Tansley insight

The role of ethylene in metabolic acclimations to low oxygen

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**Contents**

Summary 64

I. Introduction 64

II. Early ethylene signalling regulates hypoxia acclimation and anaerobic metabolism 65

III. Ethylene mediates metabolic adjustments facilitating flooding survival strategies 66

IV. A potential role for ethylene in the induction of autophagy 67

V. Ethylene ameliorates excessive reactive oxygen species damage 68

VI. Conclusions and future perspectives 68

Acknowledgements 68

References 68

**Summary**

Submerged plants ultimately suffer from shortage in cellular oxygen availability (hypoxia) as a result of impaired gas diffusion underwater. The gaseous plant hormone ethylene is rapidly entrapped in submerged plant tissues and is an established regulator of morphological and anatomical flood-adaptive responses. Multiple recent discoveries suggest that ethylene also plays a crucial role in hypoxia anticipation and metabolic acclimation during plant submergence. Ethylene was shown to accelerate and enhance the hypoxic response through enhanced stability of specific transcription factors (group VII ethylene response factors). Moreover, we suggest that ethylene could play an important role in the induction of autophagy and promote reactive oxygen species amelioration, thereby contributing to enhanced survival during flooding, hypoxia, and reoxygenation stress.

**I. Introduction**

During flooding, submerged plants are exposed to an excess of water in their direct environment. Compared with an aerated environment, gas diffusion underwater is decreased approximately 10<sup>4</sup>-fold as described in Fick’s law (Fick, 1855), which restricts oxygen (O<sub>2</sub>) and CO<sub>2</sub> exchange between submerged plant tissues and the environment (Box 1). Moreover, reduced light penetration through typically turbid floodwaters can further limit photosynthesis and subsequent carbohydrate and O<sub>2</sub> production (Pedersen et al., 2018). Consequently, submerged terrestrial plants ultimately suffer from severe O<sub>2</sub> deprivation (hypoxia), terminating mitochondrial respiration and ATP production. The resulting carbohydrate and energy crisis seriously reduces plant growth and survival. Moreover, the endogenous levels of the gaseous plant hormone ethylene, produced by all cells in nearly all higher plants, significantly increase upon submergence (Voesenek & Sasidharan, 2013). This fast cellular accumulation of ethylene in submerged plants enables this hormone to act as a reliable part of the submergence sensing mechanism and initiator of a cascade of adaptive responses (Sasidharan et al., 2018). Indeed, ethylene entrapment is at the basis of lysigenous aerenchyma formation (Drew et al., 1979), the induction and outgrowth of adventitious roots (Drew et al., 1979; Visser et al., 1996), enhancement of shoot elongation, and a more erect leaf position (hyponasty; Ku et al., 1970; Banga et al., 1997). These morphological and anatomical
features all improve the aeration status of (partially) submerged plants, thus avoiding O2 depletion.

Alternatively, plants can sustain flooding-induced hypoxia through metabolic changes that ultimately result in energy maintenance and oxidative stress management. Indeed, when O2 levels decline, mitochondrial respiration and ATP synthesis are restricted and hypoxic cells subsequently rely on glycolysis for substrate-level ATP production (Geigenberger, 2003; Bailey-Serres et al., 2012). To maintain the glycolytic flux, fermentation pathways are initiated to regenerate NAD+ (Fig. 1b). As fermentation quickly depletes the plant’s carbohydrates and contributes to cytosolic acidification, alanine synthesis is enhanced to limit this carbon loss and a γ-aminobutyric acid shunt is initiated that assists in stabilization of the cytosolic pH (Ricoul et al., 2006; Miyashita & Good, 2008). In addition, energy-consuming processes such as protein synthesis are reduced (Branco-Price et al., 2008), whereas sucrose and starch metabolism are altered in several plant species/tissues to meet the increased carbohydrate demand during hypoxia (Guglielminetti et al., 1995; Loreti et al., 2018). Moreover, some reports suggest that mitochondrial respiration maybe actively downregulated in response to hypoxia (Geigenberger, 2003; Zabalza et al., 2008; Ramirez-Aguilar et al., 2011). Finally, plant cells induce multiple pathways to limit the oxidative stress damage that occurs during hypoxia and subsequent reoxygenation (Fig. 1c, d; Gonzali et al., 2015; Yeung et al., 2018). Interestingly, these hypoxia-induced acclimations are not restricted to flooding stress but seem to be an inherent part of plant development, as hypoxia also occurs in developing seeds, fruits, meristems, vascular bundles, tubers, crown gall tumours, and lateral roots (Kerpen et al., 2019; Shukla et al., 2019; Weits et al., 2019). In recent times, our understanding of adaptive processes during flooding developed significantly, and an important role for ethylene was also established in the initiation and regulation of metabolic modifications during hypoxia. Here, we discuss these ethylene-induced metabolic adjustments that prolong survival during flooding/low O2 stress.

II. Early ethylene signalling regulates hypoxia acclimation and anaerobic metabolism

Recent research has shown that ethylene not only accumulates rapidly in submerged plant tissues (Bangs et al., 1996), but also leads to rapid ethylene-dependent signalling. Indeed, nuclear accumulation of EthyleneInsensitive3 (EIN3), the principal transcriptional regulator of ethylene signalling, increased within 1 h of submergence in Arabidopsis root tips (Hartman et al., 2019). This rapid induction of ethylene signalling enables plants to anticipate upcoming hypoxia (Box 1) and was shown as crucial for improved hypoxia tolerance through enhanced expression of a core hypoxia gene set when O2 levels declined (Hartman et al., 2019). Induction of core hypoxia genes is thought to be adaptive to survive prolonged hypoxia. This core set includes genes encoding proteins involved in fermentation, energy maintenance, oxidative stress, nitric oxide (NO) scavenging, O2 sensing, and ethylene perception and biosynthesis (Mustroph et al., 2010).

A potential role of ethylene in the induction of fermentation genes has previously been investigated. Morrell and Greenway (1989) described that both alcohol dehydrogenase (ADH) and pyruvate decarboxylase (PDC) activities in maize (Zea mays) and rice (Oryza sativa) were not significantly increased upon ethylene exposure alone. Furthermore, inhibition of the ethylene receptor ETR1 by means of silver nitrate did not reduce the enhanced activity of these two enzymes during low O2 conditions (McDaniel & Binder, 2012). However, another study revealed that the hypoxic induction of ADH in Arabidopsis could be partially inhibited by aminooxy acetic acid, an inhibitor of ethylene biosynthesis (Peng, 2001). This inhibition could be rescued by 1-aminocyclopentane-1-carboxylic acid, the direct precursor of ethylene. Furthermore, two ethylene-insensitive mutants showed a strong reduction in ADH transcripts upon hypoxia. Similar to the Morrell and Greenway (1989) study, ethylene alone was unable to induce ADH transcription under normoxic conditions in Arabidopsis. Peng (2001), therefore, concluded that ethylene is needed, but not sufficient, for the induction of the core hypoxia gene ADH during later stages of hypoxia. In the wetland plant Rumex palustris, 4 h of ethylene treatment resulted in a small, but significant, induction of the core hypoxia genes ADH, PHYTOGLOBIN1 (PGB1), and ACR7 (van Veen et al., 2013). When the ethylene treatment was followed by hypoxia there was a stronger increase in several core hypoxia gene transcripts, compared with controls that did not receive ethylene pretreatment. These results showed that ethylene is an essential signal preparing R. palustris for future hypoxia through a sensitized transcriptional hypoxia response.

Recent evidence demonstrated a similar beneficial effect of ethylene in Arabidopsis and also elucidated a mechanism by which ethylene augments both the transcriptional response to hypoxia and subsequent survival (Hartman et al., 2019). This mechanism, as described subsequently, integrates ethylene signalling with the plant’s O2-sensing machinery. During normoxia, ethylene response factor proteins belonging to the class VII (ERFVIIIs) are degraded through the arginylation branch of the proteolysis 6 (PRT6) N-degron pathway. These ERFVIIIs are broken down following the oxidation of the N-terminal amino acid cysteine by plant cysteine oxidases in the presence of O2 (Gibbs et al., 2011; Licausi et al., 2011; Weits et al., 2014). A decline in either O2 or NO stabilizes ERFVIIIs and other cysteine-initiating proteins, leading to expression of core hypoxia genes and hypoxia acclimation (Gibbs et al., 2011, 2014, 2018; Weits et al., 2019). Hartman et al. (2019) demonstrated that ethylene could also impair ERFVII proteolyis, adding a third gas to the regulation of ERFVII stability. Ethylene-induced ERFVII stability is initiated by a rapid increase of PGB1 messenger RNA and protein abundance. PGB1 is a powerful scavenger of NO (Hebelstrup et al., 2012), resulting in a substantial decline of NO and consequent stabilization of ERFVIIIs (Fig. 1a). Interestingly, the resulting nuclear accumulation of ERFVIIIs does not induce the transcription of core hypoxia genes until an additional hypoxia signal (including a drop in ATP) is introduced (Schmidt et al., 2018). This corroborates older observations that ethylene alone cannot induce expression of the full core hypoxia gene set under normoxic conditions (Morrell & Greenway, 1989; Peng, 2001; van Veen et al., 2013). However, as
soon as O₂ levels decline, the transcription of core hypoxia genes is faster and stronger than in controls without prior ethylene treatment (Fig. 1b). Taken together, these results show that ethylene entrapment can prime aerobic plant tissues for potentially impending severe hypoxia (Box 1) for as long as submergence lasts or sufficient carbohydrates are available to maintain fermentation pathways. Moreover, it provides a molecular mechanism for how ethylene integrates with O₂ sensing and facilitates the appropriate induction of genes involved in fermentation, carbohydrate metabolism, and oxidative stress management during submergence in Arabidopsis (Fig. 1a,b).

III. Ethylene mediates metabolic adjustments facilitating flooding survival strategies

Ethylene initiates both the flooding ‘escape’ and ‘quiescence’ survival strategies in several plant species (Ku et al., 1970; Xu et al., 2006; van Veen et al., 2013). For example, ethylene activates the ERFVII transcription factors SNORKEL1 and 2 in deepwater rice, which in turn enhance internode elongation to escape hypoxia through restoration of above-water gas exchange (Hattori et al., 2009). Conversely, ethylene also actively represses shoot elongation in lowland rice varieties, through induction of...
the ERFVII SUBMERGENCE 1A (SUB1A; Xu et al., 2006). Interestingly, in rice, some of these ERFVII orthologues are thought to be shielded from the PRT6 N-degron pathway, placing their protein levels under direct control of ethylene signalling (Fig. 1a; Lin et al., 2019). In addition to controlling flood-adaptive growth responses, these ethylene-mediated ERFVIIs may also contribute to metabolic acclimations that allow these constraining adaptive growth responses to occur. For instance, the elongating stems of fully submerged deepwater rice showed strong induction of fermentation and glycolysis under hypoxia (Mori et al., 2019), in turn fueling the snorkelling escape response. Conversely, in SUB1A rice cultivars where growth is restricted, ethylene-regulated SUB1A limits starch breakdown and carbohydrate metabolism under submergence and post-submergence, while increasing catabolism of several amino acids such as alanine (Barding et al., 2012; Locke et al., 2018). Similarly, ethylene was shown to control replenishment of the citric acid cycle through enhanced glutamate dehydrogenase activity and breakdown of alanine under anoxia and reoxygenation in Arabidopsis (Tsai et al., 2016). Finally, both ethylene and SUB1A are also required for enhanced fermentation and the amelioration of reactive oxygen species (ROS) during plant submergence and subsequent reoxygenation (Xu et al., 2006; Fukao et al., 2011). Together, these results illustrate that ethylene co-regulates anaerobic metabolism through altered carbohydrate and amino acid breakdown over the course of a flooding event, but that the output is tailored to the plant’s survival strategy and its specific ERFVII regulators.

IV. A potential role for ethylene in the induction of autophagy

Though the induction of fermentation is crucial for anaerobic metabolism, it will rapidly deplete the plant’s carbohydrate reserves. Indeed, under carbohydrate and light-limited conditions anaerobic metabolism is ultimately dampened downstream of ERFVII action (Loreti et al., 2018). To maintain the energy balance, plants can release alternative energy-rich substrates (such as amino acids and fatty acids) through autophagy and senescence (Barros et al., 2017). We propose that ethylene could also modulate autophagy during flooding stress. Autophagy was shown to be crucial for survival during submergence in Arabidopsis (Chen et al., 2015), and is thought to play a major role in abiotic stress tolerance in plants (Avin-Wittenberg, 2019). Recent reports suggest that ethylene controls the induction of autophagy and autophagy (ATG) genes in several plant species, but only once starvation occurs (Okuda et al., 2011; Zhu et al., 2018). This is in accordance with the observation that high glucose downregulates ethylene signalling on the level of EIN3 stability through the plant glucose sensor hexokinase (Yanagisawa et al., 2003). How ethylene exactly mediates autophagy is unclear, but it could require modulation of ROS signalling and/or direct binding of EIN3 to several ATG promoters under specific conditions (Okuda et al., 2011; Zhu et al., 2018). Interestingly, in mammalian cells, hypoxia-mediated analogous proteins of the plant’s O2-sensing ERFVIIs induce autophagy of O2-consuming mitochondria and confer anaerobic cell survival (Zhang et al., 2008). Moreover, mitochondrial breakdown under severe hypoxia in plants coincides with the timing (~12 h) of the aforementioned downregulation of fermentation genes (Vartapetian et al., 2003; Loreti et al., 2018). We therefore suggest it would be highly interesting to determine if similar O2-dependent mechanisms are at play in submerged plants and if they are co-regulated by ethylene. Taken together, these reports suggest that ethylene-induced ATG genes and autophagy could contribute to the maintenance of energy production during long-term hypoxia through both selective autophagy of energy-consuming compounds and generation of alternative energy-rich substrates (Fig. 1c).
V. Ethylene ameliorates excessive reactive oxygen species damage

Once flood waters recede, reoxygenation coincides with increased ethylene production and excessive ROS formation damaging plant cells (Yeung et al., 2019). Accordingly, enhanced control of ROS detoxification was shown to be crucial for hypoxia, reoxygenation, and flooding tolerance (Gonzali et al., 2015; Yeung et al., 2018). Although ethylene is known to control ROS production through increased NADPH oxidase levels and activity (Desikan et al., 2006), a functional link with ethylene in reducing and ameliorating ROS damage has hardly been investigated during flooding stress. However, evidence in the literature shows that ethylene regulates ROS-scavenging compounds, and we therefore propose that ethylene is also essential for ROS amelioration during flooding stress. First, one study suggests that ethylene mediates ROS detoxification during reoxygenation in Arabidopsis (Tsai et al., 2014). Moreover, ethylene-regulated oxidative stress tolerance has been extensively studied in several plant species for a plethora of other abiotic stresses, including drought, heat, freezing, and salt stress (Wu et al., 2008; Peng et al., 2014). Interestingly, heat, drought, and salt stress tolerance were also shown to be dependent on enhanced ERFVII stability (Vicente et al., 2017), and ERFVII isos regulate several genes that confer oxidative stress tolerance (Gonzali et al., 2015; Papdi et al., 2015). Finally, it was shown that ethylene, EIN3, and EIN3-target transcription factors directly control multiple genes that code for proteins involved in ROS amelioration across multiple plant species, such as carbonic anhydrase, catalase, peroxidase, and ascorbic acid biosynthesis (Wu et al., 2008; Peng et al., 2014; Zhang et al., 2016). Together, these observations support that ethylene could also play an important role in ROS detoxification and oxidative stress tolerance during flooding and reoxygenation stress (Fig. 1d).

VI. Conclusions and future perspectives

For decades, ethylene has been known as the regulator of flood-adaptive growth responses that avoid or delay hypoxia, but was not considered to mediate hypoxia acclimation in plants. Recent findings show that ethylene entrapment during flooding also plays a crucial role in hypoxia anticipation and acclimation. In addition, ethylene appears to play an important role in metabolic reconfiguration during hypoxia and reoxygenation through the induction and regulation of ERFVII transcription factors, hypoxia-adaptive gene expression, autophagy, and ROS detoxification in plants (Fig. 1). Interestingly, whereas some non-flood-adapted terrestrial plant species, such as Arabidopsis, use ethylene to acclimate to hypoxia, other species, like the wild plant Rumex acetosa and the cultivated Solanum lycopersicum, do not (van Veen et al., 2013; Hartman et al., 2019). In the future it would be worthwhile to uncover what molecular mechanisms uncouple ethylene signalling from hypoxia acclimation responses in these species, with the ultimate aim to (re)introduce adaptive mechanisms in important, but flood-sensitive crop species.

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