Ethylene Signaling in Plants: Introspection

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Syed Sabhi Ahmad, Waseem Shahri, Shiekh Tajamul Islam, Riyaz Ahmad Dar, and Inayatullah Tahir

Abstract

Ethylene is the simplest unsaturated hydrocarbon gas produced in most plants that regulates a number of biochemical processes. Ethylene regulates a wide array of developmental processes, but its precise role in the regulation of these processes is still not clear. Ethylene's role as a signal molecule depends on the cell response to its changing concentrations and the processing of this information in the form of physiological responses in the target cell. Ethylene is perceived by a family of ER-membrane-bound receptors encoded by the ethylene response 1 (ETR1) gene, and these receptors transduce the ethylene signal. Other ethylene receptors such as ERS1, ERS2, EIN4, ETR1, and ETR2 act as negative regulators via constitutive triple response 1 (CTR1) gene. The CTR1 is presumed to show similarities with Raf, a mitogen-activated protein kinase kinase kinase (MAPKKK) and thus is thought to function like Raf, in a typical MAPK cascade. It has been demonstrated that CTR1 binds ER membrane via ETR1 or by a direct association with ERS1 and ETR2 during ethylene signaling. Ethylene is thought to regulate several aspects of plant growth involving associations with other plant hormones primarily auxins and gibberellins.

Keywords

Ethylene • Ethylene receptors • Ethylene response 1 (ETR1) • Constitutive triple response 1 (CTR1) • Auxin resistant 1 (AXR1)

S.S. Ahmad • W. Shahri • R.A. Dar • I. Tahir (✉)
Plant Physiology and Biochemistry Research
Laboratory, Department of Botany,
University of Kashmir, Srinagar 190006,
Jammu and Kashmir, India
e-mail: syedsabhiindrabi@gmail.com;
waseem.bot@gmail.com; reyazadar@gmail.com;
inayatullahtahir@gmail.com

S.T. Islam
P.G. Programme in Bioresources, Department
of Botany, University of Kashmir, Srinagar 190006,
Jammu and Kashmir, India
e-mail: tajamul166@gmail.com

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17.1 Introduction

In all living organisms, cells constantly communicate with each other. In plants, cells communicate to coordinate their activities in response to several internal and external environmental changes like change in temperature, light, and darkness (Alberts et al. 2002; Abeles et al. 1992; Bleecker and Kende 2000; Argueso et al. 2007). To respond to these changes, living organisms harbor diverse and sophisticated signaling strategies (Takeshi et al. 2000). In addition to a vast number of signaling molecules like sugars and protein kinases, various plant growth regulators including auxins, abscisic acid, ethylene, cytokinins, and gibberellins help to coordinate plant growth and development by acting as signaling molecules (Takeshi et al. 2000; Alberts et al. 2002). These growth regulators readily diffuse through cell walls and act in multiple ways inside the cell. The specific effect depends on the stimulus generated by the target cell (Alberts et al. 2002). Hormonal signals combine external environmental inputs and internal developmental and translate them into desirable responses (Alberts et al. 2002; Klee 2004). Plants modulate these signals in multiple ways, and regulation can occur at the level of hormone synthesis, transport, uptake, or turnover or at the level of ethylene perception or signal transduction (Klee 2004). Among these, ethylene acts as a primary mediator to respond to and coordinate internal and external developmental cues in modulating plant growth and developmental processes (Alberts et al. 2002; Takeshi et al. 2000; Yoo et al. 2009; Ju and Chang 2012; Schaller 2012). Ethylene is the simplest unsaturated hydrocarbon gas formed in most plant and cell types and regulates diverse metabolic and developmental cues including agronomically important processes involved from seed germination to organ senescence and abscission, cell elongation, nodulation, pathogen response, and response to abiotic and biotic stresses (Abeles et al. 1992; Theologis 1998; Stepanova and Ecker 2000; Bleecker and Kende 2000; Schaller and Kieber 2002; Tsuchisaka and Theologis 2004; Guo and Ecker 2004; Klee 2004; Chen et al. 2005; Yoo et al. 2009; Ju and Chang 2012; Schaller 2012). A molecular cross talk exists between ethylene signaling pathways and other hormonal signaling molecules particularly auxins, cytokinins, abscisic acid, gibberellins, and brassinosteroids (Chen et al. 2005). The broad spectrum of ethylene effects in plant growth and development has led to its detailed investigation. Significant improvement has been made in understanding the mechanism of ethylene signal perception and transduction (Bleecker and Kende 2000; Stepanova and Alonso 2009; Ju and Chang 2012). In this review, we will focus on the role of ethylene as a signal molecule. Moreover the mechanism of ethylene signal perception and transduction will be dealt with detail.

17.2 Ethylene as a Signal Molecule

Ethylene regulates a wide array of plant processes right from seed germination up to organ abscission or senescence. Ethylene was recognized as a signal molecule with the studies of Abeles et al. (1992). The involvement of ethylene in plant growth and development was first demonstrated by Dimitry Neljubov in 1901 when it was reported that leaks in the illuminating gas caused premature senescence and defoliation of plants in greenhouse and of trees near gas lines (Abeles et al. 1992). Neljubov observed that horizontal growth habit was exhibited by etiolated pea seedlings in the laboratory in contrast to the upright habit shown by the pea seedling when grown in outside air. He later on proposed that the contaminating gas was the causative agent for the abnormal growth habit. This causative agent later on proved to be ethylene gas (Abeles et al. 1992; Bleecker and Kende 2000; Guo and Ecker 2004). This led Neljubov to propose “triple response of ethylene” on etiolated dicotyledonous seedlings. Triple response is characterized by the inhibition of root cell and hypocotyl elongation, curvature of the apical hook, and radial swelling of the hypocotyls. Later on Gane (1934) proposed that ethylene is produced by the plants internally. This proposal laid the stage for investigation of ethylene as an endogenous signal molecule in plants (Johnson and Ecker 1998; Bleecker and Kende 2000; Alberts et al. 2002). Ethylene is thought to regulate a wide array of developmental processes, but it is still unclear as to how this hormone is concerned with such varied and different functions (Leon and Sheen 2003; Alonso and Stepanova 2004; Yoo et al. 2009). Recent evidences have suggested that plant tissues differ in their sensitivity to ethylene and also with their developmental stage because of the signaling interactions with other plant growth regulators and other metabolites (Leon and Sheen 2003; Alonso and Stepanova 2004; Ramon et al. 2008; Yoo et al. 2009).

17.3 Ethylene Signaling

17.3.1 Ethylene Biosynthesis

Surprisingly, the multitude of physiological responses governed by ethylene signaling is vast, and it exhibits various morphogenetic effects (Abeles et al. 1992; Theologis 1998; Stepanova and Ecker 2000; Bleecker and Ken2000; Wang et al. 2002; Schaller and Kieber 2002; Tsuchisaka and Theologis 2004; Guo and Ecker 2004; Klee 2004; Chen et al. 2005; Yoo et al. 2009; Lin et al. 2009; Ju and Chang 2012; Schaller 2012). This wide range of specificity has been attributed to its complex biosynthetic pathway (Abeles et al. 1992; Kieber 1997; Theologis 1998; Adams and Yang 1979). Ethylene is found to be produced in almost all parts of the higher plants, and the rate of ethylene production varies from one part of the plant to another depending on the stage and type of tissue. Among different tissues, meristems are the most active regions of ethylene biosynthesis. Despite its chemical simplicity, the biosynthesis probably represents the agonies and frustration of the plant scientists who were involved with its study. Ethylene is formed from the precursor methionine (Met) via S-adenosyl methionine (AdoMet) and 1-aminocyclopropane-1-carboxylic acid (ACC) (Yang and Adams). The enzymes AdoMet synthetase, ACC synthase (requires pyridoxal phosphate as cofactor), and ACC oxidase occur in series to produce ethylene from methionine (Kende 1993). During every cycle, 5′-methylthioadenosine is generated which acts as precursor for the formation of methionine which then enters the Yang cycle to produce ethylene again via modified methionine cycle (Miyazaki and Yang 1987). This pathway provides methylthio group for ethylene production at the cost of a single ATP molecule for every cycle. ACC synthase (the main enzyme in the ethylene biosynthesis pathway) shows structural similarity with aminotransferases as11 of the 12 amino acid residues in ACC synthase are conserved in aminotransferases. The expression ACC synthase gene is regulated by various developmental, environmental, and hormonal signals (Zarembinski and Theologis 1994; Bleecker and Kende 2000). Studies on ethylene-related mutants in *Arabidopsis* showed that overproduction of ethylene in these mutants occurs as a result of the elevated ACC synthase activities (Guzman and Ecker 1990; Vogel et al. 1998; Woeste et al. 1999; Bleecker and Kende 2000). Thus, in ethylene biosynthesis, ACC synthase activity is recognized as the regulatory and limiting step. But recently it was found that ACC oxidase transcript levels and enzyme activities also increase in some plant tissues that are induced to form ethylene (Kende 1993; Chen et al. 2005). Thus, ACC oxidase along with ACC synthase regulates the ethylene biosynthesis in plants (Kende 1993; Adams and Yang 1979; Prescott and John 1996; Bleecker and Kende 2000; Chen et al. 2005) (Fig. 17.1).

17.3.2 Ethylene Perception and Signal Transduction

Biochemical and molecular characterization of ethylene biosynthetic pathway has provided insights into the mechanisms by which plants regulate the internal concentrations of this hormone (Kende 1993; Bleecker and Schaller 1996; Sakai et al. 1998). The effectiveness of ethylene as a signal molecule is determined by the capability of cells to scrutinize the varying concentrations of ethylene and transduce this information into physiological responses suitable to the cell type.

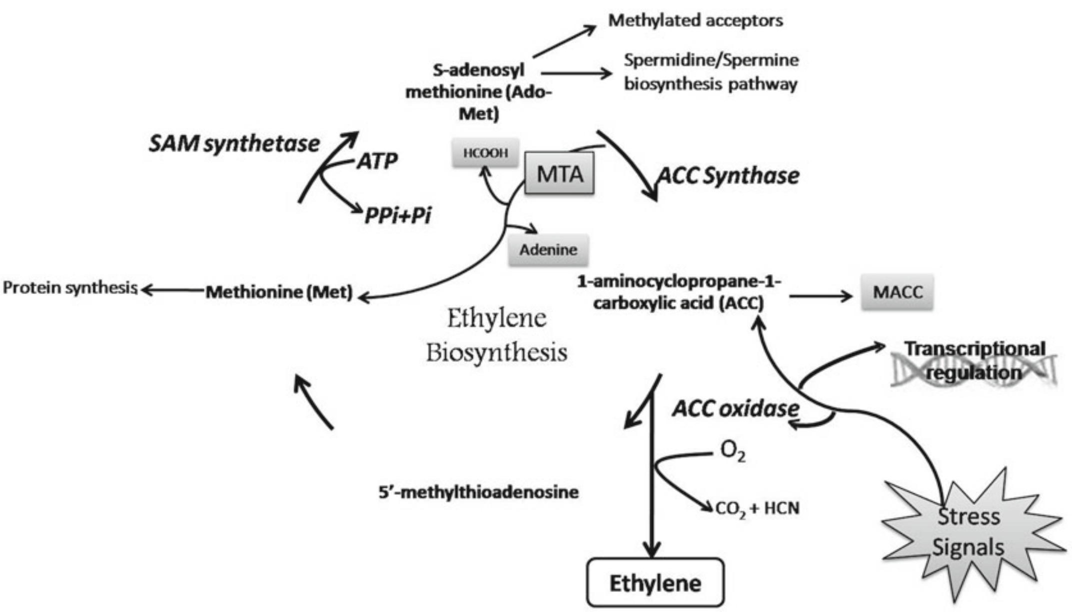

Fig. 17.1 *Biosynthetic pathway and regulation of ethylene*. The formation of *S*-AdoMet is catalyzed by SAM synthetase from the methionine at the expense of one molecule of ATP per molecule of *S*-AdoMet synthesized. *S*-AdoMet is the methyl group donor for many cellular molecules (methylated acceptors), including nucleic acids, proteins, and lipids. In addition, *S*-AdoMet is the precursor of the polyamine synthesis pathway (spermidine/spermine biosynthesis pathway). ACC is the immediate precursor of ethylene. The rate-limiting step of ethylene synthesis is the conversion of *S*-AdoMet to ACC by ACC synthase under most conditions. MTA is the by-product generated along with ACC production by ACC synthase. Recycling of MTA back to methionine conserves the methylthio group and is able to maintain a constant concentration of cellular methionine even when ethylene is rapidly synthesized. Malonylation of ACC to malonyl-ACC (MACC) deprives the ACC pool and reduces the ethylene production. ACC oxidase catalyzes the final step of ethylene synthesis using ACC as substrate and generates carbon dioxide and cyanide. Transcriptional regulation of both ACC synthase and ACC oxidase is indicated by dashed arrows. Reversible phosphorylation of ACC synthase is hypothesized and may be induced by unknown phosphatases (Ptase) and kinases, the latter presumably activated by stresses. Both native and phosphorylated forms (ACC synthase-Pi) of ACC synthase are functional, although the native ACC synthase may be less stable or active in vivo. A hypothetical inhibitor is associated with ACC synthase at the carboxyl end and may be dissociated from the enzyme if it is modified by phosphorylation at the vicinity

Understanding the mechanisms by which plant cells perceive and transduce the ethylene signal has been a difficult problem. Physiochemical considerations have prompted a number of researchers to postulate that ethylene might interact with a receptor through a protein-bound transition metal such as Cu (I) (Burg and Burg 1967; Kovacic et al. 1991; Sisler 1991; Sakai et al. 1998). Detailed studies on a number of mutants of Arabidopsis have revealed that ethylene perception and recognition occurs through a defined pathway (Ecker 1995; Bleecker and Schaller 1996). Recently it has been demonstrated that ethylene is perceived by ER-membrane-bound receptor family. These studies have revealed that ethylene response 1 (ETR1) gene encodes for ethylene receptor in plants and later on the ETR1 protein perceives and transduces the ethylene signal (Bleecker and Schaller 1996; Stepanova and Ecker 2000; Cho and Yoo 2007; Yoo et al. 2009). Genetic epistasis examination of Arabidopsis signaling mutants has revealed that ETR1 is one of the five ethylene receptors along with ETR2 (ethylene receptor 2), ERS1 (ethylene response sensor 1), EIN4 (ethylene insensitive 4), and ERS2 (ethylene response sensor 2) (Bleecker et al. 1988; Chang et al. 1993; Theologis 1998; Bleecker and Kende 2000; Stepanova and Ecker 2000; Schaller and Kieber 2002; Cho and Yoo 2007). These five ethylene membrane receptors found in

Arabidopsis are linked to two-component histidine kinase (HK) sensors found in bacteria and fungi, and the binding to ethylene occurs through *N*-terminal domain localized within the ER (Chang et al. 1993; Theologis 1998; Bleecker and Kende 2000; Binder et al. 2012; Ju and Chang 2012). Two-component systems consist of a sensor molecule with a histidine kinase domain and a response regulator with a receiver domain (Stepanova and Ecker 2000). EIN4, ETR1, and ETR2 consist of both the domains, while ERS1 and ERS2 are devoid of the receiver domain. The absence of the receiver domain indicates that ERS1 and ERS2 either use the receiver domain of EIN4, ETR1, or ETR2 or utilize other response regulators (Hua et al. 1995, 1998; Stepanova and Ecker 2000). The ethylene receptors are largely thought to be redundant because the ethylene receptor is constitutively signaling without ethylene, whereas the ethylene receptor is turned off on addition of ethylene (Qu et al. 2007; Liu et al. 2010). These receptors act as negative regulators through constitutive triple response 1 (CTR1), a genetically identified negative regulator (Kieber et al. 1993; Yoo et al. 2009). Loss of CTR1 function confers constitutive ethylene responses. From genetic and biochemical studies, it has become clear that without ethylene perception, the receptors repress ethylene responses by activating CTR1. Binding of ethylene inactivates ethylene receptor signaling and CTR1 is consequently inactive, thereby leading to ethylene response (Zhong and Chang 2012). CTR1 is presumed to show similarities with Raf, a mitogen-activated protein kinase kinase kinase (MAPKKK) and thus is thought to function like Raf, in a typical MAPK cascade (Kieber et al. 1993; Hahn and Harter 2009; Zhao and Guo 2011; Ju and Chang 2012). The association of CTR1 with the receptor protein complexes occurs chiefly through ETR1 and ERS1 (Kieber et al. 1993; Clark et al. 1998; Huang et al. 2003; Yoo et al. 2009). Moreover a membrane metal transporter EIN2 has an important role in signaling downstream of CTR1 by regulating the accessibility of EIN3 (a key transcription factor) (Chao et al. 1997; Alonso et al. 1999; Guo and Ecker 2003). EIN3 is built up and stabilized in the nucleus to activate hormone inducible primary transcription via ethylene-responsive factor 1 (ERF1) which in turn along with EIN-LIKE1 (EIL1) transcriptional factor initiates the expression of secondary response genes in ethylene-dependent transcription cascades (Alonso and Stepanova 2004; Klee 2004; Gallie and Young 2004; Guo and Ecker 2004; Kendrick and Chang 2008; Yoo et al. 2009). Additionally EIN-LIKE1 (EIL1) and EIN3 are degraded by 26S proteosome in the absence of ethylene (Potuschak et al. 2003; An et al. 2010; Ju and Chang 2012). The protein products of these genes are eventually involved in growth, defense, and survival of the plant by activating ethylene-responsive genes (Yoo et al. 2009; Ju and Chang 2012) (Fig. 17.2).

17.3.3 Nuclear Changes During Ethylene Signaling

Ethylene response results in quick early transcriptional response in the plant via the utilization of protein amendment protocols without de novo production of proteins. Proteomic analysis has suggested that the protein stability control EIN3 (key transcriptional factor in ethylene signaling) is the chief step in ethylene signaling (Chao et al. 1997; Yanagisawa et al. 2003; Gao et al. 2008; Binder et al. 2007). EIN3 accumulation occurs in the nucleus in response to ethylene of 1-amino-1-cyclopropane-1-carboxylic acid (ACC) (Guo and Ecker 2003; Gagne et al. 2004). In the absence of both ACC and ethylene, EIN3 is constantly broken down through 26S proteosome. For this degrading process of EIN3, EBF1 and EBF2 (EIN3-binding F-box proteins) serve as substrates for ubiquitin ligase to degrade EIN3. In ebf1 and ebf2 double mutants, EIN3 protein accumulates and results in strong constitutive ethylene signaling phenotypes (Gagne et al. 2004; Binder et al. 2007). Double mutant experiments with ein3 eil1 have suggested that BF1 and EBF2 act primarily through EIL1 and EIN3 during ethylene signaling. Detailed studies with ebf1 and ebf2 single mutants showed that EBF1 acts during the early stage of ethylene signaling, while EBF2 acts during the later period of ethylene responses (Yoo et al. 2009).

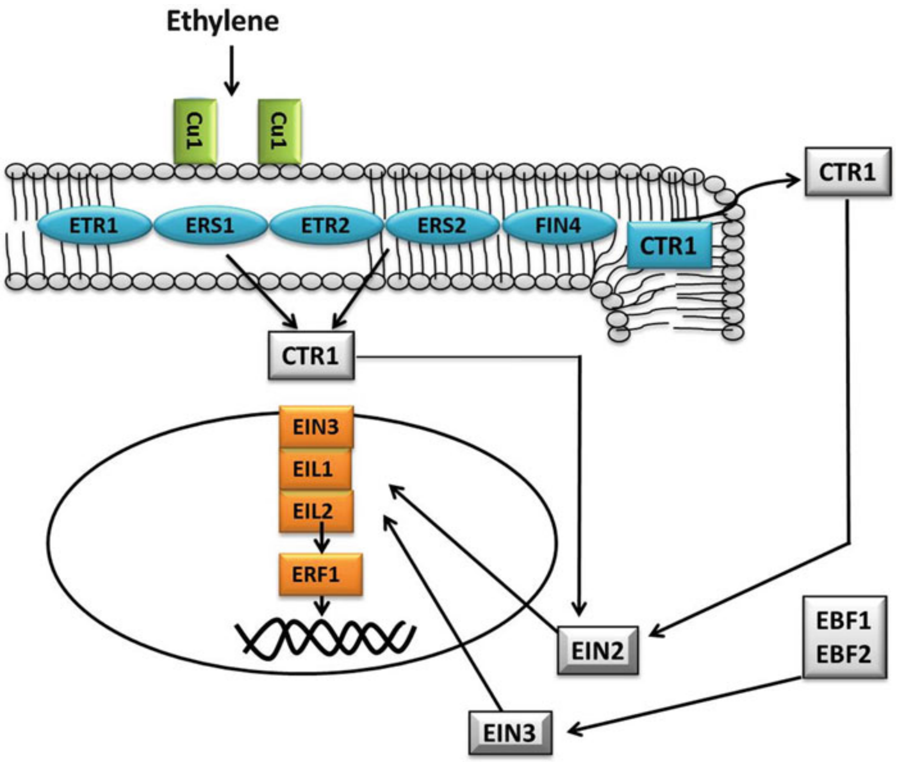

Fig. 17.2 The protein products of these genes are eventually involved in growth, defense, and survival of the plant by activating ethylene-responsive genes

17.3.4 Ethylene Perception at the Endoplasmic Reticulum

Unlike most of the signaling perception mechanisms whose receptors are located either on the plasma membrane or in the nucleus, ethylene signaling receptors are located on ER (Chen et al. 2005, 2007; Grefen et al. 2008; Zhong et al. 2008; Ju and Chang 2012). Various valid justifications have been provided by various workers for localization of ethylene receptors on ER membrane. Firstly, it is a gaseous molecule and can easily diffuse in the cell (Chen et al. 2005; Ju and Chang 2012). Secondly, ethylene receptor genes have originated from chloroplast and evolutionary trends might have resulted in the localization of these genes on ER (Bleecker 1999; Mount and Chang 2002; Chen et al. 2005; Ju and Chang 2012). More convincing argument is that ER is in contact with most of the cell organelles, and thus, the localization of ethylene receptors on ER membrane might facilitate interaction and integration with cellular responses and other signaling pathways (Ju and Chang 2012).

Protein complexes with downstream signaling component CTR1 have been found to act as receptors in ethylene signaling. It has been demonstrated by density gradient centrifugation that CTR1 binds ER membrane via ETR1 as CTR1 cannot bind the membrane by itself as it lacks membrane attachment motifs or transmembrane domains (Clark et al. 1998; Gao et al. 2003; Chen et al. 2005). In addition to ETR1 and CTR1, pull-down assay has confirmed that CTR1 has direct interaction with ERS1 and ETR2 during ethylene signaling. The key role of CTR1 in ethylene signaling and transmission has been proved by various workers (Clark et al.

1998; Cancel and Larsen 2002; Chen et al. 2005). Kinase activity on CTR1 is important in suppressing ethylene response. This was confirmed by using CTR1 mutant which resulted in constitutive ethylene response phenotype. Recent studies have revealed that kinase activity alone cannot confer to suppressing ethylene response, but location of the CTR1 to the endoplasmic reticulum through its alliance with ethylene receptors is also needed (Ju and Chang 2012; Mayerhofer et al. 2012). ctr-8 mutant (a CTR1 mutant), wherein the potential of CTR1 to interact with ethylene receptors has been disrupted, resulted in constitutive ethylene response (Huang et al. 2003; Ju and Chang 2012; Mayerhofer et al. 2012). Same results appear when ethylene receptors are eliminated. The membrane recruitment will place CTR1 with immediate downstream component of the ethylene signaling pathway, i.e., EIN2. EIN2, a subcellular localized protein, contains a highly hydrophobic *N*-terminal domain (Alonso et al. 1999). EIN2 interacts with the ethylene receptors, and its interaction with CTR1 was confirmed by fluorescence resonance energy transfer microscopy using tobacco leaf epidermal cells (Bisson and Groth 2011, 2012). Since EIN2 is located on the endoplasmic reticulum membrane along with the five ethylene receptors and CRT1, interaction between these components may occur simultaneously or synchronously. This interaction syndrome has given rise to “ER-borne ternary super-complex” (Bisson et al. 2009). EIN2 acts at or downstream of CTR1 and either can be involved in protecting EIN2 from proteosome degradation or will promote signaling (Bisson and Groth 2012; Ju and Chang 2012). Depending on the phosphorylated state of the receptor domain, a dynamic interaction might occur between ethylene receptor and EIN2 (Bisson and Groth 2011; Ju and Chang 2012). When histidine was replaced by alanine in ETR1, a fourfold increase in the affinity of EIN2 was seen, while his353Glu substitution had no effect on the interaction (Bisson and Groth 2012; Ju and Chang 2012). In vitro studies have suggested a possible link between ethylene binding and formation of the receptor-EIN2 complex.

17.4 Integration of Ethylene with Other Hormones

Genetic analysis of the plants affected in the “triple response” has led to the wonderful improvement in unraveling and understanding the ethylene signaling processes (Stepanova and Ecker 2000). Recent researches indicate that ethylene affects plant development through signaling networks involving other hormones primarily auxins and gibberellins (Stepanova and Ecker 2000; Yoo et al. 2009).

Arabidopsis mutant gene Auxin resistant1 (AXR1) is characterized by insensitivity to ethylene, but the roots and apical hook of the mutant plant show reduced sensitivity to ethylene also (Lehman et al. 1996; Stepanova and Ecker 2000). Upon cloning, AXR1 showed sequence similarity with E1, a ubiquitin-activating enzyme, and recent studies have shown that AXR1 is involved in ubiquitin-mediated protein degradation (Ruegger et al. 1998; del Pozo et al. 1998). Ethylene-insensitive root1 (eir1) and auxin1 (aux1) auxin mutants show selective resistance to ethylene in the seedling roots (Roman et al. 1995; Pickett et al. 1990). From several types of these mutant experiments, it is clear that ethylene interacts with auxins at various biochemical levels (Stepanova and Ecker 2000).

Under favorable conditions, ethylene regulates various physiological attributes of the plants along with gibberellic acid (GA). The interaction of ethylene with GA has been analyzed using stability of DELLA proteins including GA insensitive (GAI) and Repressor of ga-3 (RGA) in Arabidopsis (Weiss and Ori 2007; Chiwocha et al. 2005; Vandenbussche et al. 2007; Achard et al. 2003, 2007; Yoo et al. 2009). For example, bioactive gibberellic acid levels are low after ACC treatment and in ctr 1 mutant but increase in the ethylene-insensitive etr-2 mutant. DELLA proteins are functionally redundant and negatively regulates all aspects of GA response (Fleet and Sun 2005; Weiss and Ori 2007; Achard et al. 2003, 2006, 2007). Ethylene delays gibberellic acid-stimulated DELLA breakdown and maintains its growth suppressed, while gibberellic acid elevates plant growth via proteosome-mediated DELLA breakdown (Achard et al. 2003; Fleet and Sun 2005; Weiss and Ori 2007). Expression of bioactive GA synthesis DELLA target genes GA3ox1 and GA20ox1 is stabilized by ctr1. However, the bioactive gibberellic acid levels remain low in ctr1 mutants wherein gibberellic acid is possibly suppressed by a DELLA-independent pathway via regulation by CTR1 or EIN3 (Achard et al. 2007).

17.5 Conclusions

Plants have evolved various different mechanisms to cope up with the changing environment. Plant hormones have played a key role in the regulation of plant growth and development under varying environmental conditions. Ethylene signaling has helped the plants to adapt to these conditions. Ethylene signaling mechanism provided various insights into the role of ethylene in plant development. Much has been elucidated, but puzzles inside in the mechanism of ethylene signaling at various biochemical levels are yet to be unraveled. Genetic, molecular, and biochemical examinations have provided insights into the mechanism of ethylene signaling. With the emergence of molecular genetics, noteworthy advancements towards the explanation of ethylene action in plants have been made during the past few years. Despite our current knowledge about the mechanism of ethylene perception and transduction, many questions remain unanswered. Receptor complexes need to be characterized so as to gain insight into the actual mechanism of ethylene perception and signal transduction. Despite enough confirmation that CTR1 is directly regulated by ethylene receptors, it is yet to ascertain whether it is really so or any other protein motif helps it to bind the ER membrane and get it regulated by ethylene receptors. The function of MAPK cascade in transmission of ethylene signal is still vague and needs to be supported by further molecular evidences. The role of EIN2's association with the ethylene receptors is also intriguing. Further work is required to elucidate and unravel the various receptor complexes which might have a role in ethylene signaling. A detailed investigation of the understanding of the dynamics of protein-protein interactions such as CTR1 and EIN2 complexes is required. The protein involved in ethylene signaling needs to be crystallized for proteomics studies. It will also help in understanding the posttranslational protein modifications as well as the identification of ethylene-responsive targets. These molecular studies will build a dynamic model of the ethylene transduction pathway functional in plants (Ju and Chang 2012).

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