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Opinion

# Histone Acetylation Enzymes Coordinate Metabolism and Gene Expression

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**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.**

## 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

### 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.

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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 ε-*N*-acetyl-lysine; also called lysine (K) acetyltransferase (KAT), when modifying nonhistone proteins.
**Histone deacetylases (HDACs):** remove acetyl groups from ε-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,