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Mechanisms Regulating Ethylene Signal Transduction in Plants

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Abstract—Plant hormone ethylene regulates a wide range of physiological processes during plant development and coordinates plant responses to stresses. Ethylene controls important characteristics of agricultural crops such as the fruit ripening rate and plant resistance to adverse conditions. Understanding the molecular mechanisms of ethylene's action is one of the actual questions in both the fundamental and applied contexts. Ethylene biosynthesis from methionine and the main steps of the transduction of the ethylene signal from membrane receptors to effector genes have been studied in detail and widely discussed in many reviews. At the same time, the genetic regulation of these two processes has been poorly studied, although it is responsible for the rapid and accurate reaction of plants to various endogenous and external stimuli and for the diversity of the physiological responses of plants to ethylene. This review summarizes the information about the regulatory mechanisms of ethylene biosynthesis and signal transduction. The key factors of transcriptional and post-translational regulation, which control the expression and stability of the main components of the biosynthesis and signaling pathways of ethylene, and the multiple feedbacks supplementing the linear model of ethylene's signaling pathway are described. Special attention is paid to the role of the ethylene crosstalk with other plant hormones. Different mechanisms of hormonal interaction are illustrated by examples of the synergy or antagonism between ethylene and auxin, jasmonates, cytokinins, and brassinosteroids. The possible molecular bases of the diversity of the physiological responses to ethylene are also discussed.

Keywords: ethylene, plant hormones, morphogenesis, signal transduction pathway, transcriptional regulation, post-translational regulation

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INTRODUCTION

The study of the hormonal regulation of the growth, development, and responses to stress represents one of the fundamental issues of plant biology. Historically, ethylene is considered as the stress and ageing hormone; however, it has a significantly wider range of regulatory action. Ethylene regulates seed germination, the formation of lateral roots and root hairs, leaf epinasty, the development of flowers, fruit ripening, senescence, and abscission; in addition, it also controls plants' responses to stress (Abeles et al., 1992; McManus, 2012). Due to these effects, ethylene (in the form of ethylene releasers) and compounds inhibiting its action are widely used in agriculture. How does this plant hormone implement such diverse physiological responses? To date, the mechanism of ethylene biosynthesis and the linear signal transduction pathway have been well studied; however, this knowledge does not allow us to reveal the sources of the observed diversity of the effects. To understand this, we should obviously study the mechanisms of the molecular genetic regulation of each stage, from the ethylene biosynthesis and transport to the reception and transduction of its signal by the competent cells and activation of special cell programs. The progress in the understanding of mechanisms regulating the biosynthesis, reception, and transduction of the ethylene signal was achieved using the model plant *Arabidopsis thaliana* L. Due to the easily detected specific response of etiolated seedlings to the ethylene treatment (the "triple response", i.e., inhibition of the root and hypocotyl elongation, radial swelling of the hypocotyl, and exaggerated apical hook formation), ethylene-insensitive (*ein*) mutants, which did not demonstrate this reaction, and the mutants characterized by a constitutive triple response (*ctr*), including those characterized by the overproduction of ethylene (*eto*), were revealed (Ecker, 1995). The study of these mutants made it possible to identify the key components of the ethylene signaling pathway and to characterize some elements of the transcriptional and post-translational regulation, which control ethylene biosynthesis and signal transduction. Nevertheless, the obvious complexity and nonlinearity of the regulatory interactions limits the capacity of classic molecular genetic methods. In this situation, the use of modern full-genome approaches (RNA-seq and ChIP-seq) and in silico analysis seem to be more promising. The

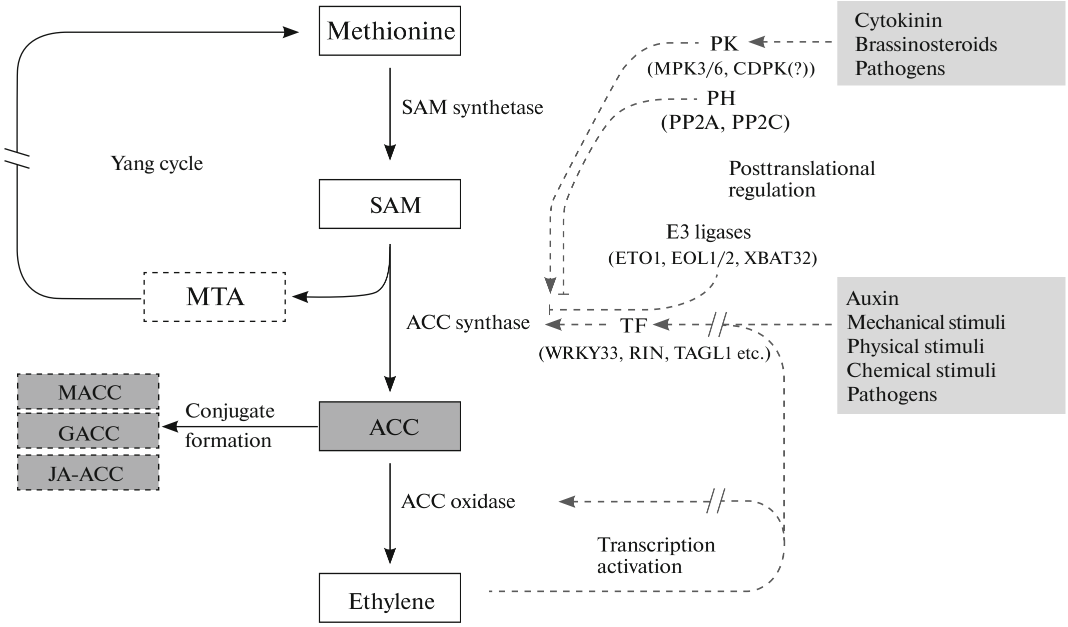

Fig. 1. Simplified scheme of ethylene biosynthesis and its regulation. PK, proteinkinases; TF, transcription factors, PH, phosphatases.

purpose of this review was to summarize the existing information on the mechanisms regulating ethylene biosynthesis and signal transduction in cells and between plant organs.

Ethylene Biosynthesis and Its Regulation

All plants, excluding algae, are able to synthesize ethylene, and almost all plant cells have the ability to synthesize this hormone. The ethylene biosynthetic pathway was determined in the 1970s during the study of ethylene synthesis in apple fruit (McKeon and Yang, 1987). Further studies demonstrated a similar mechanism of ethylene biosynthesis in other plants (rice, tomato, pea, arabidopsis, etc.) and, therefore, confirmed its universal character. Methionine is ethylene's precursor in plants. SAM synthetase activates methionine via its transformation to S-adenosylmethionine (SAM), a substrate of ACC synthase, which transforms SAM to 1-aminocyclopropane-1-carboxylic acid (ACC, Fig. 1). The second product of this reaction—5'-methylthioadenosine—is involved in the Yang cycle and after a series of successive reactions is reduced to methionine (Murr and Yang, 1975). ACC is a direct precursor of ethylene, which is produced via its oxidation by ACC oxidase in the presence of oxygen. The ACC formation is considered to be the main regulatory point of ethylene biosynthesis (Yang and Hoffman, 1984). The control occurs at the levels of both the transcriptional regulation of ACC synthase genes, which are expressed only in the presence of inducers, and post-translational regulation of the enzymes' stability (Fig. 1).

ACC synthase genes in plants are represented by a multigene family. For example, the *A. thaliana* genome contains nine ACC synthase genes (*ACS*), eight of which encode functional enzymes, and one encodes an inactive form of the enzyme (Yamagami et al., 2003). The expression of ACC synthase genes can be induced by hormonal factors, ontogenetic signals, mechanical, physical and chemical stimuli, and by plant pathogens, which, therefore, modulate the intensity of ethylene biosynthesis (Van de Poel and Van Der Straeten, 2014). However, the molecular mechanisms of the induction of various *ACS* paralogs seem to be distinct: they respond to different internal and external stimuli and are characterized by a tissue-specific expression (Tsuchisaka and Theologis, 2004). The post-translational regulation of the activity of ACC synthases via the ubiquitin-dependent degradation of these enzymes provides a low level of ethylene under normal conditions, and therefore, plays an important role in the regulation of ethylene biosynthesis. This process is mediated by E3 ligases (for example, ETO1, EOL1/2, XBAT32) interacting, with rare exceptions, with the noncatalytic C-terminal domain of ACC synthases; each enzyme has its own spectrum of E3 ligases initiating its degradation (Lyzenga and Stone, 2012; Xiong et al., 2014). Unfortunately, we still do not have a complete understanding of the molecular mechanisms regulating various homologs of ACC synthases in response to different factors; only individual components of this regulatory network have been characterized. For example, the participation of MAP kinases in the induction of ethylene biosynthesis under biotic stress conditions has been described. The experiments performed with *A. thaliana* showed that MPK3 and MPK6 stabilize ACS2 and ACS6 proteins via the phosphorylation of the specific sites of the C-terminal domain and, therefore, protect the enzyme against its proteasomal degradation (Han et al., 2010). This stabilization is reversible via dephosphorylation mediated by the PP2A and PP2C phosphatases (Skottke et al., 2011; Ludwikówa et al., 2014). In addition to the stabilization of biosynthetic enzymes, MPK3 and MPK6 also induce the transcription of the *ACS2* and *ACS6* genes via the activation of the WRKY33 transcription factor (Li et al., 2012).

The MAPK enzymes are probably able to participate in the signal transduction from other inducers of ethylene biosynthesis, for example, under cold stress conditions (Zhao et al., 2013). The induction of ethylene biosynthesis by some plant hormones (cytokinins and brassinosteroids) is also provided by the stabilization of ACC synthases (ACS5 and ACS9, respectively; Chae et al., 2003; Hansen et al., 2009). Intriguingly, ACS5 and ACS9 contain phosphorylation sites of calcium-dependent protein kinases (CDPKs), but their functional role in the stabilization of these enzymes still remains unconfirmed. A number of transcription factors (TFs), which regulate the synthesis of ethylene during fruit ripening were described (Karlova et al., 2014) including, for example, TFs from tomato, TAGL1 (Itkin et al., 2009), and RIN (Vrebalov et al., 2002; Ito et al., 2008), which stimulate the transcription of the *ACS2* and *ACS4* genes. Besides, there can be additional mechanisms regulating the ACC formation in plants. For example, ACC is transformed *in planta* into three different derivatives and it is quite possible that such transformation may control the ACC amount available for the biosynthesis of ethylene that was confirmed by the mathematical modeling of this process (Van de Poel et al., 2014). In certain cases the ACC synthase formation does not limit ethylene biosynthesis; for example, after the reaching the maximum ethylene production level during the tomato fruit ripening, the amount of ACC oxidase becomes the key regulator of ethylene biosynthesis (Van de Poel et al., 2012). Earlier it was assumed that genes encoding this enzyme are expressed constitutively. However, later it was shown that the formation of ACC oxidases is regulated at the transcriptional level and may serve as an additional regulator of ethylene biosynthesis (Rudus et al., 2013). ACC oxidases in plant genome are represented by a multigene family, and their expression is regulated by ethylene (De Paepe et al., 2004). Based on the *in silico* analysis, the existence of the post-translational regulation of the activity of ACC oxidases was assumed (Van de Poel et al., 2014).

Mechanisms of Transport and the Long-Distance Ethylene Response

The transport of plant hormones is an important part of the hormonal signal transduction. It provides the redistribution of the hormone concentration and also the possibility of its action at a large distance from the place where it was produced. Ethylene is the only gaseous plant hormone and its transport does not require any special mechanisms; the gas freely diffuses between the neighboring cells. Moreover, being released from the plant to the environment, ethylene provides a signal transduction between plants. On the other hand, the long-distance action of ethylene is provided by the transport of its precursor, ACC, which can be considered as an inactive transportable form of ethylene (Van de Poel and Van Der Straeten, 2014). ACC is usually transported via the vascular tissues. A striking example is the leaf epinasty occurring in the case of the oxygen starvation of tomato roots. ACC synthesized in response to the stress conditions is not oxidized in the roots under an oxygen deficiency, but is transported via the xylem to the leaves, where it is oxidized with the formation of ethylene. In this case, the differential expression of the ACC synthase and ACC oxidase genes in the roots and leaves, respectively, is an important factor that, along with the ACC transport, provides the long-distance ethylene response. In addition, the differential expression of these genes plays an important role in the medium- and long-distance ACC transport during a plant's development (Gallie et al., 2009; Dugardeyn et al., 2008). ACC may also be transported via the phloem (Van de Poel and Van Der Straeten, 2014). Unfortunately, the molecular mechanisms of the ACC transport still remain unclear. We know only about the existence of the directed intracellular transport of the ACC, which is assumed to be provided by the transporters of nonpolar amino acids, such as the HLT1 transporter (Shin et al., 2015).

Molecular Genetic Mechanisms of the Reception and Transduction of the Ethylene Signal

After perception of ethylene by competent cells, it activates a number of mediators, which transmit the hormonal signal and trigger the corresponding response (Merchante et al., 2013; Cho and Yoo, 2015). The current model of the ethylene signal's reception and transduction represents a linear signaling pathway containing of: (1) receptor histidine kinases, (2) serine-threonine protein kinase CTR1, (3) membrane protein EIN2, and (4) TFs from the EIN3/EIL and AP2/ERF families (Fig. 2). The homologous signaling genes were also revealed in tomato and rice, which illustrates the universal character of the mechanism of the reception and transduction of the ethylene signal in higher plants (Giovannoni, 2007; Rzewuski and Suter, 2008).

Ethylene Receptors. Ligand Binding

The perception of ethylene starts from its binding to the receptors localized in the membrane of the endoplasmic reticulum (ER) and Golgi complex (GC, Dong et al., 2008). The unusual intracellular localiza-

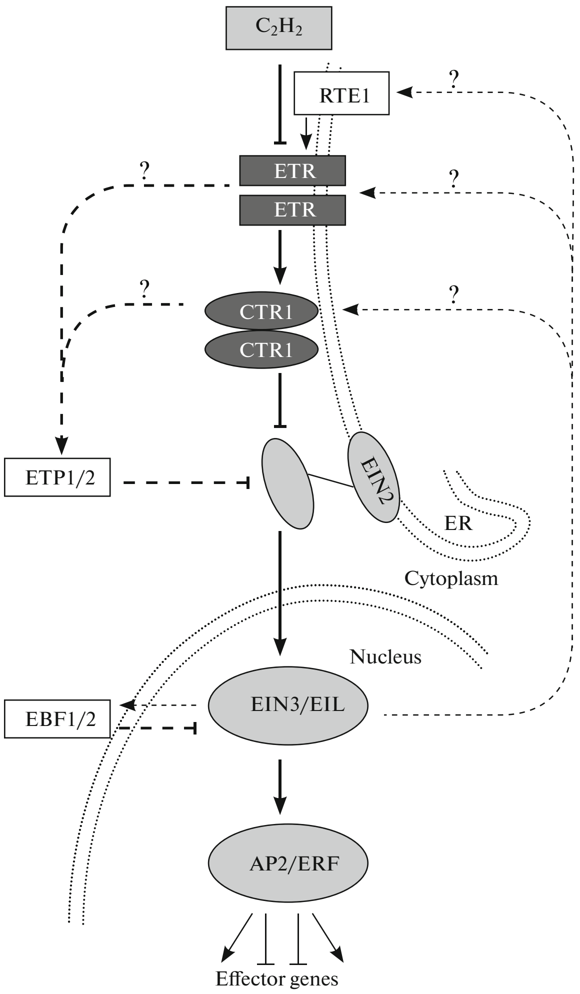

Fig. 2. Simplified scheme of the ethylene signal transduction pathway. The linear pathway is indicated by the bold lines; the posttranslational regulation of the protein stability is indicated by the bold dotted line; the feedback loops are indicated by the dotted lines. ER, endoplasmic reticulum; question marks are for potential regulatory interactions.

tion of the receptors does not prevent the perception of the hormone, since gaseous ethylene freely diffuses through the cell wall. The structure of ethylene receptors includes three main domains (Lacey and Binder, 2014). The conservative N-terminal transmembrane domain contains the ethylene-binding site. The C-terminal histidine kinase and receiver domains are similar to the bacterial two-component systems and are capable of autophosphorylation. Finally, a GAF domain regulating the heteromerous interaction between receptors is located between the N- and C-terminal structures (Liu and Wen, 2012a). The study of *A. thaliana* revealed five genes coding ethylene receptors, which can be divided into two subfamilies based on the homology of the sequences (Lacey and Binder, 2014). The *ETR1*-like subfamily includes the *ETHYLENE RECEPTOR1* (*ETR1*) and *ETHYLENE RESPONSE SENSOR1* (*ERS1*) genes, and the *ETR2*-like subfamily includes the *ETR2*, *ERS2*, and *EIN4* genes. Five receptor isoforms transduce the ethylene signal in a different manner, and the differential expression of the paralogs provides tissue- and stage-specific patterns (Kendrick and Chang, 2008). The ethylene receptors are negative regulators of the response to this hormone: in the absence of ethylene, the receptors are activated and suppress the development of a response, while the ethylene binding inactivates the receptors providing the corresponding response (Stepanova and Alonso, 2009). In *A. thaliana*, ETR1 represents the main functional isoform, and its mechanism of action is best understood. Ethylene binds to the ETR1 receptor in the presence of Cu^{2+} ions, which are transported by RAN1 ATPase localized in the GC membrane. There are also some additional regulators promoting a fine control of the ethylene signal perception. For example, the REVERSION TO ETHYLENE SENSITIVITY1 (RTE1) membrane protein stabilizes the ETR1 receptor and activates it even in the presence of ethylene. The removal of the receptor/ligand complex is provided by receptor degradation that was shown for ETR1 and ETR2 of *A. thaliana* (Chen et al., 2007; Shakeel et al., 2015). Due to the negative regulation of the response to ethylene, the degradation of the receptors results in the prolongation of the ethylene action (Kevany et al., 2007). There are no special systems to remove the excess of ethylene; the gas simply diffuses to the environment.

Linear Ethylene Signal Transduction Pathway

The negative regulation of ethylene's response by the receptors is performed via the activation of the serine-threonine kinase CTR1 suppressing the downstream signaling cascade. It is considered that the activation is achieved through the physical interaction of these regulators and corresponding conformational changes (Ju and Chang, 2012). Ethylene receptors are able to contact with other components of the signaling pathway, such as EIN2, as well. Being active in the absence of ethylene, CTR1 binds to the EIN2 protein, a positive regulator of the ethylene response, which is also localized in the ER and GC membranes, and phosphorylates its cytoplasmic C-terminal domain (Ju et al., 2012). As a result, EIN2 is inactivated, and the ethylene response is suppressed. Upon ethylene binding the receptors inactivate CTR1, which is followed by the EIN2 dephosphorylation and proteolytic cleavage of its C-terminal domain (EIN2C), therefore activating the TFs from the EIN3/EIL family by direct or indirect stabilization of these short-living proteins (An et al., 2010; Li et al., 2015).

Transcriptional Cascade.
Primary and Secondary Responses

The TFs from the EIN3/EIL family control the transcriptional response to ethylene, and the key regulator at this level is TF EIN3. This TF activates the transcription of the primary response genes (the so-called early therefore activating genes). These genes include the effector genes, whose protein products cause a physiological response to ethylene (such as *HLS1* and *PIF3*), and also the genes encoding the TFs from the AP2/ERF family (An et al., 2012; Chang et al., 2013). In addition, EIN3 is one of the feedback regulators of the ethylene response and it plays an important role on interaction with the signaling pathways of other plant hormones (see below). The analysis of the ChIP-seq data for *A. thaliana* revealed more than 1000 genes, which may be potential EIN3 targets (Chang et al., 2013). Note that the main function of EIN3 is to activate the transcription; however, in some cases (*SID2*, *CBF3*), this TF negatively regulates the expression of target gene. EIN3 controls gene transcription via the binding to EIN3-binding site (EBS) localized in the promoters of the target genes. Based on the study of the binding site of the TEIL protein of tobacco (a close homolog of EIN3 from *A. thaliana*) using SELEX-based methods, the following consensus sequence for the EBS was proposed: A[T/C]G[A/T]A[T/C]CT (Kosugi and Ohashi, 2000). However, the specific binding of TF to EBS is not always enough to change the level of gene transcription (Chang et al., 2013). Probably, in these cases the process is also regulated by the transcriptional coregulators controlled by the additional spatial and temporal stimuli. As was mentioned earlier, EIN3 activates the transcription of genes encoding the TFs from the AP2/ERF family. These TFs are found only in plants and are characterized by the presence of a highly conservative DNA-binding AP2 domain; they are able to activate or suppress the transcription of the controlled genes via binding to the specific sites in their promoters (Riechmann et al., 2000). Changing the expression of their target genes (the so-called late ethylene response genes), these TFs are a part of the transcriptional cascade, which results in the secondary physiological response (Solano et al., 1998). The ERF-binding site, or the so-called GCC box, represents a cis-element with the consensus sequence GCCGCC; the flanking regions may influence the TF's ability to bind the GCC box (Ohme-Takagi and Shinshi, 1995; Pirrello et al., 2012). Based on the *in silico* analysis, Chernykh et al. (2014) supposed that the activation of the gene expression occurs mainly in the case of the localization of the GCC box in the antisense strand relative to transcription start site. However, the character of the transcription changes may be connected with the nature of the corresponding TFs, which may function as either activators (AtERF1, AtERF2, and AtERF5), or inhibitors (AtERF3 and AtERF4) of the GCC-box dependent transcription (Fujimoto et al., 2000).

Feedback Regulation

The above-described linear pathway of the transduction of the ethylene signal is supplemented with nonlinear regulatory interactions, which include controlling the protein's stability and feedback loops; as a result, a more complex regulatory network is formed (Fig. 2; Zhao and Guo, 2011). For example, the EIN2 and EIN3/EIL1 proteins, which are positive regulators of ethylene response, undergo the ubiquitine-dependent degradation. This ethylene-regulated process is initiated by F-box proteins, ETP1/2 and EBF1/2, respectively, and provides a rapid termination of the response in the absence of a stimulus. The ethylene receptors or CTR1 may probably stabilize the ETP1/2 proteins, which mediate the proteasomal degradation of EIN2 (Stepanova and Alonso, 2009). The EBF2 protein, in turn, is a component of the negative feedback, since its coding gene represents a target for the EIN3/EIL1 TFs (Konishi and Yanagisawa, 2008). The formation of negative feedback loops allows a system to rapidly adapt to changing conditions and maintain the homeostasis. Presumably, EIN3/EIL1 TFs may also regulate the transcription of other regulators of the ethylene response, providing more feedback loops. The potential targets of these TFs are negative regulators such as the *CTR1*, *RTE1*, and genes encoding the ethylene receptors *ETR2* and *ERS1/2* (Chang et al., 2013). In addition, there are some longer positive feedback loops. For example, the genes encoding the enzymes, involved in the ethylene biosynthesis, are targets for the ethylene-dependent TFs (Fig. 1; Chang et al., 2013). Because of the complexity of the regulatory interactions, the role of bioinformatic methods in the study of the dynamics of nonlinear networks has increased (Vo et al., 2014). For example, there were several attempts to develop dynamical models for the ethylene signaling pathway in *A. thaliana* and the ethylene response, which would allow a user to simulate the response to different concentrations and temporal modes of ethylene's action (Díaz and Álvarez-Buylla, 2006).

Interaction with Signaling Pathways of Other Plant Hormones

As a rule, the regulation of plant growth and morphogenesis and the stress responses is performed by the joint rather than the independent action of the plant hormones (Gazzarrini and McCourt, 2003). The physiological and molecular genetic studies as well as microarray and whole transcriptome studies have revealed a wide range of interactions between ethylene and auxin, cytokinins, brassinosteroids, jasmonates, abscisic acid, and other plant hormones (Kudryakova et al., 2001; Zhao and Guo, 2011; Zhu and Lee, 2015). The crosstalk may occur at the level of their metabolism, transport, and signal transduction. The interactions between the signaling pathways of plant hormones result in the formation of complex gene and protein networks (Stepanova et al., 2007). In this section, we describe the best-studied crosspoints of the signaling pathways of ethylene and other plant hormones and illustrate various types of their interaction.

Ethylene and Auxin. Transcriptional Regulation at the Biosynthesis Level

The auxin concentration in a cell determines the way of its differentiation and ability to grow and divide (Takatsuka and Umeda, 2014). The ability of ethylene to modulate the action of auxin at the levels of biosynthesis and transport has been known for quite a long time; it provides a wide range of physiological effects in different plant organs and tissues (Muday et al., 2012). The most striking example of such an interaction is the mechanism providing the ethylene-induced suppression of root elongation in *A. thaliana*. The growth of a root is induced by a certain concentration of auxin in the elongation zone. Ethylene provides the activation of *ASA1/WEI2/TIR7*, *ASB1/WEI7*, and *TAA1/WEI8*, the biosynthetic genes of auxin and its precursor, tryptophan (Stepanova et al., 2005; Ruzicka et al., 2007; Swarup et al., 2007), which results in an increased auxin concentration in the root meristem. The additional auxin is transported to the elongation zone due to the ethylene-dependent synthesis of its transporters, AUX1 and PIN2/EIR1; the increased auxin concentration in this zone results in the suppression of cell elongation. Since the increased concentrations of auxin may, in turn, induce ethylene biosynthesis via the activation of the transcription of the ACC synthase gene *ACS4* (Abel et al., 1995; Tsuchisaka and Theologis, 2004), such reciprocal regulation provides an auxin-ethylene feedback system. The redistribution of the auxin concentration is probably connected with the ethylene-induced effects such as the suppression of the lateral root formation, changes in the gravitropism, the shortening of the hypocotyl, and the apical hook formation (Lewis et al., 2011). In addition to the above-mentioned AUX1 and PIN2/EIR1, ethylene enhances the transcription of genes encoding auxin transporters PIN1, PIN4, and PIN7 (Ruzicka et al., 2007; Lewis et al., 2011). The role of CTR1 as the local inhibitor of auxin's biosynthesis during the formation of root hairs was also discussed (Ikeda et al., 2009).

Ethylene and Jasmonates. Transcriptional Regulation at the Signal Transduction Level

Ethylene and jasmonates represent an example of the crosstalk at the level of signal transduction, when the components of one signaling pathway influence the activity of the TFs from another signaling pathway thereby changing the level of transcription of their target genes (Zhu and Lee, 2015). These hormones act in a synergistic and interdependent manner in response to plant pathogens. Transcription of the *PDF1.2* gene, whose product provides the antimicrobial protection of a plant, is poorly activated by ethylene or jasmonic acid, but is significantly induced by a combination of these two hormones. Expression of the *PDF1.2* gene is controlled by the TFs from the AP2/ERF family ERF1 and ORA59, whose synthesis, in turn, is regulated by the EIN3 TF (Lorenzo et al., 2003; Pre et al., 2008; Zarei et al., 2011). The signaling pathways of two plant hormones have a direct molecular connection via the EIN3 TF and JAZ protein, a component of the jasmonate signaling pathway that inactivates EIN3/EIL1 recruiting HDA6 as a corepressor. Under the action of jasmonates, JAZ degrades and, therefore, the interaction between HDA6 and EIN3/EIL1 decreases, and the transcriptional activity of the latter is restored (Zhu et al., 2011). A similar mechanism of interaction is realized in the case of the crosstalk between the ethylene and gibberellin signaling pathways (An et al., 2012).

Protein Stability Control during the Interaction of the Signaling Pathways

A controlled degradation of the signaling proteins is an important factor for regulating the ethylene response and may serve as a target for other phytohormones. For example, cytokinins and brassinosteroids activate ethylene biosynthesis via the stabilization of ACS5 and ACS9 ACC synthases (Cary et al., 1995; Vogel et al., 1998; Chae et al., 2003; Wang et al., 2004). It is also considered that the jasmonate-induced inactivation of the ethylene-dependent apical hook formation in *A. thaliana* occurs due to the activation of the EBF1 expression by the jasmonate-dependent MYC2 TF that, in turn, induces the proteasomal degradation of EIN3, a positive regulator of the ethylene response. An alternative explanation of the influence of jasmonate on the ethylene-dependent apical hook formation is the inactivation of EIN3 due to its direct interaction with the MYC2 TF (Zhang et al., 2014b).

Molecular Basis for the Diversity of the Physiological Responses to Ethylene

How does ethylene provide the observed diversity of the physiological responses? The ability to synthesize ethylene is common for almost all plant cells; however, due to the inducible character of this biosynthetic process, the level of ethylene under normal conditions is usually low except for the zones of the heightened ethylene formation, whose distribution may vary in the course of the ontogenesis or under the influence of external factors. For example, in juvenile plants, ethylene is synthesized mainly in the meristemal tissues, whereas later the maximum ethylene amount is generated in the ripening fruits. Ethylene biosynthesis is also enhanced under stress conditions. The kinetics of ethylene formation and the amount of the synthesized hormone differ depending on the internal and external stimuli (Li et al., 2012). There are several factors which may hypothetically explain these phenomena. First, a multilevel regulation of the enzymes of ethylene biosynthesis (ACC synthase and ACC oxidase) provides alternative controlling points at the transcriptional and post-translational levels. Second, enzymes involved in ethylene biosynthesis are encoded by multigene families. Paralogs are characterized by a differential tissue- and stage-specific expression patterns; isozymes, which are homodimers, differ in their properties and are synthesized in response to different stimuli. Moreover, the crossing of the expression patterns of various paralogs illustrates the possibility of the simultaneous presence of different isozymes in the same cell, for most of which a functional heterodimerization was shown *in vitro* and *in planta* (Tsuchisaka et al., 2009). Thus, a unique composition of enzymatic complexes is formed, which provides a possibility of a fine regulation of ethylene biosynthesis. Another explanation of the patterns of ethylene formation is the existence of different mechanisms regulating its biosynthesis. For example, at least two successively acting mechanisms were proposed for the regulation of ethylene biosynthesis during the ripening of the climacteric fruits (biosynthetic systems 1 and 2). As the fruits ripen, the transition from one system to another transforms the autoinhibition to the autostimulation of the ethylene biosynthesis (Alexander and Grierson, 2002). At the level of the ethylene perception the diversity of the responses may be due to its dose-dependent character, which was predicted by mathematical modeling (Díaz and Álvarez-Buylla, 2006), and also due to the different sensitivity of the cells to ethylene. This question still remains poorly studied at the molecular level; nevertheless, a certain role of the differential expression of the paralogs of the ethylene receptors and the heterodimerization of their protein products is assumed (Liu and Wen, 2012b). Since the ethylene-triggered transcriptional response differs in different tissues and at the different stages, but is controlled by only two key factors (EIN3 and EIL1) (Alonso et al., 2003), it is obvious that additional regulation should occur at this and later steps. According to the results of the RNA-seq analysis, the temporal dynamics of the ethylene-induced transcriptional activity represents four successively developing waves, whose development is controlled by EIN3, which means the existence of several levels of transcriptional control (Chang et al., 2013). Moreover, the ethylene response is modulated by additional spatial and temporal signals, such as other plant hormones, which provided the required direction of the response. Such interactions may be very complex and include the crosstalk of more than two regulatory circuits. For example, the signaling pathways of auxin, ethylene, and cytokinins have a common POLARIS peptide (PLS) that suppresses the ethylene and cytokinin response and positively regulates the homeostasis and transport of auxin (Chilley et al., 2006). Brassinosteroids are able to induce the ethylene biosynthesis in synergy with auxin (Joo et al., 2006). Moreover, there is some evidence supporting the existence of alternative ethylene signaling pathways (Zhang et al., 2014a).

Ethylene regulates many physiological processes, including stress responses, and initiates a wide range of plant responses to various internal and external stimuli. These processes are based on the functioning of a multifactor regulation system that works at each stage of the ethylene signaling. The investigations performed in recent decades and that were based on the modern molecular and bioinformatic methods have provided a better understanding of the mechanisms of ethylene biosynthesis and signal transduction and the principles of their regulation. Nevertheless, many questions still remain unclear, including revealing new regulatory elements, the interaction between different regulatory circuits, the search and description of alternative signaling pathways, and the establishment of a connection between the ethylene pathway and the ontogenetic programs and stress signals. The further study of these questions will provide a better understanding of the mechanisms responsible for the functioning of this hormone.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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