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Chromatin Regulation in the Response of Ethylene: Nuclear Events in Ethylene Signaling

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Abstract

Plant hormones, produced in response to environmental stimuli, regulate almost all aspects of plant growth and development. Ethylene is a gaseous plant hormone that plays pleotropic roles in plant growth, plant development, fruit ripening, stress responses, and pathogen defenses. After decades of research, the key components of ethylene signaling have been identified and characterized. Although the molecular mechanisms of the sensing of ethylene signal and the transduction of ethylene signaling have been studied extensively, how chromatin influences ethylene signaling and ethylene response is a new area of research. This review describes the current understanding of how chromatin modifications, specifically histone acetylation, regulate ethylene signaling and the ethylene response.

Keywords

chromatin; ethylene response; ethylene signaling; histone acetylation; transcription

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Conflict of Interest

The authors declare no conflict of interest.

1. Introduction to Ethylene Signaling

Ethylene, a gaseous plant hormone, is important for a myriad of physiological and developmental processes including seed germination, plant growth, fruit ripening, organ abscission, and senescence. It is also involved in the responses to stresses such as drought, cold, flooding, and infection.[1,2] The common aquatic ancestor of plants, which existed about 450 million years ago, possessed an ethylene signaling pathway that was similar to that of modern *Arabidopsis*.[3] The typical "triple response phenotype" of *Arabidopsis* seedlings grown in the dark and treated with ethylene has enabled scientists to identify genes that when mutated cause hyper- and hyposensitive responses to ethylene.[4–6]

A model of ethylene signaling pathway has been established based on decades of genetic and molecular biology research (Figure 1). In brief, ethylene is perceived by five receptors anchored to the endoplasmic reticulum (ER): ethylene response1 (ETR1), ETR2, ethylene response sensor1 (ERS1), ERS2, and ethylene insensitive4 (EIN4).[7–10] A copper transporter responsive-to-antagonist1 (RAN1) is required for both ethylene binding and the function of receptors.[11] reversion-to-ethylene sensitivity1 (RTE1) colocalizes with ETR1 to promote its function.[12] Upon the perception of ethylene, the functions of receptors and of the downstream factor constitutive triple response1 (CTR1) are repressed,[13] activating EIN2, which is another ER anchored protein.[14] The activated EIN2 transduces the ethylene signal to two main downstream transcription factors EIN3 and ein3-like1 (EIL1).[15] The activated EIN3 and EIL1 bind to the promoter regions of genes encoding downstream factors to regulate their expression.[16] In the absence of ethylene, EIN2 protein and EIN3 protein levels are regulated by F-box proteins.[17] Also, upon perception of ethylene, the cleaved EIN2 carboxy-terminal (C-terminal) domain translocates to the cytosol and binds to mRNAs that encode ein3-binding f box protein1 (EBF1) and EBF2. This complex moves to the processing body (P-body) where *EBF1* and *EBF2* are degraded by ethylene insensitive5 (EIN5), which is a $5'\rightarrow3'$ exoribonuclease that degrades these mRNAs in the presence of ethylene.[6,18–20] As EBF1 and EBF2 target EIN3 and EIL1 for degradation in the nucleus, inhibition of translation of *EBF1* and *EBF2* stimulate the ethylene response.

Among the many important factors that are involved in ethylene signaling, EIN2 is the key mediator of the signal from the ER to the nucleus. The *Arabidopsis* knockout *ein2* mutant shows complete insensitivity in all examined ethylene-regulated responses.[14] The *EIN2* gene encodes a 1294-amino acid protein, and EIN2 is localized to the ER membrane in the absence of ethylene. Its amino terminus (N-terminus) has a predicted 12-fold hydrophobic transmembrane domain with sequence similarity to the conserved NRAMP family of metal ion transporters,[14] although as of now, no metal transport activity has been shown for EIN2.[21] The C-terminus of EIN2 has a hydrophilic domain, and overexpression of the C-terminal domain activates the ethylene responses in both etiolated seedlings and light-grown *Arabidopsis* plants.[14,22]

Both genetic and molecular studies have demonstrated that EIN3 and EIL1 are the positive regulators that are necessary and sufficient for the ethylene response.[15,17,23] In the absence of nuclear-localized EIN3, plants are insensitive to ethylene both at the morphological and molecular levels.[15,17] The EIN3 binding motif was identified after analysis of the genes

such as *ERF1* and *EDF2* that are highly upregulated by ethylene followed by validation using an electrophoresis mobility shift assay (EMSA).[16,24–29] Using the EMSA assay, EIN3 was shown to form a homodimer in the presence of DNA in vitro.[16] A number of transcription factors form homodimers or heterodimers, which increases specificity and affinity for certain DNA motifs. Whether dimerization is necessary for function of EIN3 in vivo is currently unknown.

2. Histone Acetylation in the Ethylene Response

In eukaryotes, transcription factor binding is mainly determined by the state of the genome packaging with specific structural proteins, mainly histones. A histone modification is a covalent post-translational modification (PTM) to histone proteins which includes methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation. The PTMs made to histones can impact gene expression by altering chromatin structure or recruiting histone modifiers. The histone modifications involved in plant hormone signaling have been reviewed recently by Yamamuro et al.[30] The studies of chromatin regulation in ethylene signaling have focused primarily on histone acetylation regulation. In *Arabidopsis,* there are 12 histone acetyl transferases (HATs) classified into four families.[31] The HATs that are involved in particular plant hormone responses are listed in Table 1.

A few studies have focused specifically on HATs that are involved in the ethylene response. For example, in *Arabidopsis*, GCN5 and CLV1 act together to repress the ethylene-induced genes expression.[34] The *gcn5clv1* mutant displays a hypersensitive ethylene response phenotype.[34] The acetylation of H3K9 and H3K14 in the promoter regions of ethylene responsive genes are elevated in the *gcn5clv1* mutant, and the elevation is associated with the upregulation of expression of these genes.[34] Thus, there is an anticorrelation between histone acetylation levels as well as expression of ethylene-regulated genes and the function of histone acetyltransferase GCN5 and CLV1. HAC1 and HAC5, from the HAC family, which are homologs of CBP/p300 from mammals,[31,71] also repress ethylene-regulated genes. The *hac1hac5* double mutant has a constitutive triple response phenotype: root and hypocotyl elongation, an exaggerated apical hook, and a thickening of the hypocotyls.[44] It was expected that gene expression would be downregulated in the *hac1hac5* double mutant due to the reduction of histone acetylation levels; however, the downstream ethylene responsive genes are elevated in *hac1hac5* double mutant,[44] suggesting an indirect regulation of ethylene responsive genes by HAC1 and HAC5.

In addition to HATs, histone deacetylases (HDACs) are involved in responses of plants to hormones as summarized in Table 2. Several HDACs are implicated in the ethylene response. For example, levels of HDA19 are specifically elevated by ethylene treatment.[45] Interestingly, the expression of ethylene responsive gene *ERF1* is increased in *35S:HDA19* transgenic plants, however, the levels of histone H3 acetylation in *ERF1* gene are decreased in *35S*:*HDA19* transgenic plants, suggesting that HDA19 indirectly influences *ERF1* gene expression. In general, acetylation neutralizes the positive charges of lysine residues and decreases the interaction between histone and DNA, leading to a more relaxed chromatin structure, which is associated with transcriptional activation. In contrast, deacetylation induces a compact chromatin structure, which is associated with transcriptional repression.

[72–74] Notably, the studies mentioned above revealed anticorrelations between HAT or HDAC activity and histone acetylation levels or expression of the genes regulated by ethylene. This anticorrelation strongly suggests that either the effects of HATs and HDACs on expression of ethylene-regulated genes are indirect or that other regulatory mechanisms are involved.

Recent studies from our lab provide evidence that levels of H3K14Ac and H3K23Ac, but not the classical histone acetylation marks H3K9Ac, H3K18Ac, and H3K27Ac, in the promoters of ethylene-regulated genes are positively correlated with gene expression.[75,76] Interestingly, even though the levels of H3K9Ac are not regulated by ethylene, the levels of H3K9Ac in the promoters of ethylene upregulated genes are higher than in promoters of ethylene downregulated genes both with and without ethylene treatment.[75,76] Presumably, H3K9Ac is a pre-existing mark that labels genes regulated by ethylene, whereas the elevation of H3K14Ac and H3K23Ac is required for gene activation. In a recent study from our lab demonstrated that a low level of H3K9Ac over ethylene-repressed genes leads to a downregulation of gene expression. Two HDACs, SRT1 and SRT2, partially mediate the transcriptional repression by regulating the levels of H3K9 acetylation during ethylene signaling, and evidence suggests that these are direct regulators of the ethylene response.[70]

It is now well established that many of the effects exerted by transcription factors in eukaryotes are mediated through interactions with coregulators that modify the chromatin state, resulting in a more open (in case of activation) or closed conformation (in case of repression). These coactivators typically consist of (or recruit) chromatin modifier complexes that either displace or evict nucleosomes or covalently modify histones to loosen their interactions with DNA. The discovery of the regulation of histone acetylation in ethylene response is presumably the tip of an iceberg of chromatin regulation necessary for the responses to hormones such as ethylene.

3. EIN2 Mediates the Interplay between Ethylene Signaling and Histone Acetylation

The work of Zhang et al. revealed for the first time that H3K14Ac and H3K23Ac are positively associated with gene expression in response to ethylene and that the ethylene-induced change of histone acetylation is EIN2 dependent.[75] By ectopically expressing the EIN2 C-terminus in an *ein2–5* mutant using the CRISPR/dCas9 system, Zhang et al. demonstrated that the EIN2 C-terminal domain directly regulates histone acetylation.[77] However, the EIN2 C-terminal domain has no previously characterized histone or a DNA binding domain. Furthermore, no binding of EIN2 to DNA was detected by standard chromatin immunoprecipitation coupled with quantitative PCR (ChIP-qPCR) or ChIP-seq protocols (unpublished data), suggesting that EIN2 does not bind DNA or histones directly. The question of how the EIN2 C-terminal domain regulates histone acetylation in response to ethylene was partially answered by the identification of ein2 nuclear associated protein1 (ENAP1), a histone binding protein that interacts with the EIN2 C-terminus as shown using ChIP–reChIP experiments.[77] In the presence of ethylene, the EIN2 C-terminal fragment is translocated into the nucleus where it interacts with ENAP1. This complex associates with

chromatin over ethylene-responsive genes to regulate acetylation of H3K14 and H3K23, leading to an EIN3-dependent transcriptional regulation (Figure 1).

At the molecular level, the mechanisms involving EIN2, ENAP1, and EIN3 in the regulation of histone acetylation during the ethylene response remain unclear. Specifically, how the target loci for histone acetylation are determined, how acetylation at different lysines is coordinated to regulate gene expression in the ethylene response, and whether other histone modifications are involved are unknown. Moreover, the biochemical functions of the full-length EIN2 and the EIN2 C-terminus are unknown. One possibility is that the EIN2 C-terminal domain is itself a HAT; however, no HAT activity of EIN2 C-terminus has been detected (unpublished results from the Qiao lab). Alternatively, the C-terminal fragment of EIN2 may act as a scaffolding protein to recruit and assemble histone modification complexes in the presence of ethylene. If it is the case, identification of HAT or HDAC that functions in cooperation with the EIN2 C-terminal domain with a positive correlation would validate this assumption.

4. Conclusions

Ethylene is important for plant development and stress responses, and understanding this response is relevant due to the function of this hormone in agricultural crops during unfavorable environmental conditions. As a key component in the ethylene signaling pathway, EIN2 mediates the connection between upstream receptors bound to the ER membrane to the downstream factors in the nucleus and P-body that are involved in translational regulation of ethylene-responsive genes. The discovery of the importance of the C-terminal domain of EIN2 in the ethylene response revealed for the first time a direct connection between ethylene signaling and chromatin regulation. Although it is clear that EIN2 integrates into EIN3-dependent transcriptional regulation, the detailed molecular mechanism of how EIN2 transduces ethylene signaling to mediate histone acetylation is still largely unknown. Characterization of the biochemical function of the EIN2 C-terminus and identification of the HAT or HDAC involved are priorities. Many levels of regulation are involved in establishment of chromatin structure; histone acetylation is just one of these. Further study to establish whether other chromatin modifications are involved in mediating ethylene signaling and whether the higher order structure of chromatin is involved are of interest.

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Biography

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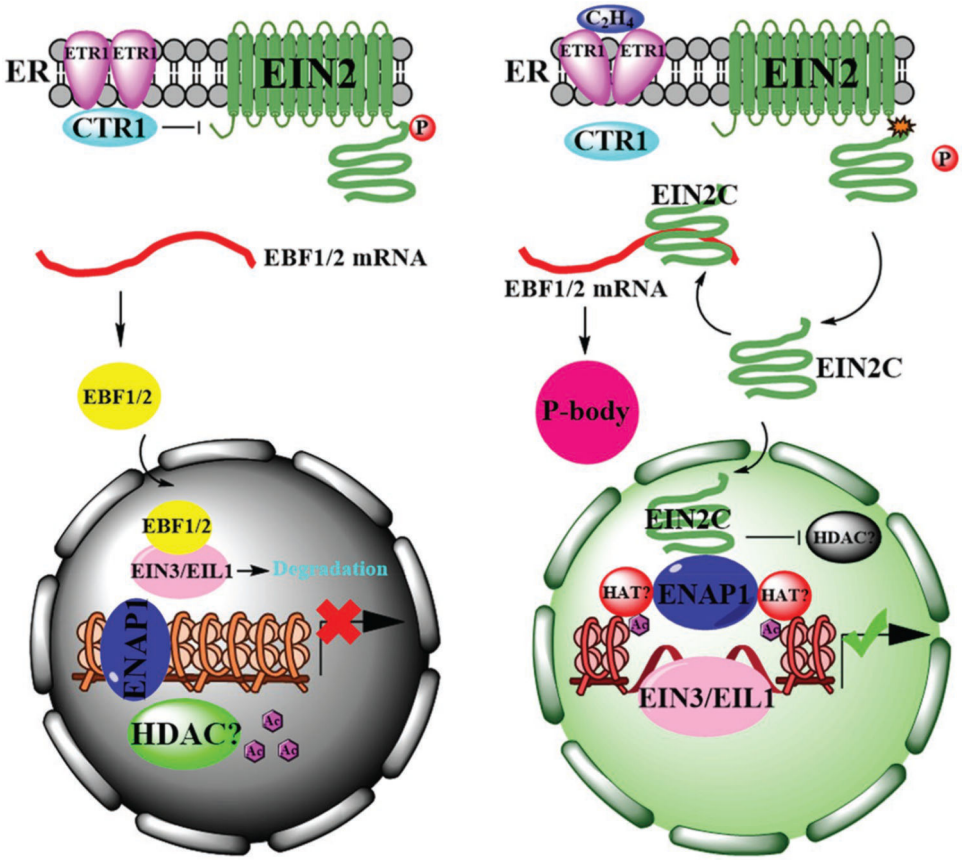

Figure 1.

A proposed model of how EIN2 controls signal transduction in response to ethylene. In the absence of ethylene (left panel), EIN2 is localized on the ER membrane and is constitutively phosphorylated by CTR1.[78] EBF1 and EBF2 proteins target EIN3 and EIL1 for degradation in the nucleus.[18,19] ENAP1 docks on chromatin and histone proteins are deacetylated potentially by HDACs in the nucleus, resulting in suppression of ethylene responses.[75] Upon the perception of ethylene (right panel), the activities of the receptor ETR1 and of CTR1 are suppressed, resulting in dephosphorylation of EIN2,[13,78] which leads to proteolytic cleavage and release of the EIN2 C-terminal domain (EIN2-C), which rapidly translocates to the nucleus and to the cytosol.[6,20,22] In the nucleus, EIN2-C interacts with ENAP1 and this complex likely recruits an unknown HAT to acetylate specific histone residues.[75] Simultaneously, the activities of HDACs are inhibited, leading to a relax chromatin status at ethylene-responsive loci, resulting in EIN3/EIL1-dependent transcription regulation.[70] In the cytosol, EIN2-C binds to the 3′ untranslated regions of *EBF1* and *EBF2* and targets these mRNAs to the P-body inhibiting the translation of EBF1 and EBF2.[6,20] This in turn promotes the accumulation of EIN3 and EIL1. Abbreviations: P, phosphorylation; Ac, acetyl group; C_2H_4, ethylene.

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Table 1.

HATs that are involved in plant hormone responses.

HAT family	Protein name	Species	Physical interacting partners	Plant hormone response[a)]	Associated histone acetylation	Refs.
GNAT	GCN5	*Arabidopsis*	N/A	Represses the ABA response	N/A	[32]
			PRZ1	Positively regulate gene expression in response to Auxin	H3K9, H3K14, H3K27, H4K8, and H4K12	[33–37]
			N/A[b)]	together with CLV1 to suppress the ethylene response	H3K9 and H3K14	[34]
	ELP3	*Arabidopsis*	ELP1, ELP2, ELP4, and ELP6	Represses the ABA response	N/A	[38–40]
			N/A	Represses the Auxin response	H3K14	[38]
			N/A	Represses the ethylene response	N/A	[38]
			N/A	Represses the JA response	N/A	[38]
	OsHAG702	Rice	N/A	*OsHAG702* expression is elevated by ABA	N/A	[41]
	OsHAG703	Rice	N/A	*OsHAG703* expression is elevated by ABA	N/A	[41]
	HvGCN5	Barley	N/A	*HvGCN5* expression is elevated by ABA	N/A	[42]
	HvELP3	Barley	N/A	*HvELP3* expression is elevated by ABA	N/A	[42]
MYST	OsHAM701	Rice	N/A	*OsHAM701* expression is elevated by ABA	N/A	[41]
	HvMYST	Barley	N/A	*OHvMYST* expression is elevated by ABA	N/A	[42]
HAC	HAC1	*Arabidopsis*	N/A	Represses the GA response	N/A	[43]
			N/A	Represses the ethylene response	N/A	[44]
	HAC4	*Arabidopsis*	N/A	Represses the ethylene response	N/A	[44]
	HAC5	*Arabidopsis*	N/A	Represses the ethylene response	N/A	[44]
	OsHAC701	Rice	N/A	*OsHAC701* expression is elevated by ABA	N/A	[41]
	OsHAC703	Rice	N/A	*OsHAC703* expression is elevated by ABA	N/A	[41]
			N/A	*OsHAC703* expression is reduced by SA	N/A	[41]
	OsHAC704	Rice	N/A	*OsHAC704* expression is reduced by SA	N/A	[41]

[a)] ABA, abscisic acid; JA, jasmonic acid; GA, gibberellic acid; SA, salicylic acid

[b)] N/A, not available.

Table 2.

HDACs that are involved in plant hormone responses.

HDAC family	Protein name	Species	Physical interacting partners	Plant hormone response[a)]	Histone acetylation sites	Refs.
RPD3/ HDA1	HDA6	*Arabidopsis*	JAZ1, JAZ3, and JAZ9	Represses the JA response	N/A[b)]	[45–47]
			EIN3/EIL1	Represses the ethylene response	N/A	[47]
			HDC1	Repress the ABA response	H3K9 and H3K14	[48,49]
			HD2C	Represses the ABA response	N/A	[50]
			BIN2	Promotes the BR response	N/A	[51]
	HDA9	*Arabidopsis*	N/A	Auxin signaling is influenced by HDA9	N/A	[52]
	HDA19	*Arabidopsis*	N/A	JA	N/A	[45]
			SNL1 and SNL2	Represses the ethylene response	H3K9, H3K14, and H3K18	[45,53,54]
			SAP18, ERF3, and ERF4	AtSAP18, HDA19, and ERF3 act together to repress transcription of genes involved in ethylene response	N/A	[55]
			SNL1 and SNL2	Represses ethylene signaling to establish seed dormancy	H3K9 and H3K18	[56]
			WRKY38 and WRKY62	Promotes SA-mediated disease resistance	H3K9	[57,58]
			SIN3	Represses the ABA response	N/A	[59,60]
			N/A	Represses the ABA response	N/A	[61]
			HDC1	Represses the ABA response	H3K9 and H3K14	[49]
			MSI1	Represses the ABA response	H3K9	[54]
			SNL1 and SNL2	Responses to ABA	H3K9, H3K14 and H3K18	[53,54]
			SNL1 and SNL2	Promotes ABA signaling to establish seed dormancy	H3K9 and H3K18	[56]
			SNL1 and SNL2	Represses Auxin levels during seed germination	H3K9 and H3K18	[56]
			BZR1	Promotes BZR1- targeted genes expression	N/A	[56,62]
	OsHDA705	Rice	N/A	JA induces the accumulation of HDA705	N/A	[63]
	HvHDAC1s	Barley	N/A	JA regulates *HvHDAC1s* genes expression	N/A	[64,65]
HD2	HD2A	*Arabidopsis*	N/A	Represses the ABA response	N/A	[50,66]
	HD2B	*Arabidopsis*	N/A	*HD2B* expression is repressed by ABA	N/A	[50,66]
	HD2C	*Arabidopsis*	HDA6	Represses the ABA response	H3K9 and H3K14	[50,66,67]
	HD2D	*Arabidopsis*	N/A	*HD2D* expression is repressed by ABA	N/A	[50,66]
	OsHDT701	Rice	N/A	Represses the ABA response	N/A	[63,68]
			N/A	Represses the GA response	N/A	[63,68]

HDAC family	Protein name	Species	Physical interacting partners	Plant hormone response[a)]	Histone acetylation sites	Refs.
	OsHDT702	Rice	N/A	*OsHDT702* expression is induced by SA	N/A	[63,68]
			N/A	*OsHDT702* expression is induced by JA	N/A	[63]
			N/A	*OsHDT702* expression is repressed by ABA	N/A	[63]
	HvHDAC2–1	Barley	N/A	*HvHDAC2–1* expression is induced by JA	N/A	[65]
			N/A	*HvHDAC2–1* expression is induced by ABA	N/A	[65]
			N/A	*HvHDAC2–1* expression is induced by SA	N/A	[65]
	HvHDAC2–2	Barley	N/A	*HvHDAC2–2* expression is induced by JA	N/A	[65]
			N/A	*HvHDAC2–2* expression is repressed by ABA	N/A	[65]
SIR2	SRT2	*Arabidopsis*	N/A	Suppresses SA biosynthesis	N/A	[69]
	SRT2	*Arabidopsis*	ENAP1	Promotes the ethylene response	H3K9	[70]

*a)*JA, jasmonic acid; ABA, abscisic acid; BR, brassinosteroid; SA, salicylic acid; GA, gibberellic acid

*b)*N/A, not available.