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REVIEW

Advances in understanding the roles of plant HAT and HDAC in non-histone protein acetylation and deacetylation

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Abstract

Main conclusion **This review focuses on HATs and HDACs that modify non-histone proteins, summarizes functional mechanisms of non-histone acetylation as well as the roles of HATs and HDACs in rice and Arabidopsis.**

Abstract The growth and development of plants, as well as their responses to biotic and abiotic stresses, are governed by intricate gene and protein regulatory networks, in which epigenetic modifying enzymes play a crucial role. Histone lysine acetylation levels, modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), are well-studied in the realm of transcriptional regulation. However, the advent of advanced proteomics has unveiled that non-histone proteins also undergo acetylation, with its underlying mechanisms now being clarified. Indeed, non-histone acetylation influences protein functionality through diverse pathways, such as modulating protein stability, adjusting enzymatic activity, steering subcellular localization, influencing interactions with other post-translational modifications, and managing protein–protein and protein–DNA interactions. This review delves into the recent insights into the functional mechanisms of non-histone acetylation in plants. We also provide a summary of the roles of HATs and HDACs in rice and Arabidopsis, and explore their potential involvement in the regulation of non-histone proteins.

Keywords HAT · HDAC · Acetylation · Non-histone protein · Post-translational modification · Plant development

Introduction

Post-translational modifications (PTMs) are a diverse array of covalent alterations to a protein's structure that take place after its synthesis by the ribosome. These modifications are integral to the regulation of protein function and are crucial for a myriad of cellular processes (Verdin and Ott 2015). In recent years, the term PTMs has become more synonymous with the covalent addition of small molecules to proteins, particularly the enzymatic attachment of groups such as acetyl, methyl, or phosphate groups to amino acid side chains (Suskiewicz 2024). This specificity allows PTMs to modulate protein activity with a precision that surpasses other regulatory mechanisms. The initial discovery in the realm of PTMs was the identification of reversible protein phosphorylation, which serves as a key regulatory mechanism for enzyme function in humans (Sutherland and Wosilait 1955). Since then, a spectrum of PTMs, including ubiquitination, acetylation, and methylation, has been unveiled (Gough and Sadanandom 2021). Among these, lysine acetylation (LysAc) stands out as a highly conserved and reversible PTM across both prokaryotic and eukaryotic organisms, affecting not only histones but also a wide array of non-histone proteins (Zhang et al. 2009; Rao et al. 2014; Kumar et al. 2021).

Acetyl-coenzyme A (acetyl-CoA), a key molecule in cellular metabolism, serves a dual role as both the acetyl donor for protein acetylation and a precursor for the biosynthesis of various phytochemicals (Chen et al. 2017). Protein LysAc involves the transfer of an acetyl group from acetyl-CoA to the ε-amino position of a lysine residue within a protein. This process neutralizes the positive charge of the lysine side chain (Ali et al. 2018). LysAc is catalyzed by lysine

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acetyltransferases (KATs, also named as HATs), which are the ‘writers’ that transfer acetyl groups from acetyl-CoA to lysine residues, while lysine deacetylases (KDACs, also named as HDACs) remove these groups, thus acting as the ‘erasers’ of the epigenetic code (Choudhary et al. 2014; Narita et al. 2019; Tyagi et al. 2021). The interplay between these ‘writers’ and ‘erasers’ is meticulously balanced, as evidenced by the genome-wide identification of HAT and HDAC genes in plants such as Arabidopsis and rice (Hou et al. 2021; Chen et al. 2020; Pandey et al. 2002; Liu et al. 2012). These enzymes through interacting with histone octamer contribute to the dynamic regulation of histone acetylation, which in turn influences chromatin structure and gene expression.

In addition to histones, the mammalian p53 protein was the first non-histone protein recognized for its ability to undergo acetylation and deacetylation, highlighting the broad impact of these modifications on cellular function (Gu and Roeder 1997). By 2019, acetylation had been identified on over a hundred types of proteins in mammalian cells, including enzymes, transcription factors, and nuclear receptors (Narita et al. 2019). In plants, the discovery of Lys-acetylated sites on 74 proteins across different Arabidopsis organs in 2011 marked a significant step forward in understanding the role of LysAc in non-histone proteins (Finkemeier et al. 2011). With the advent of acetylated proteomics, a wealth of non-histone lysine acetylation modifications in plants has been revealed, implicating their involvement in diverse biological processes such as catalysis and binding (Fang et al. 2015).

While much attention has been given to the acetylation of histone proteins and its epigenetic implications for plant phenotypes, the non-histone acetylation/deacetylation landscape in plants remains less explored. This review aims to bridge this gap by providing a comprehensive overview of the role of HDACs and HATs in the post-translational regulation of non-histone proteins. We broaden the scope of research into post-translational modifications and explore the biochemical outcomes of these processes, including the influence on protein stability, changes in enzymatic activity, adjustments in cellular localization, and the modulation of interactions between protein–protein and protein–DNA. These processes are intricately linked to various signaling pathways and metabolic processes, ultimately shaping plant growth, development, and stress responses.

Functional mechanisms of non-histone acetylation modifications

Regulation of enzyme activity

Non-histone acetylation modification has been identified as a regulator of enzyme activity. In Arabidopsis, it has been discovered that histone deacetylase 6 (HDA6) can bind to the negative regulatory factor BRASSINOSTEROID INSENSITIVE 2 (BIN2), which plays a significant role in plant development, and deacetylate the lysine 189 (K189) site, resulting in a reduction of its kinase activity (Hao et al. 2016). Similarly, in rice, OsHDAC1 deactivates OsGSK2, thereby preventing the degradation of the downstream transcriptional factor OsBZR1 and controlling lateral root formation (Hou et al. 2022). However, deacetylation can also activate the enzyme activity of target proteins. For instance, empirical evidence has identified that the cytoplasmic histone deacetylase FolSir2 in tomato can bind to the kinase FolGSK3 and deacetylate the lysine 271 (K271) site, thereby activating FolGSK3-kinase activity and promoting pathogenic fungal infection (Zhang et al. 2023). Many metabolic enzymes have also been shown to be regulated by acetylation/deacetylation. For example, in Arabidopsis, lysine deacetylation significantly increases the activity of the Rubisco large subunit as well as other central metabolic enzymes, such as the Calvin cycle enzyme phosphoglycerate kinase, the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase, and the tricarboxylic acid (TCA) cycle enzyme malate dehydrogenase (Finkemeier et al. 2011). Plant mitochondria are crucial for plant growth and development. All of the TCA cycle enzymes in mitochondria have been identified to be lysine-acetylated, including most components of the pyruvate dehydrogenase complex (König et al. 2014). In *Pisum sativum* mitochondria, a minimum of 358 acetyl-proteins have been identified in pea seedlings, with 93 of these proteins found to be acetylated, including NDP-kinase, AAA +, LMW-Hsp, cytochrome b5 reductase, and formate dehydrogenase (Smith-Hammond et al. 2014). These findings indicate that histone deacetylases can act as dual regulators, capable of both activating and inhibiting the activity of target proteins, and play a pivotal role in signaling and metabolism pathways (Fig. 1A).

Regulation of protein degradation and synthesis

In mammalian cells, it has been observed that LysAc plays a dual role in regulating protein degradation, affecting both proteasome-dependent and -independent pathways (Narita et al. 2019). In plants, acetylation appears to prevent

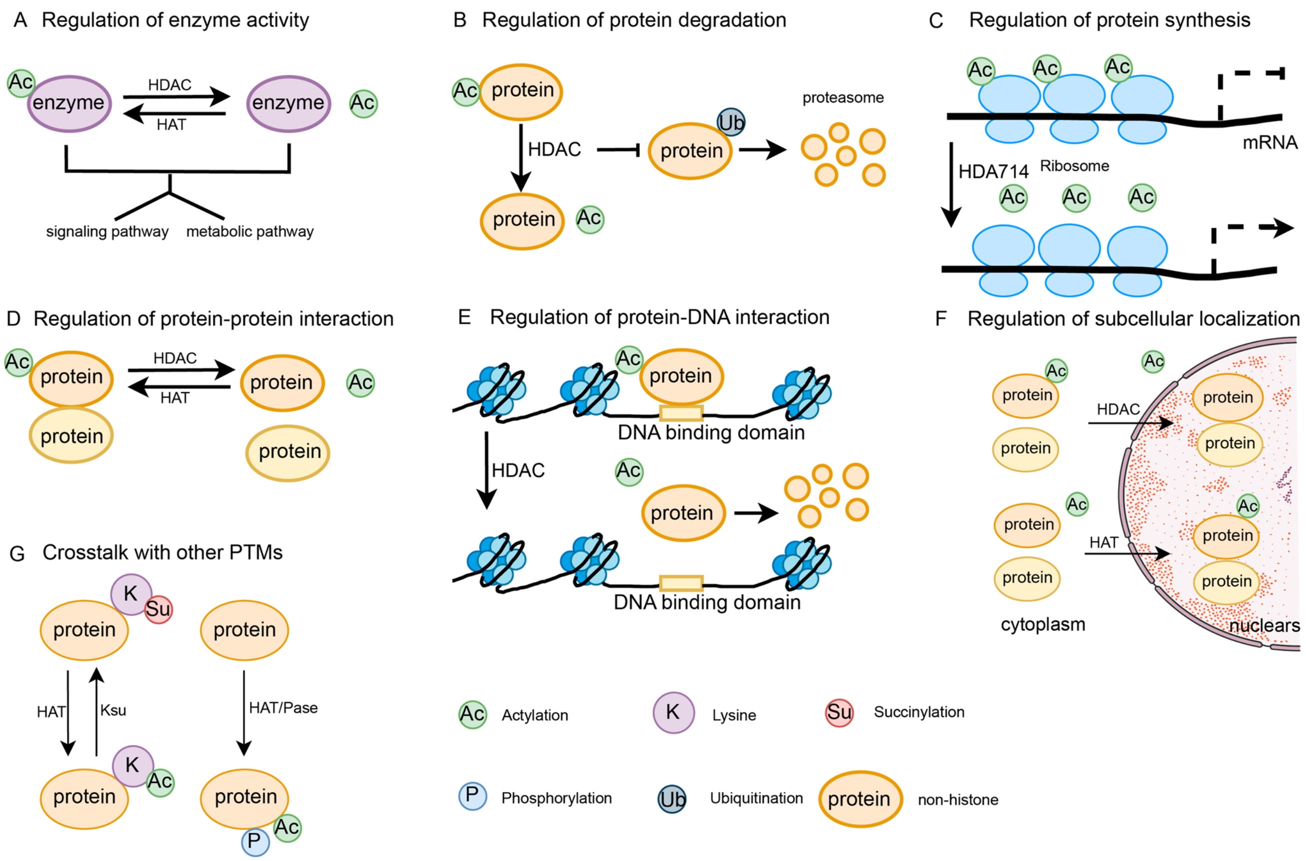

Fig. 1 Functional mechanisms of non-histone protein acetylation. **A** Regulation of enzyme activity. Acetylation acts as a regulator within signaling pathways, influencing the catalytic activities of numerous metabolic enzymes. **B** Regulation of protein degradation. In plants, acetylation-dependent proteins can prevent protein ubiquitination, thereby influencing degradation process of proteins. **C** Regulation of protein synthesis. The enzyme OsHDA714 can remove acetyl groups from ribosomal proteins, thereby facilitating the translation process. **D** Regulation of protein–protein interactions. The acetylation of certain non-histone proteins can modulate their interactions with other proteins. **E** Regulation of protein–DNA interactions. Deacetylation by HDACs on non-histone proteins can diminish their DNA binding capacity. **F** Regulation of subcellular localization. Deacetylation or acetylation of non-histones may induce the translocation of these proteins within the cell. **G** Crosstalk with other PTMs. Acetylation can interact with other PTMs, such as succinylation and phosphorylation, indicating a complex regulatory network

ubiquitination of proteins, thus inhibiting proteasome-mediated degradation (Fig. 1B). For instance, in rice, the histone deacetylase OsHDA706 has been shown to reduce the ubiquitination level of the key enzyme OsLOX14 in the jasmonic acid (JA) biosynthesis pathway by deacetylating specific lysine residues (K204, K216, K310, and K317). This action prevents OsLOX14 from being degraded by the 26S proteasome, enhancing its stability and contributing to the accumulation of JA, which in turn improves the plant's broad-spectrum antiviral defense. However, the precise mechanism by which OsHDA706 deacetylates OsLOX14 to reduce its ubiquitination level remains to be elucidated (Yang et al. 2024). Similarly, another study in rice has identified that the histone deacetylase OsHDA716 can bind to and reduce the acetylation level at specific lysine residues (K263, K281, and K294) of the transcription factor OsbZIP46. This reduction in acetylation promotes the ubiquitination and subsequent degradation of OsbZIP46 by the 26S proteasome complex, which negatively impacts the cold tolerance of rice (Sun et al. 2024).

In Arabidopsis, AtMBP-1, a transcriptional repressor involved in stress tolerance and glycolytic gene expression, is subject to LysAc, making it susceptible to proteasome degradation. However, the deacetylase AtSRT1 can remove this acetylation, significantly enhancing AtMBP-1's stability in vivo (Liu et al. 2017). Additionally, OsHDA714 has been found to interact with ribosomal proteins, reducing their acetylation levels and thus preventing modifications by ubiquitination complexes. This action increases the abundance of ribosomal proteins and facilitates the translation process, thereby controlling protein homeostasis and coordinating stress responses, metabolism, and ribosome function (Xu et al. 2021) (Fig. 1C). These findings indicate that the modulation of acetylation levels on different proteins can either be beneficial or detrimental to ubiquitination, impacting protein stability and potentially influencing protein synthesis.

Regulation of protein–protein and protein–DNA interactions

Acetylation of non-histone proteins plays a crucial role in modulating their interactions with other protein factors (Fig. 1D). In Arabidopsis, the NINJA-TPL complex serves as a pivotal negative regulator within JA signaling pathways. HDA6-mediated acetylation of TPL diminishes its interaction with the NINJA protein, whereas acetylation by GCN5 counteracts this effect, restoring TPL's binding capacity. This dynamic regulation is essential for orchestrating a genome-wide transcriptional program that underpins plant immunity and adaptive growth (An et al. 2022). In rice, the interaction between OsGSK2 and OsBZR1 leads to an increase in OsBZR1's phosphorylation levels within the nucleus, promoting its subsequent ubiquitination and degradation. Conversely, deacetylation of OsGSK2 by OsHDAC1 precludes its binding to OsBZR1 (Hou et al. 2022). This finding uncovers a dual mechanism by which OsHDAC1 not only suppresses enzymatic activity but also modulates the binding capabilities of this protein. Similarly, protein acetylation can influence protein–DNA interactions (Fig. 1E). In Arabidopsis has demonstrated that the deacetylase HDA9 interacts with the transcription factor WRKY53, deacetylating it and thereby inhibiting its binding to the W-Box element. This results in a reduced trans-activation function, affecting the expression of downstream target genes such as WRKY13, WRKY15, WRKY18, WRKY22, WRKY29, and WRKY62, and also activating WRKY6 and WRKY42, which in turn repress Arabidopsis's tolerance to salt stress (Zheng et al. 2020). Furthermore, the deacetylation of OsbZIP46, which is involved in the regulation of cold tolerance, is controlled by OsHDA716. This modification not only mediates the ubiquitination and subsequent degradation of OsbZIP46 but also impacts its DNA binding capacity due to the acetylation site located within the DNA binding domain. Consequently, this leads to a decrease in its transcriptional activity (Sun et al. 2024).

Regulation of subcellular localization

Numerous studies of plant proteins have shown that that post-translational modifications, such as phosphorylation and ubiquitination, can significantly influence the intracellular distribution of proteins. These modifications can enhance nuclear and cytoplasmic localization, facilitate the release of plasma membrane proteins into the cell interior, and regulate the export of cytoplasmic proteins (Zhang and Zeng 2020). Recent studies have highlighted the impact of acetylation on protein localization within plant cells. For instance, the histone deacetyltransferase FolSir2 mediates the deacetylation of FolSrpk1, reducing its acetylation level and causing its dissociation from the cytoplasmic FolAha1 protein. This process leads to the nuclear translocation of FolSrpk1, uncovering a conserved mechanism where FolSir2-mediated cytoplasmic protein deacetylation plays a role in plant-fungal pathogenicity (Zhang et al. 2023, 2024). Additionally, the protein FolSvp1 directly binds to and translocates the tomato pathogenesis-related protein SlPR1 from the apoplast, the space outside the plasma membrane, to the host nucleus. This translocation is facilitated by the nuclear localization signal present in FolSvp1. The activity of FolSvp1 is contingent upon covalent acetylation modification, which is essential for its full virulence in host tomato tissues. This acetylation is catalyzed by the lysine acetyltransferase FolArd1 prior to the secretion of FolSvp1 (Li et al. 2022). These findings suggest that acetylation not only modulates the subcellular localization of proteins but also has a profound influence on the disease resistance mechanisms in plants (Fig. 1F and Table 1).

Crosstalk between acetylation and other PTMs

Non-histone proteins are often subjected to multiple PTMs, which can interact in a process known as PTM crosstalk (Soufi et al. 2012). The interaction between LysAc and other PTMs facilitates the integration of various biological signals to regulate life processes under diverse conditions. In this context, the focus is on the crosstalk between LysAc and two other PTMs: succinylation and phosphorylation (Fig. 1G).

Acetyl-CoA and succinyl-CoA, key metabolites in cellular energy production, are associated with enzymes that are modified by both LysAc and succinylation, indicating a functional link between these two PTMs (He et al. 2016). In rice, 699 acetylated sites across 389 proteins and 665 succinylated sites across 261 proteins were identified, with 133 sites on 78 proteins being dually modified. These modifications are crucial for seed germination and are predominantly found in ribosomal and proteasome proteins, hinting at roles in protein synthesis, repair, and degradation post-infection (Zhou et al. 2018).

Phosphorylation is another PTM that interacts with LysAc. In Arabidopsis, the diurnal changes in acetylated and phosphorylated proteins regulate circadian rhythms and light responses, with acetylation mainly affecting metabolic and stress response proteins, and phosphorylation impacting RNA processing and cell cycle proteins (Uhrig et al. 2017, 2019). A total of 909 acetylated and 2549 phosphorylated proteins were identified, with 134 proteins involved in core cellular processes showing dual modifications, suggesting a synergistic control over these processes (Uhrig et al. 2019). In wheat, both

Table 1 List of HDACs/HATs: targets, mechanisms, and functions in non-histone proteins

Species	Gene name	HDAC/HAT	Accession no.	Target	Mechanism	Function	References
At	HDA6	HDAC	At5G63110	BIN2	Regulation of enzyme activity	Influent plant development	Hao et al. (2016)
	AtSRT1	HDAC	At5G55760	AtMBP-1	Regulation of protein degradation	Improve stress tolerance	Liu et al. (2017)
	HDA6	HDAC	At5G63110	TPL	Regulation of protein-protein interactions	Improve JA-responsive gene expression	An et al. (2022)
	GCN5	HAT	At3G54610			Impress JA-responsive gene expression	
	HDA9	HDAC	At3G44680	WRKY53		Repress Arabidopsis salt stress-tolerance	Zheng et al. (2020)
Os	OsHDAC1	HDAC	Os06g38470	OsGSK2	Regulation of enzyme activity Regulation of protein-protein interactions	Control lateral root formation	Hou et al. (2022)
	OsHDA706	HDAC	Os06g37420	OsLOX14	Regulation of protein degradation	Improve broad-spectrum rice antiviral defense	Yang et al. (2024)
	OsHDA714	HDAC	Os12g08220	Ribosomal proteins		Coordinate stress, metabolism and ribosome function	Xu et al. (2021)
	OsHDA716	HDAC	Os05g36930	OsbZIP46	Regulation of protein-protein interactions	Represse cold tolerance of rice	Sun et al. (2024)
Fol	FolSir2	HDAC	Undefined	FolSrpk1	Regulation of enzyme activity	Involved in plant-fungal pathogenicity	Zhang et al. (2023, 2024)
				FolGSK3	Regulation of subcellular localization	Promote pathogenic fungal infection	Zhang et al. (2023)
	FolArd1	HAT	Undefined	FolSvp1		Influent virulence	Li et al. (2022)

At: *Arabidopsis thaliana*, Os: *Oryza sativa*, Fol: *Fusarium oxysporum* f. sp. *lycopersici*

LysAc and phosphorylation are present in two key enzymes including sucrose synthase (SuSy) and ADP glucose pyrophosphorylase (AGPase) for starch biosynthesis, indicating a role in yield formation under drought stress (Zhu et al. 2018). In rice anthers, 189 proteins with dual lysine acetylation and phosphorylation modifications were identified, with 103 preferentially expressed in meiocytes, highlighting the regulation of the diurnal cycle, stress responses, and pollen development (Li et al. 2018).

To sum up, the crosstalk between LysAc and succinylation or phosphorylation, is widespread in plants and is integral to metabolic processes, seed development, stress responses, and the diurnal cycle (Xia et al. 2021). These interactions likely play a coordinated role in the regulation of the plant life cycle.

Regulation of plant phenotypes and biological functions by HATs and HDACs

Extensive research has shown HATs and HDACs are involved in various plant developmental processes, including root growth, leaf development, flowering time regulation, and seed germination by regulating the transcription of target genes through the acetylation or deacetylation of histones. In addition to histones, lysine acetylation and deacetylation also play roles in the function of certain non-histone proteins in plants, as previously discussed. This section further elaborates on the functions of HATs and

HDACs and explores their potential in modifying non-histone proteins (Supplementary Table 1).

Class I type-HDACs

In Arabidopsis, there are six Class I type-HDACs, including HDA6, HDA9, HDA19, HDA7, HDA17, and HDA10. Among these, HDA6, HDA19, and HDA9 have been extensively characterized and studied. For instance, HDA6 has been reported to regulate leaf development, flowering, and salt stress response by repressing *KNOX*, *FLC*, *FT*, and *ABIs*, respectively (Yu et al. 2011, 2017; Luo et al. 2012a, b). Interestingly, HDA6 also targets the non-histone protein BIN2, which is involved in flowering and salt stress response (Kim et al. 2023; Ju et al. 2023; Zhu et al. 2023), suggesting that HDA6 can control these traits through BIN2 as well. Similarly, HDA9 promotes leaf development and flowering, enhances salt tolerance, and weakens heat tolerance by repressing *GI*, *HsfA2*, and *WRKY33*, respectively (Yu et al. 2011; Suzuki et al. 2018; Park et al. 2019; Mayer et al. 2019; Niu et al. 2022; Yang et al. 2023). Recently, another non-histone target, WRKY53, was reported to function in regulating leaf development (Andrade Galan et al. 2024; Wang et al. 2023a, b), suggesting another potential connection between WRKY53 and HDA9 in leaf development.

HDA19, another widely studied Arabidopsis histone deacetylase, is reported to be involved in root and flower development, seed maturation, dormancy, oxidative stress tolerance, and pathogen defense (Niu et al. 2019; Ning et al. 2019; Chen et al. 2019; Gao et al. 2015; Zhou et al. 2013; Wang et al. 2013; Krogan et al. 2012; Zheng et al. 2023). A large number of downstream deacetylation genes involved in these phenotypes have been identified. However, the role of HDA9 in non-histone proteins remains unclear.

In addition, HDA7 has been identified as being required for female gametophyte and embryo development (Cigliano et al. 2013). HDA6, HDA9, and HDA19 were reported to be localized in the nucleus (Alinsug et al. 2012), suggesting that Class I members of HDACs might jointly regulate phenotypes in the nucleus by modifying both histones and non-histones.

Unlike Arabidopsis Class I members, which are located in the nucleus, rice Class I members HDA701, HDA702, and HDA710 are found in both the nucleus and cytoplasm (Hou et al. 2024; Ullah et al. 2020). Functional studies have found that HDA701, HDA702, and HDA705 negatively regulate rice broad-spectrum disease resistance, and HDA710 negatively regulates salt tolerance by mediating histone modification levels (Chen et al. 2021, 2022; Hou et al. 2022; Zhao et al. 2016; Ullah et al. 2020). Currently, the non-histone target OsGSK2 of HDA702, which controls root growth, has been identified in both the nucleus and cytoplasm (Hou et al. 2022). OsGSK2 also controls disease resistance (He et al. 2020; Meng et al. 2024), suggesting that HDA702 might regulate rice disease resistance through the GSK2 pathway. However, the non-histone targets of HDA701, HDA705, and HDA710 in the cytoplasm remain unclear. Furthermore, HDA703 is located in the nucleus and has been found to regulate rice growth and heading date through repression of Ghd7 (Wang et al. 2023a, b, 2021). The functions of other Class I members, including HDA707 and HDA709, have not yet been revealed.

Class II-type HDACs

Class II members of HDACs including HDA5, HDA8, and HDA14 have been localized to the cytoplasm (Alinsug et al. 2012), while HDA15 and HDA18 exhibit localization in both the nucleus and cytoplasm (Alinsug et al. 2012; Liu et al. 2013), implying that Class II-HDACs may act as key regulators of non-histone protein modifications. In line with this hypothesis, HDA14 has been found to deacetylate tubulin (Tran et al. 2012). Similarly, HDA5 has been shown to deacetylate the stress-responsive transcription factor GT2L and the dehydration-related protein ERD7, thereby regulating the response to salt stress (Tilak et al. 2023). Furthermore, it has been observed that white light can facilitate the translocation of HDA15 from the cytoplasm into the nucleus, where it represses hypocotyl growth by modulating histone acetylation (Liu et al. 2013; Zhao et al. 2019). When located in the nucleus, HDA15 can repress leaf senescence, flowering, and enhance resistance to salt stress through the action of WRKYs, LOX2, LARP1C, and NCED3 (Huang et al. 2022; Truong et al. 2021; Lee and Seo 2019). HDA18 is known to influence Arabidopsis root development by modulating histone acetylation at four kinase genes (Liu et al. 2013). The non-histone targets of HDA8, HDA15, and HDA18 remain unidentified.

In rice, there are five Class II-type HDAC members, including HDA704, HDA712, HDA713, HDA714, and HDA716. HDA714 has been found in the cytoplasm, and HDA716, which is localized in the nucleus, has been shown to deacetylate RPS6 and bZIP46 (Sun et al. 2024). Additionally, HDA704 has been reported to enhance salt tolerance by reducing the acetylation level of ABI5 (Guo et al. 2023). The non-histone targets of HDA712 and HDA713, however, remain unclear.

Class III (SIR2) and class IV-type HDACs

In humans, previous reports have showed that seven SIR2 HDACs require NAD$^+$ as a cofactor for their enzymatic activity, and these members were located in the nucleolus, cytosol, and mitochondria (Seto and Yoshida 2014). This multi-pattern localization reveals that they function in deacetylating numerous non-histone and histone proteins (Seto and Yoshida 2014). Unlike humans, only two SIR2-type HDACs have been identified in Arabidopsis and rice (Hou et al. 2021). Among them, Arabidopsis SRT1 and SRT2 can control the development of hypocotyls in the nucleus through histone modification pathways (Zhang et al. 2018). Similarly, rice SRT701 is a nuclear-localized protein (Chung et al. 2009), which can control rice seed development and leaf senescence through the histone modification pathway (Zhang et al. 2016). However, the non-histone targets within the nucleus of AtSRT1, AtSRT2, and OsSRT701 remain unknown.

Unlike AtSRT1, AtSRT2, and OsSRT701, a previous report showed that SRT702 is a chloroplast-localized protein (Chung et al. 2009), implying that it serves as the main regulator of non-histone modifications. However, recent studies have found that SRT702 is also localized in the nucleus and can negatively regulate rice broad-spectrum disease resistance through histone modification pathways (Chen et al. 2024), suggesting that SRT702 is functionally similar to human SIRTs. The role of SRT702 in non-histone protein deacetylation requires further identification.

HD2-type HDACs

Unlike mammalian cells and yeast, HD2-type HDACs are uniquely identified in plants. In Arabidopsis, there are four HD2 members: HD2A, HD2B, HD2C, and HD2D, which are predominantly located in the nucleolus (Zhou et al. 2004). Multiple studies have demonstrated that HD2A, HD2B, and HD2C regulate the balance between embryonic, seed, and root development, as well as drought stress, by controlling rRNA processing (Pontes et al. 2007; Kim et al. 2014; Chen et al. 2018; Luo et al. 2022; Tahir and Tian 2021; Han et al. 2023a, b). This suggests that HD2-type HDACs may play crucial roles in rRNA production. However, in contrast to Arabidopsis HD2-type HDACs, the rice HDT701 has been found to be involved in flowering and resistance to fungal and bacterial pathogens by modulating the expression of OsIDS1 or pathogenesis-related proteins (PRs) (Ding et al. 2012; Cho et al. 2018; Li et al. 2021).

GNAT, MYST, CBP and TAF250-type HATs

Although research on plant HATs has been less extensive compared to HDACs, recent studies have shed more light on their roles. For instance, the Arabidopsis AtGCN5, located in the nucleus, modulates JA signaling to mediate plant defense through reversible acetylation of TOPLESS (An et al. 2022). Additionally, AtGCN5 is implicated in regulating salicylic acid (SA) homeostasis by adjusting histone acetylation levels (Kim et al. 2020). Given that SA is a key player in bolstering plant disease resistance, AtGCN5 is likely to exert control over this resistance via both histone and non-histone protein pathways. Similarly, the rice GCN5 has been identified to influence crown root development by deacetylating non-histone ADA2 and histone H3 (Zhou et al. 2017; Yu et al. 2024). Furthermore, Arabidopsis HATs HAG3, HAC1, and HAF1 have been found to impact UV-B responses negatively by regulating the expression of DNA repair enzymes and sunscreen content (Fina and Casati 2015; Fina et al. 2017). HAC1 also promotes leaf senescence and modulates the expression of ERF022 (Hinckley et al. 2019). The specific functions of other HATs and their non-histone targets remain largely unknown. Apart from the rice GCN5, the roles of HATs are yet to be fully elucidated. However, subcellular localization studies (Liu et al. 2012), have indicated that OsHAC701, OsHAG703, and OsHAG704 are present in both the nucleus and cytosol, suggesting a potential role for these HATs in non-histone acetylation within the cytosol.

Future perspectives

The exploration of acetylation modifications in non-histone proteins has significantly broadened our comprehension of lysine acetylation. This modification is not confined to the histones within the nucleus; it also plays a more extensive role in the regulation of non-histone proteins across various metabolic pathways and functions within subcellular organelles such as chloroplasts and mitochondria, as well as in the cytoplasm. The acetylation of non-histone proteins modulates their functionality, which in turn influences plant growth, development, and stress responses.

While proteomic analyses have shed light on the subcellular distribution of acetylated proteins and identified numerous lysine acetylation sites through gene ontology (GO) term annotations (Xiong et al. 2016), the specific roles of various proteins acetylated by HATs are still largely unexplored. The mechanisms by which individual HATs and HDACs select their targets remain largely unknown. A key question is what guides the specificity of HATs or HDACs towards non-histone proteins. Answering these questions will likely necessitate a biochemical characterization of enzyme complexes and their subcellular localization. It is worth noting that, although HDACs are primarily nuclear, some, such as HDAC6 (Hubbert et al. 2002), have also been detected in the cytoplasm.

The interaction mechanisms of these PTMs remain unclear due to the limitations of current detection technologies. There is an urgent need to enhance the temporal and spatial resolution of mass spectrometry-based assays to enable high-throughput detection of multiple PTMs. Enzyme-catalyzed proximity labeling is an emerging method for studying the spatial and interaction characteristics of proteins within living cells. By expressing TurboID in cells, fused with target proteins of interest, the enzyme catalyzes the formation of biotin-5’-AMP from biotin, facilitated by ATP and biotin. This compound diffuses from the active site and binds to lysines of nearby endogenous proteins, leading to biotinylation of these proteins and thus facilitating the identification of neighboring proteins in physical space (Branon et al. 2018). This technique may prove valuable for large-scale identification of PTM crosstalk in non-histone proteins.

Analyzing molecular and genetic evidence of the interactions between multiple PTMs will yield new insights into the regulatory mechanisms governing plant growth, development, and adaptation to environmental changes. Elucidating the specific pathways of acetylation regulation in non-histone proteins and the crosstalk among PTMs opens up new avenues for genetic improvement and plant breeding. Techniques such as site-directed mutagenesis or CRISPR/Cas technology could be employed to modify lysine acetylation sites, altering enzyme activity, and potentially enhancing or reducing phenotypic plasticity. This approach could lead to the emergence of new plant variants, although the establishment of such modifications still requires further research and validation.

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Declarations

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