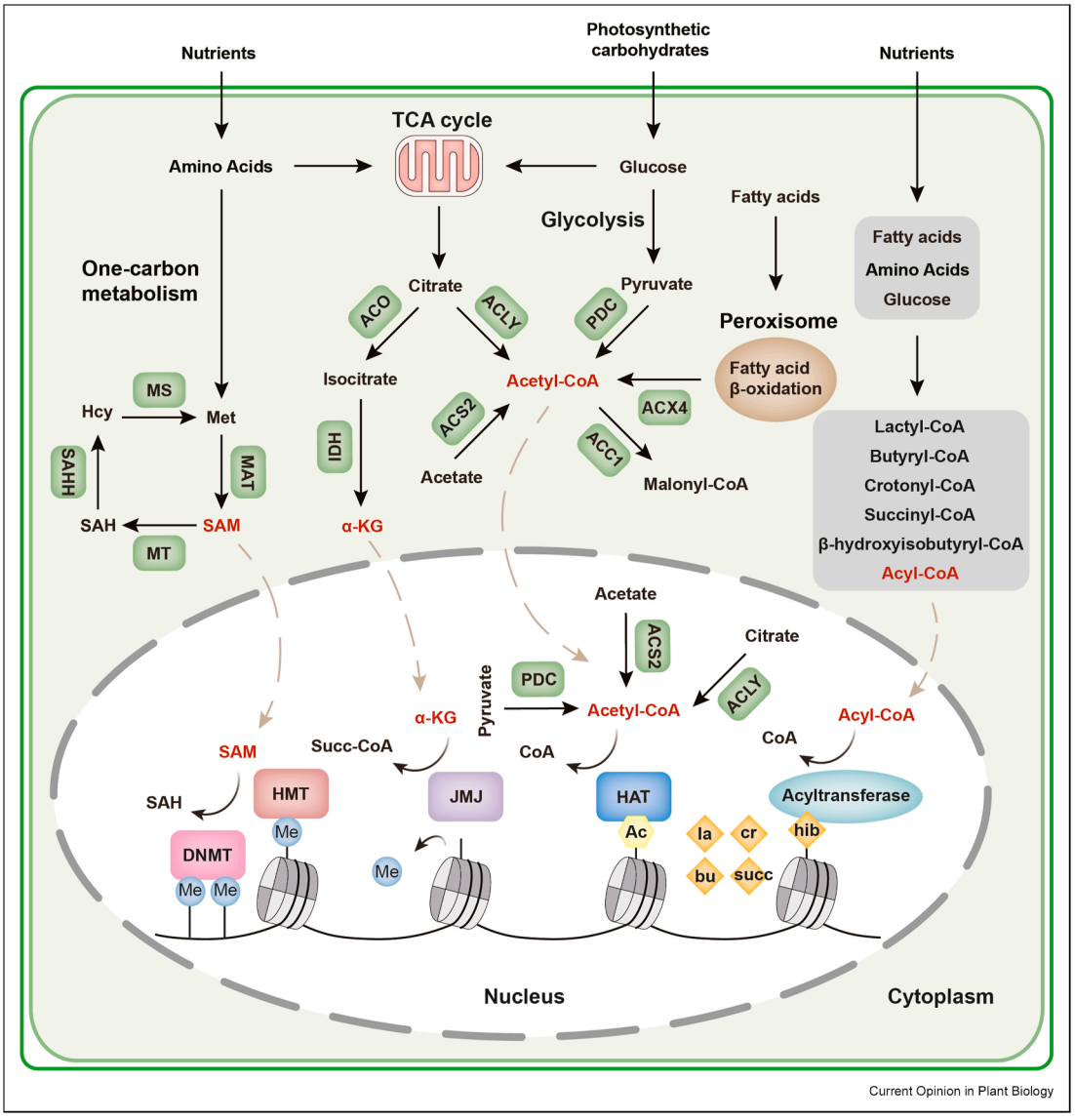
Plants dynamically modulate their growth and development in response to fluctuating environmental conditions and nutrient availability to ensure survival and reproductive success. Nutrients serve dual roles as both energy sources and structural components while simultaneously functioning as key environmental regulators of developmental processes across kingdoms [1–6]. In plants, growth and developmental trajectories, which are critical determinants of agricultural productivity, are intricately tied to nutrient availability and usage efficiency. Plants have evolved multiple mechanisms to sense and respond to nutrient signals [1–4].

Epigenetic modifications throughout the genome enable plants to adjust gene expression dynamically in response to internal and external stimuli, such as nutrient availability and environmental changes, without modifying the DNA sequence itself [7,8]. This regulatory mechanism is crucial for plant growth, development, and adaptability. Nutrients and their metabolic pathways have been identified as key regulators of the epigenome across diverse organisms from yeasts, plants, animals to humans [5,8–11]. The epigenome can function as a platform that responds directly to nutrient-derived metabolites or indirectly through nutrient-mediated signaling pathways. These interactions allow plants to adjust their epigenetic states in real-time according to nutrient availability, to optimize resource use and developmental outcomes under fluctuating conditions. This review highlights emerging molecular mechanisms underlying the connection between nutrient and epigenome regulation.

Modulating chromatin-modifying enzymes by metabolites

Research on the molecular link between nutrients and epigenetic regulation has primarily focused on the roles of nutrient-derived metabolites as substrates or cofactors of chromatin-modifying enzymes [10,11] (Figure 1). S-adenosyl-L-methionine (SAM) originated from the one-carbon metabolism pathway provides methyl donor for both DNA and histone methyltransferases [12]. Numerous mutations disrupting SAM biosynthesis differentially modulate histone lysine methylation levels, highlighting the sensitivity of these epigenetic marks to metabolic perturbations [13–20]. Alpha-ketoglutarate (α-KG) is a rate-limiting substrate for Jumonji C (JMJ) domain histone demethylases [21,22]. Disruption of α-KG production through loss of isocitrate dehydrogenase (IDH) elevates global histone H3 lysine 4 trimethylation (H3K4me3) levels and exacerbates defects caused by

Figure 1



Overview of key metabolites shaping chromatin modifications. Photosynthetic carbohydrates and nutrients supply can change the pools of cytosolic/nuclear SAM (S-adenosyl-L-methionine), α-KG (alpha-ketoglutarate), and acetyl-CoA (acetyl coenzyme A) in plant cells. These metabolites serve as co-factors or substrates of DNA/histone methyltransferase (DNMT/HMT), Jumonji C domain–containing histone demethylases (JMJ) and histone acetyltransferase (HAT) for DNA/histone methylation, histone demethylation and histone acetylation, respectively. Acyl-CoAs, produced from fatty acids, amino acids or glucose, can also be utilized for histone acylations. MS, methionine synthase; MAT, methionine adenosyltransferase; MT, methyltransferases; SAHH, S-adenosylhomocysteine hydrolase; Hcy, homocysteine; MET, methionine; SAH, S-adenosyl-L-homocysteine; ACO, aconitase; IDH, isocitrate dehydrogenase; ACLY, ATP citrate lyase; ACS2, acetyl-CoA synthase 2; PDC, pyruvate dehydrogenase complex; ACX4, acyl-CoA oxidase 4; ACC1, acetyl-CoA carboxylase 1; CoA, coenzyme A; succ-CoA, succinyl-CoA; Me, methyl group; Ac, acetyl group; la, lactylation; cr, crotonylation; hib, β-hydroxyisobutyrylation; bu, butyrylation; succ, succinylation. Key metabolites emphasized in red font. Larger font sizes are used to represent cellular compartments, organelles and key metabolic pathways.

demethylase JMJ14 mutation in the plant thermosensory response [23] (Figure 1).

Acetyl coenzyme A (acetyl-CoA) serves as a substrate for histone acetyltransferases (HATs) to regulate global histone acetylation and is generated through multiple metabolic pathways, including glycolysis, tricarboxylic acid (TCA) cycle, fatty acid β-oxidation, and the direct conversion of acetate in plant cells [24–26]. Disruption of cytosolic acetyl-CoA carboxylase 1 (ACC1) in *Arabidopsis* elevates acetyl-CoA levels, driving hyperacetylation of histone H3K27 [25]. In *Arabidopsis*,

drought triggers a metabolic shift to acetate synthesis, increasing acetyl-CoA to enhance histone H4 acetylation and jasmonic acid (JA) signaling, which bolster drought resilience [27]. Significantly, exogenous acetate application mimics this drought-responsive mechanism to improve stress tolerance in diverse species, including *Arabidopsis*, rapeseed, maize, rice, and wheat [27] (Figure 1). In addition, short-chain Lysine (K) acylations on histone residues including, succinylation (succ), crotonylation (cr), butyrylation (bu), β-hydroxyisobutyrylation (hib), and lactylation (la) are emerging as critical regulators in both plants and animals [28–35] (Figure 1). These modifications are dynamically regulated by different acyl-CoA substrates derived from the intracellular metabolism of fatty acids, amino acids and glucose in response to environmental changes such as starvation and submergence, suggesting a potential connection between metabolic flux and epigenetic control [34–36].

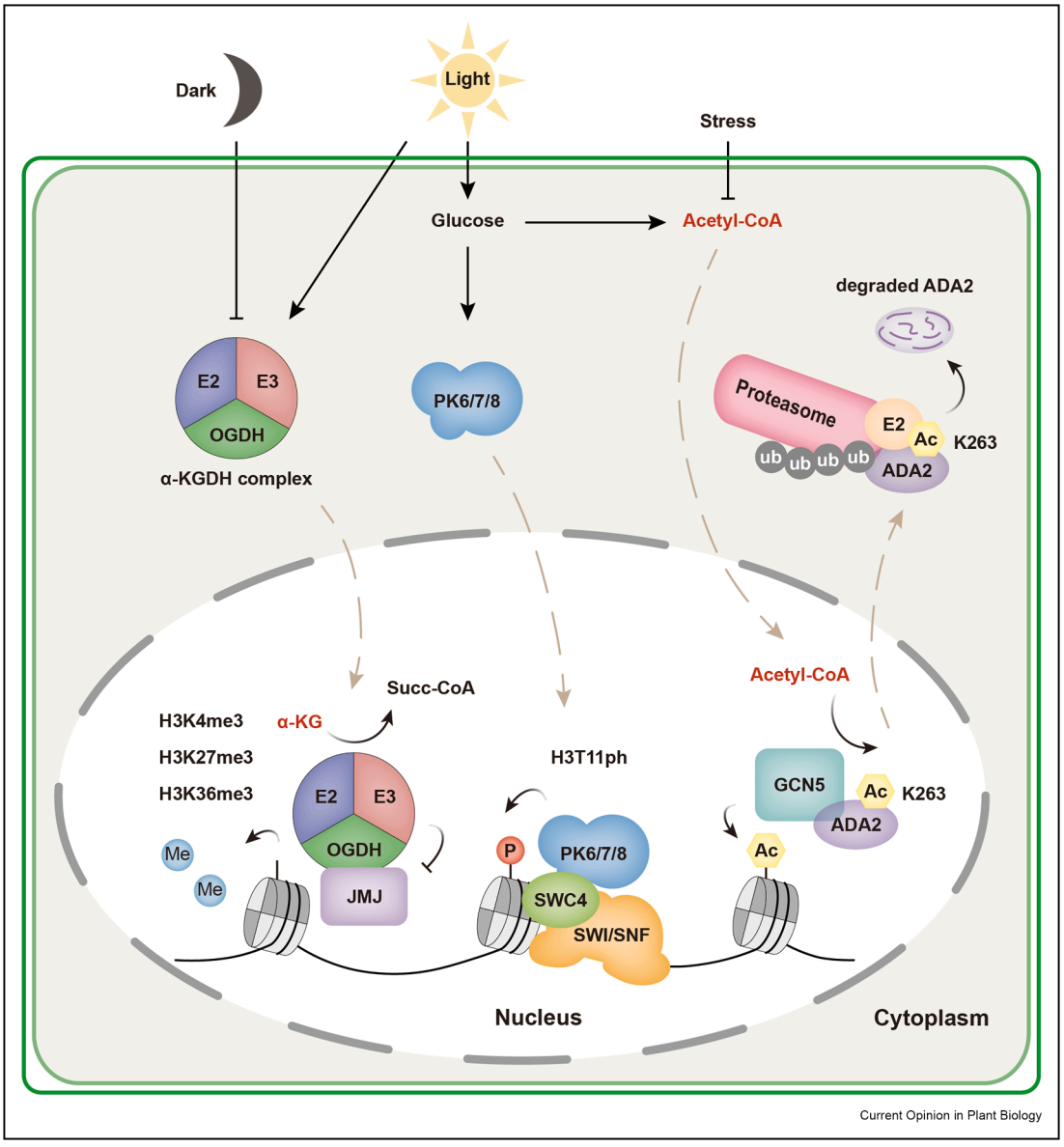
Although chromatin can directly perceive and react to nutrient-derived metabolites [10,11,37], our current understanding of metabolite-driven epigenetic regulation primarily stems from research on loss-of-function mutants [13–26]. These examples may not always accurately mirror the true regulatory roles of metabolites in physiological settings. The precise mechanisms through which metabolite levels or states selectively modulate the enzymatic activity of specific chromatin-modifying enzyme remain poorly understood. In fact, the catalytic efficiency of chromatin-modifying enzymes is directly modulated by the nuclear concentration and availability of metabolites. While metabolites may enter the nucleus through diffusion or active transport, some highly compartmentalized metabolites such as mitochondrial acetyl-CoA cannot. These instead require local synthesis within the nucleus to ensure a sufficient supply for regulating epigenetic modifications. In plant cell, acetyl-CoA can be generated directly within the nucleus by nuclear targeted metabolic enzymes like ATP-citrate lyase (ACLY), acetyl-CoA synthetase 2 (ACS2) and pyruvate dehydrogenase complex (PDC) [38–40] (Figure 1). In plants, most α-KG dehydrogenase (KGDH) enzyme subunits including oxoglutarate dehydrogenase (OGDH, E1 subunit), dihydrolipoamide succinyltransferase (DLST, E2 subunit) and dihydrolipoamide dehydrogenase (DLD, E3 subunit) are targeted to the mitochondria for α-KG decarboxylation in the TCA cycle. Light prompts a small portion of KGDH to move into the nucleus. KGDH directly interacts with various JMJ demethylases and limits their access to α-KG by catalyzing its decarboxylation, thus inhibiting their activity and modulating environmental fitness-related genes in *Arabidopsis* [41] (Figure 2, left panel). Mutations in KGDH lead to significant reductions in multiple histone methylation marks, including H3K4me3, H3K9me2, H3K27me3, and H3K36me3 due to elevated JMJ activities [41]. This mechanism exemplifies metabolite-driven epigenetic regulation in plant environmental adaptation. In human cells, the KGDH is also localized in nucleus and interacts with lysine acetyltransferase 2A (KAT2A) to generate succinyl-CoA [42]. Critically, KAT2A exhibits higher binding affinity for succinyl-CoA than acetyl-CoA, redirecting its activity toward H3K79 succinylation over histone acetylation to drive oncogenic transcription and tumorigenesis [42]. This suggests that the specificity of metabolic-guided epigenetic regulation may also arise from variations in the substrate-binding affinities of epigenetic enzymes. Whether plants employ similar mechanisms remains an open question for future research.

Moonlighting functions of metabolic enzymes

Metabolic enzymes traditionally catalyze biochemical reactions but increasingly are recognized for their "moonlighting" functions—biochemically distinct roles unrelated to their primary activity, as well as utilization of non-canonical substrates to exert new biological effects [43]. In epigenetic regulation, these enzymes directly influence histone modifications, uncoupled from and beyond metabolite production. Strikingly, numerous cytoplasmic and mitochondrial metabolic enzymes moonlight in the nucleus, where they exert canonical roles by generating metabolites essential for epigenetic reactions as discussed above and non-canonical roles such as acting as scaffolds for chromatin-modifying complexes or displaying unexpected enzymatic activities, for instance, protein kinase [44,45]. This underscores their versatility as molecular integrators, bridging cellular metabolism with epigenetic control.

A novel example is pyruvate kinase (PK), a central glycolytic enzyme that catalyzes the conversion of phosphoenolpyruvate to pyruvate. Beyond its metabolic role, mammalian PKM2 isoforms have been shown to phosphorylate histone H3 at threonine 11 (H3T11), driving gene transcription and cancer progression [44]. Remarkably, recent studies in *Arabidopsis* uncovered nuclear-localized PK isoforms (PK6, PK7, PK8) with analogous histone kinase activity (Figure 2, middle panel). Under energy-rich conditions (abundant glucose/light), these plant PKs translocate to the nucleus and partner with the chromatin-associated protein SWI2/SNF2-RELATED 1 COMPLEX 4 (SWC4), which recruits them to specific genes. Then, they deposit H3T11ph and enhance the expression of developmental regulators for flowering control [45]. This conserved mechanism in plants and mammals highlights how metabolic enzymes moonlight as epigenetic regulators, bridging energy status with gene expression. Future studies may help to uncover more metabolic enzymes moonlighting in epigenetic regulation.

Figure 2



Emerging metabolic-chromatin effector crosstalk mechanisms. Metabolic enzymes can not only provide energy but also possess non-canonical nuclear or "moonlighting" functions in response to ambient or nutrient signaling and participate in epigenetic regulation. Left panel, related to nuclear localized metabolic enzymes. In *Arabidopsis*, light promotes the nuclear targeting of the α-ketoglutarate dehydrogenase (KGDH) complex, composed of oxoglutarate dehydrogenase (OGDH), dihydrolipoamide succinyltransferase (E2), and dihydrolipoamide dehydrogenase (E3), to facilitate its interaction with JMJ histone demethylase enzymes. KGDH controls the nuclear availability of α-KG for histone demethylation by JMJs. Middle panel, related to moonlighting function of metabolic enzymes. In *Arabidopsis*, pyruvate kinases PK6/7/8 enter the nucleus under conditions of sufficient glucose and light exposure. PK6/7/8 interacts with and is recruited by SWI2/SNF2-RELATED 1 COMPLEX 4 (SWC4) to deposit histone H3 at threonine 11 (H3T11ph) and promote transcription. Right panel, related to chromatin regulators as metabolic sensors. In rice, stress-induced low acetyl-CoA levels can be directly sensed by the acetylation of adaptor protein ADA2 at lysine 263 (K263) via acetyltransferase General Control Nonderepressible (GCN5). This acetylation stabilizes ADA2, enhancing the capture of acetyl-CoA by GCN5 and sustaining GCN5's histone acetyltransferase (HAT) activity.

Epigenetic regulators as metabolic sensors

Beyond chromatin-modifying enzymes influenced by substrate metabolites, many epigenetic regulators could also act as metabolic sensors that detect and respond to non-canonical metabolite fluctuations. While direct evidence in plants is limited, conserved mechanisms exist in mammals and *Drosophila*. For instance, in human cells, Ten-eleven translocation (TET) family proteins and JMJ histone demethylases can directly sense and be inhibited by TCA cycle intermediates such as succinate

and fumarate [46]. The O-linked-N-acetylglucosaminylation (O-GlcNAc) of proteins serves as an essential metabolic sensor to regulate multiple important biological processes including epigenetics in response to the changes of glucose and other nutrients. In mammals and *Drosophila*, the Enhancer of Zeste 2 (EZH2) subunit of Polycomb Repressive Complex 2 (PRC2) undergoes nutrient-responsive O-GlcNAc, enhancing its stability and modulating H3K27me3 deposition [47]. Interestingly, in *Arabidopsis*, O-GlcNAc transferase SECRET AGENT (SEC) modifies and activates the histone methyltransferase ARABIDOPSIS HOMOLOG OF TRITHORAX1 (ATX1) via O-GlcNAc, promoting H3K4me3 modifications at *FLOWERING LOCUS C* (*FLC*) locus to repress flowering [48]. Proteomic studies have revealed that multiple chromatin remodeling factors are O-GlcNAcylated in *Arabidopsis* [49]. A recent study identified hundreds of proteins O-fucosylated by SPINDLY (SPY), including modifiers involved in histone modification, DNA methylation, and chromatin remodeling [50]. Together, these O-GlcNAc and O-fucosylation targets thus represent potential nodes for crosstalk between sugar signaling and epigenetic control. Intriguingly, histone acetyltransferase General Control Nonderepressible (GCN5) could acetylate its adaptor protein ADA2 in rice (Figure 2, right panel). The acetylation of this non-histone protein was proposed as a metabolic sensing mechanism linking acetyl-CoA availability to chromatin modification. Under nutrient-rich conditions, high acetyl-CoA levels promote GCN5 mediated ADA2 acetylation and E3 ligase-mediated degradation, reducing GCN5 activity to prevent excessive histone acetylation. Osmotic stress-induced ADA2 accumulation could stimulate GCN5 HAT activity to compensate for the reduced acetyl-CoA levels for histone acetylation [51]. This feedback loop dynamically adjusts histone acetylation in response to metabolic shifts, ensuring metabolic homeostasis and stress resilience.

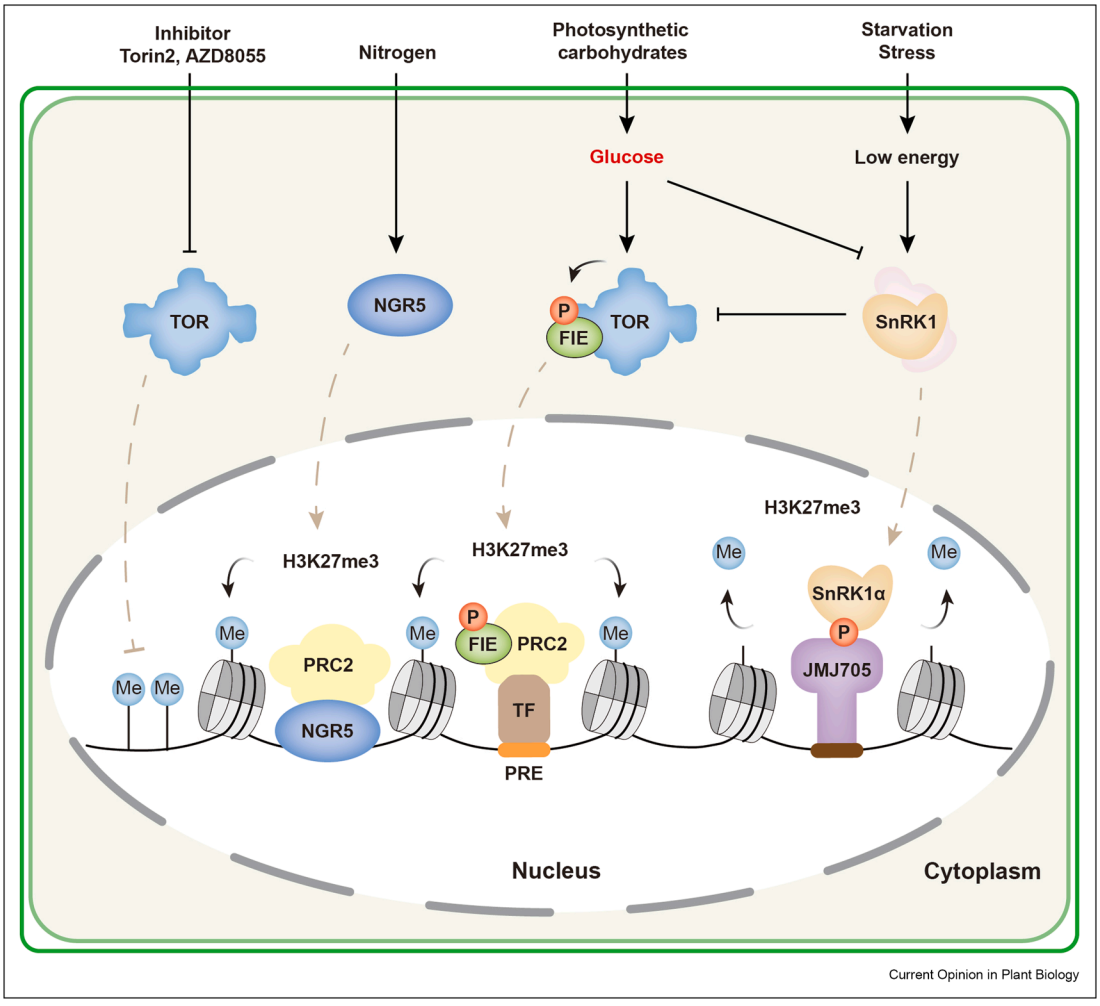
Epigenomic fluctuations mediated by nutrient signaling

Nutrients and metabolites not only directly influence the modification of chromatin, but also act as signaling molecules to regulate the epigenome through signaling cascades. Recent research has discovered that cellular nutrient and energy states are dynamically sensed by two evolutionarily conserved, antagonistic signaling hubs, the Target-of-Rapamycin (TOR) and Sugar Non-Fermenting1-Related Kinase1 (SnRK1), the plant ortholog of human AMP-activated Protein Kinase (AMPK) and yeast Snf1 [1,3,4,6,52,53]. Under nutrient-rich conditions, TOR is activated to promote cell growth and proliferation by stimulating protein production and other anabolic activities, while suppressing catabolic activities [1,3,4,6,53]. In contrast, energy or nutrient scarcity triggers plant SnRK1 and animal AMPK, to suppress growth and promote catabolic pathways to replenish ATP, and prioritize survival [1,6,52]. Beyond metabolic regulation, TOR and SnRK1 coordinate plant growth and developmental programs to align with nutrient availability, suggesting their possible link to epigenetic regulation [1,3,4,6,52,53] (Figure 3).

Sugar and nitrogen serve as fundamental nutrients for plant growth and development, playing pivotal roles in regulating key agronomic traits such as shoot branching/tillering, flowering, and fruit and seed development, all of which are crucial determinants of crop yield [1,2]. Recent studies have shown that these nutrients specifically drive epigenetic reprogramming, particularly through the dynamic regulation of H3K27me3 [54]. In *Arabidopsis*, glucose-activated TOR kinase phosphorylates FERTILIZATION-INDEPENDENT ENDOSPERM (FIE), a unique and essential PRC2 component, promoting its nuclear translocation to enhance PRC2 activity (Figure 3). Within the nucleus, the FIE-PRC2 complex is likely recruited by *cis*- and *trans*-regulatory elements to deposit H3K27me3, silencing key transcription factors that regulate developmental transitions [54]. This glucose-TOR-FIE axis provides a mechanistic link between nutrient signaling and epigenetic regulation, explaining how sugar availability orchestrates key phases of postembryonic development in plants. Importantly, this mechanism may also address the longstanding question of how sugars support the vernalization-induced floral transition [54]. In *Arabidopsis*, TOR inhibition by AZD8055 or RNAi has also been shown to reduce global H3K27me3 levels, leading to the derepression of transcriptional stress responses [55]. Similarly, sugar starvation has also been reported to induce a global reduction of H3K27me3 in rice (Figure 3). Under low-energy stress, SnRK1 accumulates in the nucleus, activating JMJ705 demethylase via phosphorylation. JMJ705 then removes H3K27me3 from energy homeostasis-related transcription factors, activating them to sustain metabolic balance during starvation [56]. Similarly, energy starvation activates AMPK, which phosphorylates EZH2 and inhibits PRC2 activity, repressing H3K27me3-targeted tumor suppressors and curbing tumor growth in mammals [57]. These findings highlight an evolutionarily conserved mechanism: sugar and energy signals, mediated by TOR in nutrient-rich conditions and SnRK1/AMPK during starvation, directly regulate H3K27me3 dynamics to regulate growth, development and stress responses across eukaryotes [2,4,6,52–57].

Notably, nitrogen was also shown to activate TOR and repress SnRK1 to promote root development, tillering, and leaf expansion in plants [58]. In rice, nitrogen boosts tillering via Nitrogen-mediated Tiller Growth Response 5 (NGR5)-guided H3K27me3 dynamics (Figure 3). Under high nitrogen, NGR5 recruits PRC2 to deposit H3K27me3 at tillering inhibitor gene loci, silencing their expression and promoting tillering and grain yield [59].

Figure 3



Epigenetic dynamics driven by nutrient sensing and signaling. Both nutrients and energy stress can trigger the reprogramming of DNA and histone methylation landscape in plants. In rice, nitrogen promotes the nuclear accumulation of Nitrogen-mediated Tiller Growth Response 5 (NGR5), which interacts with and recruits Polycomb repressive complex 2 (PRC2) complex to repress branching-inhibitory genes via H3K27me3 modification. Low energy stress increases the nuclear translocation of the catalytic α subunit of Sugar Non-Fermenting1-Related Kinase1 (SnRK1), which interacts with and phosphorylates JMJ705 to stimulate its H3K27me3 demethylase activity, promoting the expression of starvation-responsive transcription factor genes. In *Arabidopsis*, glucose-activated Target-of-Rapamycin (TOR) kinase phosphorylates FERTILIZATION-INDEPENDENT ENDOSPERM (FIE), a unique component of PRC2, enhancing its nuclear translocation and controlling genome-wide H3K27me3. TOR inhibition can also decrease the whole genome DNA methylation. PRE, Polycomb response element.

Intriguingly, in the glucose-TOR-FIE-PRC2 regulatory cascade, PRC2 is proposed to interact with *cis*- and *trans*-regulatory elements to orchestrate locus-specific H3K27me3 deposition [54]. Given these findings, a compelling avenue for future investigation is whether and how the TOR-PRC2 module functionally integrates with the NGR5-PRC2 pathway to coordinate glucose and nitrogen crosstalk via responsive H3K27me3 dynamics.

Additionally, TOR inhibition in *Arabidopsis* reduces global DNA methylation but elevates mCHH methylation at promoter regions, likely due to differential regulation of related methyltransferases [60] (Figure 3). In mammals, AMPK activates stress-responsive transcription by directly interacting with chromatin and phosphorylating histone H2B at Ser36 (H2BS36) [61]. In yeast, the kinase Snf1 phosphorylates histone H3 at serine 10 (H3S10), which is associated with enhanced histone acetylation and activation of transcription [62]. Beyond their established roles in chromatin regulation, TOR and SnRK1 may also directly modulate histone acetylation. A large-scale phosphoproteomic study in *Arabidopsis* cell cultures revealed that sugar-TOR signaling regulates phosphorylation of histone

acetyltransferase GCN5 and Histone Deacetylase 19 (HDA19) [63]. Separately, the same group showed that SnRK1 could interact with and phosphorylate acetyl-CoA metabolic enzymes ACS and ACC1 (Figure 1), potentially altering acetyl-CoA availability for histone acetylation [64]. Moreover, the catalytic α subunit of SnRK1 translocates to the nucleus under energy stress, suggesting its capacity to phosphorylate chromatin-associated substrates and mediate epigenetic regulation [65] (Figure 3). Further studies are needed to define these potential regulatory roles of TOR and SnRK1 in epigenetic mechanisms. In summary, the direct targeting of chromatin modifiers or even the chromatin itself by nutrient-sensing and signaling pathways represents a pivotal breakthrough in elucidating how plants relay on nutrient status to reconfigure the epigenome, thereby coordinating transcriptional regulation and developmental programming.

Perspectives and future directions

Recent evidence highlights that nutrients and metabolites serve as direct and indirect regulators of epigenetic dynamics in the plant epigenome, facilitating adaptive responses in growth, development, and metabolic processes to environmental and nutrient fluctuations. Future research efforts will further clarify the causal links between physiologically relevant metabolic shifts and specific epigenetic regulation in key developmental processes, such as vernalization-induced flowering and nitrogen-enhanced tillering [54,59]. Uncovering the specificity of metabolic regulation of the epigenome requires an integrated study of spatiotemporally restricted metabolite availability, metabolite-dependent modulation of enzymatic activity, specific regulation by nutrient signaling pathways, and targeted recruitment by *cis*-elements and *trans*-regulators. These regulatory mechanisms often collaborate through synergistic interactions rather than acting independently to determine epigenetic outcomes. Furthermore, current research relying heavily on whole-plant analyses under steady-state conditions obscures critical insights into specific metabolic–epigenetic interactions and their temporal dynamics. To address this gap, future studies should integrate cutting-edge methodologies including single-cell or cell-type-resolved profiling of the transcriptome, epigenome, and metabolome, coupled with genetically encoded biosensors capable of real-time imaging of metabolic fluxes and nutrient signaling [66,67]. By capturing spatiotemporal heterogeneity and dynamic crosstalk between metabolic and epigenetic states, these approaches will reveal novel mechanistic insights and lead to discoveries in this emerging field. Advances in elucidating the metabolic regulation of the epigenome will enable precision epigenetic engineering through metabolic modulation, offering targeted strategies to enhance crop resilience and optimize nutrient use efficiency.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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