CellPress

Opinion

Histone Acetylation Enzymes Coordinate Metabolism and Gene Expression

Yuan Shen,[1] Wei Wei,[2] and Dao-Xiu Zhou[1,*]

Histone lysine acetylation is well known for being important in the epigenetic regulation of gene expression in eukaryotic cells. Recent studies have uncovered a plethora of acetylated proteins involved in important metabolic pathways, such as photosynthesis and respiration in plants. Enzymes involved in histone acetylation and deacetylation are being identified as regulators of acetylation of metabolic enzymes. Importantly, key metabolites, such as acetyl-CoA and NAD^+, are involved in protein acetylation and deacetylation processes, and their cellular levels may regulate the activity of histone acetyltransferases (HAT) and deacetylases (HDAC). Further research is required to determine whether and how HATs and HDACs sense cellular metabolite signals to control gene expression and metabolic enzyme activity through lysine acetylation and deacetylation.

Trends

Protein lysine acetylation has recently emerged as a widespread reversible modification occurring on histones and nonhistone proteins, including key metabolic enzymes.

Histone acetylation level is controlled by the activity of both histone acetyltransferases (HATs) and deacetylase (HDACs), some of which have been identified to acetylate or deacetylate nonhistone proteins.

Acetyl-CoA can act as a metabolic signal for cell growth by promoting histone acetylation at growth-related genes via regulating the activity of specific acetyltransferase, whereas the NAD^+ level may influence NAD^+-dependent Sirtuin 2 (SIR2) lysine deacetylases. Thus, HATs and HDACs may sense cellular metabolite levels to coordinate cellular energy and redox status with gene expression and metabolic activity to control plant growth.

Protein Lysine Acetylation

Protein lysine epsilon acetylation (see Glossary) is a reversible and highly regulated post-translational modification of proteins. It is well known that histone lysine acetylation has a pivotal role in chromatin regulation and gene expression in eukaryotic cells. In general, histone acetylation is associated with an active chromatin state of genes, whereas histone deacetylation represses gene expression [1]. Recent results have shown that, in addition to its occurrence on histone proteins, lysine acetylation is a widespread post-translational modification, occurring in a large number of proteins of diverse biological function in various organisms, including Eubacteria [2], Archaea [3], Fungi [4], plants [5–7], and mammals [8]. Enzymes of central carbon metabolism are particular targets, with most enzymes of glycolysis and the tricarboxylic acid (TCA) cycle in different organisms, as well as photosynthesis in plants, being acetylated, and their acetylation status affecting enzymatic activities and regulating metabolic flux through these pathways [5,6,9,10]. Therefore, protein lysine acetylation has an important role in not only the epigenetic regulation of gene expression, but also the control of metabolic enzyme activity. Conversely, important metabolites, such as acetyl-CoA and NAD^+, are the substrates or cofactors involved in the lysine acetylation and deacetylation reactions, respectively. This suggests that primary metabolic activity and gene expression is coordinated to regulate plant growth and raises the possibility that histone lysine acteylation and/or deacetylation enzymes may reprsent the nexus in the coordination. In this opinion, we discuss the possible regulation of histone acetylation enzymes by cellular metabolite levels and their potantial function in coordinating plant metabolic activity and gene expression to enable plants to cope with adverse and varying enviornmental conditions for optimal growth.

Are HATs and HDACs Involved in the Acetylation and Deacetylation of Plant Metabolic Enzymes?

Recent data indicate that in Arabidopsis (Arabidopsis thaliana), many metabolic proteins are acetylated that are involved in a range of cellular processes, including photosynthesis and

[1]Institute of Plant Sciences Paris-Saclay (IPS2), University Paris-sud 11, 91405 Orsay, France
[2]Institute of interdisciplinary Scientific Research, Jianghan University, 430056, Wuhan, China

*Correspondence:
dao-xiu.zhou@u-psud.fr (D.-X. Zhou).

 http://dx.doi.org/10.1016/j.tplants.2015.07.005
© 2015 Elsevier Ltd. All rights reserved.

CrossMark

respiration [5–7]. Several important enzymes involved in primary and secondary metabolism were identified to be acetylated, including the small and large subunit of Rubisco (RBCS1A and RBCL), light-harvesting chlorophyll a/b-binding protein (LHCB), ATP synthase complex (ATP1, ATP3, and ATP17), ATP/ADP carrier proteins (AAC), a terpene synthase-like protein (TPS17), a 3-ketoacyl-CoA synthase (KCS21) involved in very long-chain fatty acid biosynthesis, a fructose-bisphosphate aldolase (FBA1), a pyruvate decarboxylase (PDC), a cinnamyl-alcohol dehydrogenase (CAD), a cytochrome P450 (CYP707A3), several isoforms of glutamine synthase (GLN1.3, GS2, and GSR1), a malate dehydrogenase (MDH), a phosphoglycerate kinase (PGK1), and a glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [5–7]. Importantly, for several key enzymes, the acetylation status may affect enzyme activity and the direction of energy and carbon flux in a pathway. For example, in human liver cells, fatty acids lead to increased acetylation of the beta-oxidation multifunctional enzyme enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (EHHADH), and increased activity of the enzyme [10]. In addition, acetylation affects the stability of phosphoenolpyruvate carboxykinase (PEPCK), which is a rate-limiting enzyme in the switch in glycolysis and gluconeogenesis in animal cells [10]. Other examples of the control of metabolism via acetylation of enzymes include the inactivation of the mitochondrial acetyl-CoA synthetase (AceCS) via acetylation of the active site [11]. In plants, deacetylation of Rubisco, phosphoglycerate kinase, and GAPDH resulted in an increase in their activities, whereas deacetylation of malate dehydrogenase led to a decrease in activity [5]. For Rubisco, several acetylated lysine residues were previously found to be important either in catalysis or for interaction between domains, suggesting an important role of acetylation on Rubisco activity [5]. Arabidopsis mitochondrial ATP synthase and ATP/ADP carrier proteins (AAC1–3) are acetylated. Deacetylation of the proteins is important for coupling ATP synthesis and respiration, and ADP uptake [6,12].

The level of histone acetylation is determined by the activity of both HATs and HDACs. Several HDACs have been shown to be involved in deacetylation of metabolic enzymes and nonhistone proteins in yeast and animal cells [13–22]. The HATs in Arabidopsis are encoded by 12 genes and can be grouped into four classes: General control nondepressible 5 (GCN5)-related N-Acetyl Transferase (GNAT); MOZ-YBF2/SAS3-SAS2/TIP60 (MYST); cAMP-responsive element-Binding Protein (CBP); and TATA-binding protein Associated Factor 1 (TAF1) [23]. The HDACs in Arabidopsis are encoded by 18 genes and can be grouped into four type: Reduced Potassium Dependency 3 (RDP3); Histone DeAcetylase 1 (HDA1); Silent Information Regulator 2 (SIR2); and the plant-specific Histone Deacetylase 2 (HD2). The SIR2 family of HDAC, also called sirtuins, is distinct from the other groups of HDAC in catalyzing deacetylation via a reaction depending on NAD^+.

Many of the Arabidopsis and rice (Oryza sativa) HATs and HDACs have been studied for their function in chromatin modification and epigenetic regulation of developmental and stress-responsive genes [24–28]. Interestingly, some HATs and HDACs are not exclusively localized to the nucleus (Figure 1). For instance, Arabidopsis HDAC members are localized in chloroplasts (e.g., HDA14), mitochondria (e.g., AtSRT2 and HDA14), or cytoplasm (e.g., HDA5, HDA8, and HDA18), whereas others (e.g., HDA15) shuttles between nucleus and cytoplasm depending on the presence or absence of light [12,29–32]. In rice, OsSRT2 protein is localized in the mitochondria, OsHDAC6 in chloroplasts, and OsHDAC10 in both chloroplast and mitochondria [33]. Given the mitochondrial or chloroplast localization, these HDACs may be implicated in the regulation of metabolic pathways. However, their function in plant metabolism regulation is generally not known, except for recent results showing that AtSRT2 is involved in mitochondrial energy metabolism [12]. AtSRT2 localizes predominantly at the inner mitochondrial membrane and interacts with a few protein complexes mainly involved in energy metabolism and metabolite transport. Loss of AtSRT2 function leads to an increase of acetylation of several of these proteins and affects coupling of ATP synthesis to mitochondrial respiration, increases ADP uptake into

Glossary

Acetyl-CoA synthetase (AceCS): an enzyme that catalyzes the ligation of acetate with CoA to produce acetyl-CoA.
Acetyl co-enzyme A (Acetyl-CoA): an important metabolite required for many biochemical reactions (Figure 2, main text).
ATP citrate lyase (ACL): the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA.
General control nondepressible 5 (GCN5): a ubiquitous HDAC initially identified in yeast and conserved in higher eukaryotes, including plants.
Glyceraldehyde 3-phosphate dehydrogenase (GAPDH): catalyzes the conversion of glyceraldehyde 3-phosphate to glycerate 1,3-bisphosphate, the sixth step of glycolysis.
Histone acetyltransferase (HAT): acetylates lysine amino acid residues of histone and nonhistone proteins, such as transcription factors, by transferring an acetyl group from acetyl-CoA to form e-N-acetyl-lysine; also called lysine (K) acetyltransferase (KAT), when modifying nonhistone proteins.
Histone deacetylases (HDACs): remove acetyl groups from e-acetyl-lysines of histones and nonhistone proteins. HDACs are also known as lysine deacetylases (KDAC) when deacetylating nonhistone proteins.
Lysine epsilon acetylation: a reversible protein acetylation process that occurs at the amino group of the side chain of internal lysine residues. Besides epsilon acetylation, protein acetylation includes other two forms: O-acetylation, the addition of acetyl group to internal serine or threonine residues; and lysine alpha acetylation, an irreversible process occurring on the N-terminal amino acid of proteins.
NAD^+: acts as a coenzyme involved in redox reactions as well as a substrate of sirtuin or SIR2 enzymes for protein deacetylation.
RBCS and RBCL: small and large subunits of the chloroplast photosynthetic enzyme Rubisco.
Ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco): involved in the first major step of carbon fixation.
Silent information regulator 2 or sirtuin (Sirt2): a class of NAD^+-dependent protein deacetylases that produce deacetylated lysine,

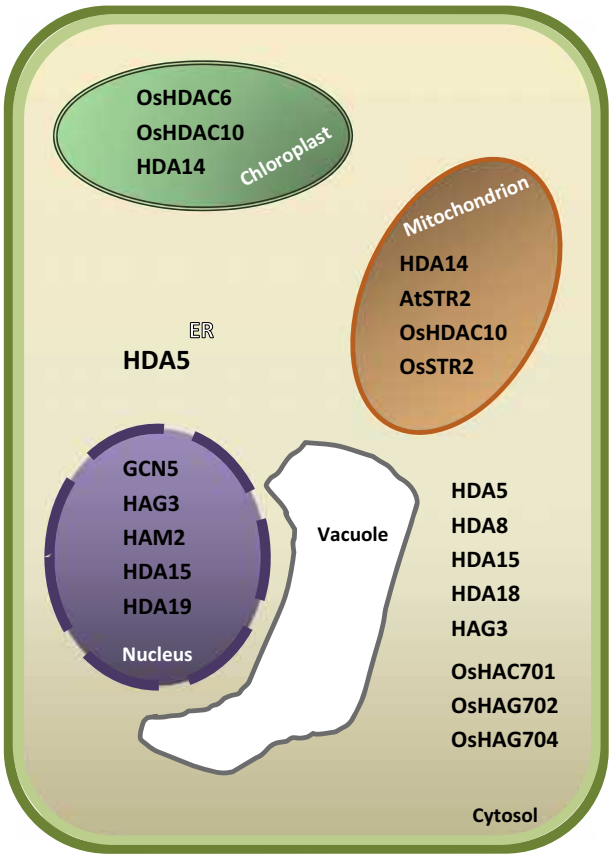

Figure 1. Subcellular Localization of Histone Acetyltransferases (HATs) and Deacetylases (HDACs) in the Plant Cell. Proteins shown include Arabidopsis HATs (GCN5, HAG3, and HAM2) and HDACs (HDA5, HDA8, HDA14, HDA15, HDA18, HDA19 and AtSRT2) and rice HATs (OsHAC701, OsHAG702, and OsHAG704) and HDACs (OsHDAC6, OsHDAC10, OsHDAC14 and OsSRT2). Abbreviation: ER, endoplasmic reticulum.

nicotinamide, and $2^{\prime}$-O-acetyl-ADP-ribose (Figure 3).

Spt-Ada-Gcn5 acetyltransferase (SAGA): a coactivator complex involved in gene transcriptional initiation in yeast that is conserved in higher eukaryotes.

Tricarboxylic acid (TCA) cycle: also called the Krebs cycle and citric acid cycle; the second stage of cellular respiration.

mitochondria, and affects the content of sugars, amino acids, and ADP [12], suggesting that AtSRT2-mediated protein deacetylation is important for energy metabolism in mitochondria.

Knowledge of the enzymes involved in the acetylation of non-nuclear proteins is largely lacking, except the report of mammalian GCN5-like protein 1 (GCN5L1), homologous to yeast GCN5, which acetylates lysine proteins belonging to the respiratory electron transport chain in mammal mitochondria [34]. In addition, the Elongator protein 3 (ELP3), a GNAT-family HAT, has been shown to be tail anchored to the mitochondrial outer membrane in Toxoplasma gondii [35]. Recent result suggests that lysine acetylation also occurs nonenzymatically in mitochondria (auto-acetylation), indicating a combined operation of spontaneous lysine acetylation and enzyme-catalyzed acetylation [7,36]. Most of the studied Arabidopsis HAT proteins appear to be mainly localized in the nucleus, except HAG2 and HAG3 (also called ELP3). HAG2 protein is closely related to the B-type HATs that shuttle between cytoplasm and nucleus in yeast and animal cells [37]. HAG3 (ELP3) has been shown to acetylate tubulins in cytoplasm in Arabidopsis [30]. In rice, several HAT proteins (i.e., HAT701, HAG702, and HAG704) localize in both nucleus and cytosol [38]. Identification of specific HATs and HDACs that are involved in the control of acetylation and activities of metabolic enzymes would be essential to understand the signaling and regulatory mechanisms of metabolisms by lysine acetylation.

Does Plant Acetyl-CoA Level Control HAT Activity?

Protein lysine acetylation requires acetyl-CoA, which is an important metabolite in plants. In addition to being involved in protein lysine acetylation, acetyl-CoA drives the TCA cycle for the production of ATP under aerobic conditions and is a basic precursor for amino acids, lipids, and

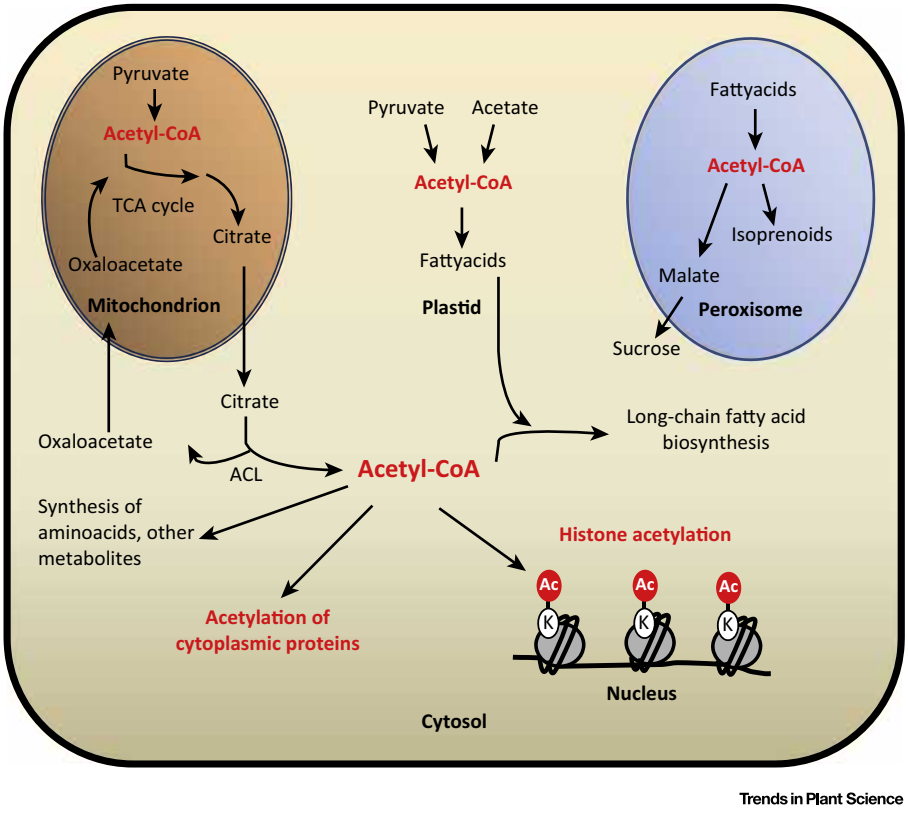

Figure 2. Acetyl-CoA is at the Nexus of Metabolism, Histone and Nonhistone Protein Acetylation and Gene Expression. In plant cells, acetyl-CoA is produced in different compartments, including mitochondria, plastids, peroxisomes, and cytosol. The cytosolic pool of acetyl-CoA produced by ATP citrate lyase (ACL) is used for histone and nonhistone protein acetylation in the nucleus and cytoplasm.

many other components required for cell growth in plants. Acetyl-CoA can be produced through a variety of metabolic pathways involving pyruvate, citrate, acetate, and various amino acids, and by fatty acid beta-oxidation (Figure 2). The conversion of pyruvate into acetyl-CoA via the mitochondrial pyruvate dehydrogenase complex during the oxidation of glucose and the beta-oxidation of fatty acids are major sources of cellular acetyl-CoA. Citrate produced in the TCA cycle can be exported from the mitochondria. In the cytoplasm, citrate with ATP and CoA can be converted to acetyl-CoA and oxaloacetate via the ATP citrate lyase (ACL) enzyme, thereby providing a cytoplasmic pool of acetyl-CoA. In plants, acetyl-CoA synthesis occurs also in plastids and peroxisomes (Figure 2). In addition, a pool of acetyl-CoA must exist in the nucleus to mediate histone acetylation, which at least partially derives from the diffusion of acetyl-CoA from cytoplasm through the nuclear pores [39].

Considering that acetyl-CoA is a central intermediate in numerous plant metabolic pathways as well as an essential substrate for protein acetylation, it can be speculated that acetyl-CoA has a pivotal role in regulating metabolic pathways via its effects on both histone and metabolic protein acetylation in plants. As described above, HAT enzymes use acetyl-CoA to modify histone lysines to establish the epigenetic state of chromatin in eukaryotic cells (Figure 3). The question remains whether gene activity is modulated via histone acetylation in accord with the accumulation of acetyl-CoA in plant cells.

Indeed, global histone acetylation levels were shown to depend on ACL-produced nuclear acetyl-CoA in mammalian cells [40]. Similarly, in yeast, the production of nuclear and cytoplasmic

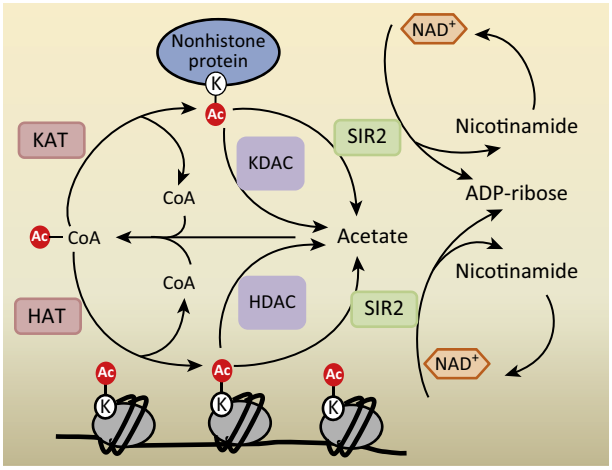

Figure 3. Involvement of Acetyl-CoA and NAD^+ in Protein Lysine Acetylation and Deacetylation. Histone or lysine acetyltransferases (HAT or KAT) use acetyl-CoA to acetylate histones or nonhistone proteins, which can be reversed by histone or lysine deacetylases (HDAC or KDAC), generating acetate in the cell. Sirtuin 2 (SIR2) proteins are NAD^+-dependent HDAC or KDACs. SIR2-mediated deacetylation uses NAD^+, generating ADP-ribose (ADPr), acetate, and nicotinamide. Nicotinamide is recycled to synthesize NAD^+.

acetyl-CoA by acetyl-CoA synthetases, which are functional homologs of ACL, provides a source for histone acetylation [41]. It has also been affirmatively shown that unusually high levels of acetyl-CoA have a determinative role in epigenetic regulation of gene expression [42]. Many acetylation marks on histone lysine residues (H3K9/14/23/27 and H4K5/8/12) only appear at the same time as the peak levels of intracellular acetyl-CoA. Furthermore, a set of approximately 1000 genes that are important for yeast growth, such as those encoding ribosome biogenesis and G1 cyclin CLN3, are especially reliant on histone acetylation for their activation [42,43]. Likely, levels of acetyl-CoA can be instructive for growth through modulating histone acetylation and transcription.

The histone acetyltransferase GCN5 of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex has been identified as the critical enzyme responsive to acetyl-CoA fluctuation in yeast, because the SAGA complex is selectively associated with the promoters of the entire set of responsive genes only during the window of peak acetyl-CoA accumulation [42]. It is possible that GCN5 requires high levels of acetyl-CoA to acetylate histones. More recent studies have shown that increased rates of acetyl-CoA synthesis enable the GCN5-containing SAGA complex to catalyze histone acetylation at growth-related genes to promote entry into the cell division cycle [43], suggesting that acetyl-CoA-induced histone acetylation is modulated by the GCN5 complex.

Acetyl-CoA in plant cells is controlled by photosynthesis, respiration, and beta-oxidation, and the plant cell respiration rate differs depending on the amount of light available; thus, cytosolic acetyl-CoA levels may be likely to fluctuate diurnally, although this remains to be determined. In addition, acetyl-CoA levels may considerably vary among different plant tissues or organs, and adverse growth conditions affecting photosynthesis or respiration may limit acetyl-CoA production in plant cells. It will be interesting to examine whether fluctuation of cytosolic acetyl-CoA in plant cells affects the activity of HATs and, consequently, genome-wide histone and metabolic enzyme acetylation and gene expression.

In Arabidopsis, decreased expression of the cytosolic ACL reduces the accumulation of cytosolic acetyl-CoA-derived metabolites, accompanying many plant developmental abnormalities [44]. These data indicate that ACL is required for normal plant growth and development and that no other source of acetyl-CoA can compensate for ACL-derived acetyl-CoA. However, it remains unknown whether the deficiency of cytosolic acetyl-CoA affects the activity of lysine acetyltransferases that acetylate metabolic enzymes and/or histones. Arabidopsis GCN5 is one of the best-characterized GNAT-type HATs in plant [24]. The Arabidopsis gcn5 mutant shows various developmental and stress-responsive defects [24,45,46]. It remains unknown whether

Key Figure

Histone Acetyltransferases (HATs) and Deacetylases (HDACs) are Key Players in Coordinating Metabolism and Gene Expression Under Varying Growth Conditions.

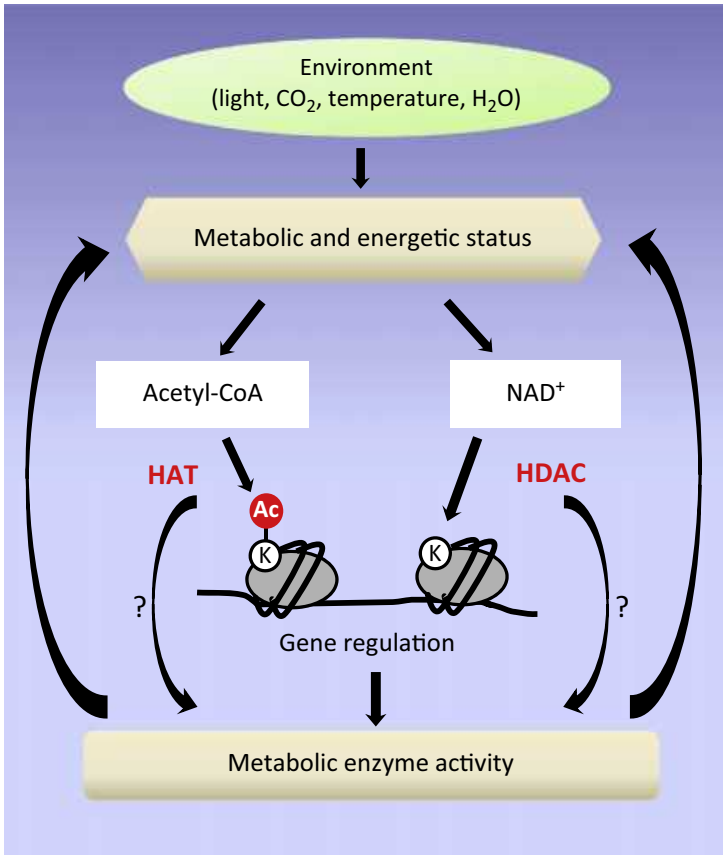

Figure 4. Acetyl-CoA and NAD^+ that reflect the metabolic and energetic status of the cell may regulate the activity of HAT and HDAC, and, consequently, acetylation of histones and metabolic enzymes, which in turn control metabolic flux in the cell.

AtGCN5 activity for histone acetylation is regulated by acetyl-CoA levels and AtGCN5 itself is involved in regulation of metabolic enzyme activity through acetylation.

Does NAD^+ Metabolism Control Gene Expression via Sir2 Proteins in Plants?

NAD^+ is a key electron carrier in the oxidation of carbohydrate compounds. Upon electron acceptance, NAD^+ is converted to the reduced form NADH. NAD^+ levels reflect both cellular redox and energy states. SIR2 is an NAD^+-dependent lysine deacetylase, yielding the deacetylated substrate, nicotinamide, and O-acetyl-ADP-ribose as products [47] (Figure 3). Considerable attention has been paid to the hypothetical role of fluctuating NAD^+ levels as a function of energetic state and the activity of SIR2 deacetylase enzymes in animal and yeast cells [48,49]. It becomes apparent that SIR2 serves as both an energy and redox sensor and transcriptional regulator by controlling acetylation states of histones and nonhistone proteins. NAD^+ levels may

increase upon decrease of glucose levels in yeast and animal cells, thereby offering an alternative means of SIR2 activation [50]. However, whether SIR2 activity is operatively linked to metabolic state via fluctuations in the intracellular levels of NAD^+ in plants remains unclear.

In plant cells, fluctuation of NAD^+ reflects activities of a complex metabolic network (e.g., respiration–photosynthesis–photorespiration–pentose-phosphate cycle, etc.) as well as redox states due to both metabolic activities and biotic and abiotic stress responses [51–53]. In addition, the levels of NAD^+ in leaf and pollen cells vary during plant development [54,55]. It will be interesting to study whether intracellular levels of NAD^+ in plants are linked to activation of SIR2 proteins to control gene expression, metabolic activity, and stress tolerance. Knockdown mutants and overexpression lines of NAD^+ synthesis genes display sensible changes in NAD^+, photosynthesis, and growth phenotypes [56,57]. Conversely, downregulation of the rice nuclear SIR2 protein gene OsSRT1 leads to oxidative burst and cell death, whereas its overexpression enhances tolerance to oxidative stress [58]. It is unclear whether the phenotypes of NAD^+ synthesis genes and OsSRT1 are related to the alteration of SIR2 proteins or NAD^+ accumulation in the respective transgenic plants.

Outstanding Questions

Acetyl-CoA and NAD^+ levels may vary in different plant tissues and in photosynthesis or respiration during adverse environmental conditions. Do metabolic variations affect HAT and HDAC activities to regulate histone acetylation and gene expression?

What are the specific HATs and HDACs that are involved in lysine acetylation of metabolic enzymes?

How do HATs and HDACs sense metabolic signals to regulate lysine acetylation of histones and metabolic enzymes?

Concluding Remarks

Coordination between plant metabolism and epigenetic regulation of gene expression is of primary importance for plants to cope with varying environmental conditions for adaptation and for optimal growth. Given that HAT and HDAC regulate not only gene expression, but also metabolic enzyme activity and are in turn controlled by important metabolites, such as acetyl-CoA and NAD^+ (Figure 4, Key Figure), studying the metabolic signaling and regulation of histone acetylation enzyme activities will be essential to understand the coordination between metabolism and gene expression in plants. A first step would be to analyze whether metabolic fluctuation in plant cells affects HAT and HDAC-dependent genome-wide dynamics of histone modification and gene expression under different environmental conditions. Identifying specific HAT and HDAC involved in acetylation of metabolic enzymes and in regulation of important metabolic pathways would be an important step towards elucidation of the underling mechanism of the coordination, for which HAT and HDAC inhibitors and gene mutants could be exploited. In vivo and in vitro approaches of protein interaction could be used to identify HAT and HDAC-targeted metabolic enzymes for acetylation and deacetylation. In parallel, mutants or overexpression plants of acetyl-CoA and NAD^+ synthesis genes would be useful to explore the effect of acetyl-CoA and NAD^+ accumulation on HAT and HDAC activity and genome-wide histone acetylation and deacetylation. Understanding the precise mechanisms of coodination between metabolism and gene expression will provide possibilities to conceive strategies to regulate metabolite flux and enhance plant productivity.

Acknowledgments

This work was supported by the French Agence Nationale de la Recherche (ANR-12-BSV6-0010, NERDPATH).

References

1. Berger, S.L. (2007) The complex language of chromatin regulation during transcription. Nature 447, 407–412
2. Zhang, J. et al. (2009) Lysine acetylation is a highly abundant and evolutionarily conserved modification in Escherichia coli. Mol. Cell. Proteomics 8, 215–225
3. Altman-Price, N. and Mevarech, M. (2009) Genetic evidence for the importance of protein acetylation and protein deacetylation in the halophilic archaeon Haloferax volcanii. J. Bacteriol. 191, 1610–1617
4. Henriksen, P. et al. (2012) Proteome-wide analysis of lysine acetylation suggests its broad regulatory scope in Saccharomyces cerevisiae. Mol. Cell. Proteomics 11, 1510–1522
5. Finkemeier, I. et al. (2011) Proteins of diverse function and subcellular location are lysine acetylated in Arabidopsis. Plant Physiol. 155, 1779–1790
6. Wu, X. et al. (2011) Lysine acetylation is a widespread protein modification for diverse proteins in Arabidopsis. Plant Physiol. 155, 1769–1778
7. Konig, A.C. et al. (2014) The mitochondrial lysine acetylome of Arabidopsis. Mitochondrion 19, 252–260
8. Choudhary, C. et al. (2009) Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science 325, 834–840
9. Wang, Q. et al. (2010) Acetylation of metabolic enzymes coordinates carbon source utilization and metabolic flux. Science 327, 1004–1007
10. Zhao, S. et al. (2010) Regulation of cellular metabolism by protein lysine acetylation. Science 327, 1000–1004

11. Hallows, W.C. et al. (2006) Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. Proc. Natl. Acad. Sci. U.S. A. 103, 10230–10235
12. Konig, A.C. et al. (2014) The Arabidopsis class II sirtuin is a lysine deacetylase and interacts with mitochondrial energy metabolism. Plant Physiol. 164, 1401–1414
13. Hallows, W.C. et al. (2012) Regulation of glycolytic enzyme phosphoglycerate mutase-1 by Sirt1 protein-mediated deacetylation. J. Biol. Chem. 287, 3850–3858
14. Hallows, W.C. et al. (2011) Sirt3 promotes the urea cycle and fatty acid oxidation during dietary restriction. Mol. Cell 41, 139–149
15. Hirschey, M.D. et al. (2010) SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 464, 121–125
16. Tao, R. et al. (2010) Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. Mol. Cell 40, 893–904
17. Parmigiani, R.B. et al. (2008) HDAC6 is a specific deacetylase of peroxiredoxins and is involved in redox regulation. Proc. Natl. Acad. Sci. U.S.A. 105, 9633–9638
18. Zhang, M. et al. (2014) HDAC6 deacetylates and ubiquitinates MSH2 to maintain proper levels of MutSalpha. Mol. Cell 55, 31–46
19. Kaluza, D. et al. (2011) Class IIb HDAC6 regulates endothelial cell migration and angiogenesis by deacetylation of cortactin. EMBO J. 30, 4142–4156
20. Mortenson, J.B. et al. (2015) Histone deacetylase 6 (HDAC6) promotes the pro-survival activity of 14-3-3zeta via deacetylation of lysines within the 14-3-3zeta binding pocket. J. Biol. Chem. 290, 12487–12496
21. Vidal-Laliena, M. et al. (2013) Histone deacetylase 3 regulates cyclin A stability. J. Biol. Chem. 288, 21096–21104
22. Karolczak-Bayatti, M. et al. (2011) Acetylation of heat shock protein 20 (Hsp20) regulates human myometrial activity. J. Biol. Chem. 286, 34346–34355
23. Pandey, R. et al. (2002) Analysis of histone acetyltransferase and histone deacetylase families of Arabidopsis thaliana suggests functional diversification of chromatin modification among multicellular eukaryotes. Nucleic Acids Res. 30, 5036–5055
24. Servet, C. et al. (2010) Histone acetyltransferase AtGCN5/HAG1 is a versatile regulator of developmental and inducible gene expression in Arabidopsis. Mol. Plant 3, 670–677
25. Chen, X. and Zhou, D.X. (2013) Rice epigenomics and epigenetics: challenges and opportunities. Curr. Opin. Plant Biol. 16, 164–169
26. Hu, Y. et al. (2009) Rice histone deacetylase genes display specific expression patterns and developmental functions. Biochem. Biophys. Res. Commun. 388, 266–271
27. Grandperret, V. et al. (2014) Type-II histone deacetylases: elusive plant nuclear signal transducers. Plant Cell Environ. 37, 1259–1269
28. Liu, X. et al. (2014) Transcriptional repression by histone deacetylases in plants. Mol. Plant 7, 764–772
29. Alinsug, M.V. et al. (2012) Subcellular localization of class II HDAs in Arabidopsis thaliana: nucleocytoplasmic shuttling of HDA15 is driven by light. PLoS ONE 7, e30846
30. Tran, H.T. et al. (2012) Arabidopsis thaliana histone deacetylase 14 (HDA14) is an alpha-tubulin deacetylase that associates with PP2A and enriches in the microtubule fraction with the putative histone acetyltransferase ELP3. Plant J. 71, 263–272
31. Liu, C. et al. (2013) HDA18 affects cell fate in Arabidopsis root epidermis via histone acetylation at four kinase genes. Plant Cell 25, 257–269
32. Liu, X. et al. (2013) PHYTOCHROME INTERACTING FACTOR3 associates with the histone deacetylase HDA15 in repression of chlorophyll biosynthesis and photosynthesis in etiolated Arabidopsis seedlings. Plant Cell 25, 1258–1273
33. Chung, P.J. et al. (2009) Subcellular localization of rice histone deacetylases in organelles. FEBS Lett. 583, 2249–2254
34. Scott, I. et al. (2012) Identification of a molecular component of the mitochondrial acetyltransferase programme: a novel role for GCN5L1. Biochem. J. 443, 655–661
35. Stilger, K.L. and Sullivan, W.J., Jr (2013) Elongator protein 3 (Elp3) lysine acetyltransferase is a tail-anchored mitochondrial protein in Toxoplasma gondii. J. Biol. Chem. 288, 25318–25329
36. Shi, L. and Tu, B.P. (2015) Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. Curr. Opin. Cell Biol. 33, 125–131
37. Parthun, M.R. (2012) Histone acetyltransferase 1: more than just an enzyme? Biochim. Biophys. Acta 1819, 256–263
38. Liu, X. et al. (2012) Histone acetyltransferases in rice (Oryza sativa L.): phylogenetic analysis, subcellular localization and expression. BMC Plant Biol. 12, 145
39. Morrish, F. et al. (2010) Myc-dependent mitochondrial generation of acetyl-CoA contributes to fatty acid biosynthesis and histone acetylation during cell cycle entry. J. Biol. Chem. 285, 36267–36274
40. Wellen, K.E. et al. (2009) ATP-citrate lyase links cellular metabolism to histone acetylation. Science 324, 1076–1080
41. Takahashi, H. et al. (2006) Nucleocytosolic acetyl-coenzyme a synthetase is required for histone acetylation and global transcription. Mol. Cell 23, 207–217
42. Cai, L. et al. (2011) Acetyl-CoA induces cell growth and proliferation by promoting the acetylation of histones at growth genes. Mol. Cell 42, 426–437
43. Shi, L. and Tu, B.P. (2013) Acetyl-CoA induces transcription of the key G1 cyclin CLN3 to promote entry into the cell division cycle in Saccharomyces cerevisiae. Proc. Natl. Acad. Sci. U.S.A. 110, 7318–7323
44. Fatland, B.L. et al. (2005) Reverse genetic characterization of cytosolic acetyl-CoA generation by ATP-citrate lyase in Arabidopsis. Plant Cell 17, 182–203
45. Bertrand, C. et al. (2003) Arabidopsis histone acetyltransferase AtGCN5 regulates the floral meristem activity through the WUSCHEL/AGAMOUS pathway. J. Biol. Chem. 278, 28246–28251
46. Benhamed, M. et al. (2006) Arabidopsis GCN5, HD1, and TAF1/HAF2 interact to regulate histone acetylation required for light-responsive gene expression. Plant Cell 18, 2893–2903
47. Feldman, J.L. et al. (2012) Sirtuin catalysis and regulation. J. Biol. Chem. 287, 42419–42427
48. Canto, C. and Auwerx, J. (2011) NAD^+ as a signaling molecule modulating metabolism. Cold Spring Harb. Symp. Quant. Biol. 76, 291–298
49. Guarente, L. (2011) The logic linking protein acetylation and metabolism. Cell Metab. 14, 151–153
50. Kaelin, W.G., Jr and McKnight, S.L. (2013) Influence of metabolism on epigenetics and disease. Cell 153, 56–69
51. De Block, M. and Van Lijsebettens, M. (2011) Energy efficiency and energy homeostasis as genetic and epigenetic components of plant performance and crop productivity. Curr. Opin. Plant Biol. 14, 275–282
52. Hashida, S.N. et al. (2009) The role of NAD biosynthesis in plant development and stress responses. Ann. Bot. 103, 819–824
53. De Block, M. et al. (2005) Poly(ADP-ribose) polymerase in plants affects energy homeostasis, cell death and stress tolerance. Plant J. 41, 95–106
54. Queval, G. and Noctor, G. (2007) A plate reader method for the measurement of NAD, NADP, glutathione, and ascorbate in tissue extracts: application to redox profiling during Arabidopsis rosette development. Anal. Biochem. 363, 58–69
55. Hashida, S.N. et al. (2013) NAD+ accumulation during pollen maturation in Arabidopsis regulating onset of germination. Mol. Plant 6, 216–225
56. Petriacq, P. et al. (2012) Inducible NAD overproduction in Arabidopsis alters metabolic pools and gene expression correlated with increased salicylate content and resistance to Pst-AvrRpm1. Plant J. 70, 650–665
57. Petriacq, P. et al. (2013) NAD: not just a pawn on the board of plant–pathogen interactions. Plant Signal. Behav. 8, e22477
58. Huang, L. et al. (2007) Down-regulation of a SILENT INFORMATION REGULATOR2-related histone deacetylase gene, OsSRT1, induces DNA fragmentation and cell death in rice. Plant Physiol. 144, 1508–1519