Signal Dynamics and Interactions during Flooding Stress[1][OPEN]

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Flooding is detrimental for nearly all higher plants, including crops. The compound stress elicited by slow gas exchange and low light levels under water is responsible for both a carbon and an energy crisis ultimately leading to plant death. The endogenous concentrations of four gaseous compounds, oxygen, carbon dioxide, ethylene, and nitric oxide, change during the submergence of plant organs in water. These gases play a pivotal role in signal transduction cascades, leading to adaptive processes such as metabolic adjustments and anatomical features. Of these gases, ethylene is seen as the most consistent, pervasive, and reliable signal of early flooding stress, most likely in tight interaction with the other gases. The production of reactive oxygen species (ROS) in plant cells during flooding and directly after subsidence, during which the plant is confronted with high light and oxygen levels, is characteristic for this abiotic stress. Low, well-controlled levels of ROS are essential for adaptive signaling pathways, in interaction with the other gaseous flooding signals. On the other hand, excessive uncontrolled bursts of ROS can be highly damaging for plants. Therefore, a fine-tuned balance is important, with a major role for ROS production and scavenging. Our understanding of the temporal dynamics of the four gases and ROS is basal, whereas it is likely that they form a signature readout of prevailing flooding conditions and subsequent adaptive responses.

Global flood risk under climate change has increased dramatically in recent decades (Hirabayashi et al., 2013). In the last 50 years, increasingly frequent and severe flooding events have negatively impacted terrestrial plant life. When flooded, gas exchange is severely restricted between the plant and its environment, causing several internal changes in plants. Flooded plant organs can experience a shortage of oxygen and/or CO_2 and accumulate high levels of the volatile hormone ethylene. In addition, there are changes in the concentrations of oxygen-derived free radicals, nitric oxide (NO), and reactive oxygen species (ROS; Bailey-Serres and Voesenek, 2008). The generation, dynamics, concentration, and exact balance of these substances in flooded cells depend on the plant organ and type of flooding. We propose that these substances and their interaction during flooding provide plants with a signature readout of prevailing flooded conditions, which elicits an appropriate

ADVANCES

- Plants use spatial and temporal dynamics in ethylene, O_2, NO, and ROS to convey information about flooding conditions.
- A complex web of interactions between these various signals fine-tunes plant flooding responses.
- Ethylene accumulates during submergence regardless of water turbidity and light penetration, making it a reliable flooding signal.
- The hypoxia-induced NO burst is critical for hypoxia acclimation, possibly via *S*-nitrosylation of key proteins involved in flooding adaptation.
- ROS homeostasis is important for hypoxia survival.
- Ethylene, NO, and ROS dynamics could also be important signals during recovery, with roles that are distinct from those during flooding.

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adaptive response. Here, we outline current knowledge regarding the generation, dynamics, and interactions of these signals in flooded plants and their influence on downstream responses affecting plant survival.

SIGNAL GENERATION

Tissue-Level Variation in Oxygen and CO_2

Light energy drives the fixation of CO_2 into carbohydrates via photosynthesis. These carbohydrates are vital structural building blocks for plants and also are respired to generate energy, a process that requires sufficient oxygen supply. Flooding-induced reduction in oxygen and CO_2 hinders respiration and photosynthesis and imposes a severe energy and carbohydrate deficit in submerged plants. Oxygen and CO_2 dynamics are the direct result of consumption, production, and diffusive resistance, and these factors can vary considerably depending on organ and flooding type (Voesenek and Sasidharan, 2013).

Light availability is determined by floodwater clarity and depth. Murky water can almost completely block light reaching the plant surface (Vervuren et al., 2003), thus hampering underwater photosynthesis. Furthermore, limited CO_2 access would severely reduce the rate of carbon capture and limit oxygen release from the plant (Mommer and Visser, 2005). Studies have shown that, in clear water, submerged shoots do not have an oxygen deficit (Mommer et al., 2007; Lee et al., 2011; Vashisht et al., 2011; van Veen et al., 2013) and, in some cases, can even be hyperoxic (Pedersen et al., 2016). Such high oxygen levels combined with CO_2 limitation most likely lead to increased photorespiration and prevent any net carbon gain for the plant (Mommer et al., 2005; Mommer and Visser, 2005). When plants are submerged in dark conditions, internal oxygen levels decline rapidly as a result of respiratory consumption and limited diffusion from the environment. However, shoot internal oxygen levels rarely decline to zero (Vashisht et al., 2011; Winkel et al., 2013). Although gas diffusion is impaired, the leaf tissue is surrounded by water that usually has close to ambient oxygen levels. The flat leaf, sometimes in combination with gas films, then does allow some gas exchange (Pedersen et al., 2009; Verboven et al., 2014).

Roots experience a completely different environment when submerged. Flooded soils are rapidly depleted of oxygen, as water fills existing airspaces and respiring microorganisms and roots consume the available oxygen, leading to an anoxic environment. Heterotrophic roots invariably will rapidly consume internal oxygen and, by virtue of their cylindrical anatomy, have less favorable environmental gas exchange (Greenway et al., 2006). Arabidopsis (*Arabidopsis thaliana*) roots were hypoxic even under well-drained conditions, but when submerged, they became anoxic within 15 min (Vashisht et al., 2011). This was alleviated by submerging in light conditions, indicating that, even in Arabidopsis, internal shoot-to-root oxygen diffusion is important. This highlights the importance of tissue porosity, tissue tortuosity, and diffusion distance for root oxygen supply (Colmer, 2003). CO_2 from respiring roots and rhizosphere microorganisms can lead to a high-CO_2 environment. This could possibly influence roots via an effect on intracellular pH and some key metabolic enzymes (Greenway et al., 2006).

Oxygen sensing was recently shown to occur via the proteolysis of group VII ethylene response factors (ERFVIIs). ERFVIIs are important transcriptional regulators of hypoxia responses via the control of hypoxia-adaptive gene expression (Hinz et al., 2010; Gibbs et al., 2011; Licausi et al., 2011; Gasch et al., 2016). Studies in Arabidopsis have revealed that the presence of a characteristic N-terminal motif makes ERFVIIs direct targets of the N-end rule pathway of proteolysis, where, in the presence of both ambient NO and oxygen, these proteins are ubiquitinated and degraded (Gibbs et al., 2011, 2014; Licausi et al., 2011). When either the NO or oxygen concentration declines, ERFVIIs are no longer flagged for ubiquitination, accumulate, and activate downstream target genes, including those required for fermentation.

Starvation Strongly Influences Flooding Responses

During complete submergence, plants experience a strong decline in energy and carbon availability. This is due to reduced photosynthesis, either through a lack of light or a reduced rate of CO_2 diffusion, and due to impaired respiration through reduced oxygen availability. Plants can sense and integrate a variety of signals relaying cellular energy and carbon status. This includes Suc sensing via trehalose metabolism (Schluepmann et al., 2003), Glc via Hexokinase1 (Moore et al., 2003), and Fru via NAC089 (Li et al., 2011). These responses are tightly balanced by the opposing actions of the conserved kinases Suc-nonfermenting1-related protein kinase1 (SnRK1) during starvation and by target of rapamycin kinase during energy abundance (Lastdrager et al., 2014; Baena-González and Hanson, 2017). These central regulators maintain energy homeostasis and stress acclimation through major transcriptomic, translatomic, and metabolic reprogramming (Lastdrager et al., 2014). Low-energy signaling is intricately connected with plant hormone signaling pathways, especially abscisic acid and ethylene (Yanagisawa et al., 2003; Finkelstein and Gibson, 2002; Cho et al., 2010; Ljung et al., 2015).

Starvation leads to the down-regulation of energetically expensive secondary metabolic processes and protein translation, a crucial adaptation to prioritize energy expenditure during flooding (Branco-Price et al., 2008; Edwards et al., 2012; Sorenson and Bailey Serres, 2014). Arabidopsis plants experiencing starvation in darkness had a highly similar transcriptomic response to those under submerged conditions (Lee et al., 2011; van Veen et al., 2016). This indicates that low-energy signaling occurs via a generic signaling mechanism regardless of the origin of the starvation stress.

However, the regulatory action of the low-energy-sensing machinery might not always be beneficial during flooding. For instance, some rice (*Oryza sativa*) accessions can germinate under anoxic conditions but require a large amount of readily available sugars to do so (Magneschi and Perata, 2009; Loreti et al., 2016). One way these sugars are perceived is by trehalose-6-phosphate (T6P) levels, which directly reflect Suc availability (Yadav et al., 2014). However, in rice, high T6P levels prevent starch degradation via the inhibition of SnRK1 activity, an undesirable process during germination. This is avoided by T6P degradation via the induction of a T6P phosphatase in varieties that harbor a specific T6P phosphatase gene (*OsTPP7*). Active T6P removal reduces the sensitivity of rice to its available sugar levels and facilitates starch mobilization to create a strong flux of sugars that fuels anaerobic germination (Kretzschmar et al., 2015). Energy levels during the anoxic establishment of plants thus can be surprisingly high (Ishizawa et al., 1999). The regulation of energy signaling (e.g. trehalose metabolism) occurs during flooding in several species and tissues (Jung et al., 2010; van Veen et al., 2013; Kretzschmar et al., 2015; Akman et al., 2017), suggesting that adjusting sensitivity to sugar and energy signaling could be an essential part of regulating flooding responses.

Ethylene Invariably Accumulates to High Concentrations

All plant cells, except those of a few aquatic plant species with a permanently submerged life style (Voesenek et al., 2015), are capable of synthesizing ethylene, and endogenous levels are determined by production rates and loss via diffusion to the atmosphere. Ethylene biosynthesis starts with the conversion of the amino acid Met to S-adenosyl-L-Met (SAM) by SAM synthetase. The enzyme 1-aminocyclopropane-1-carboxylic acid (ACC) synthase (ACS) then catalyzes the production of ACC from SAM followed by its oxidation to ethylene by ACC oxidase (ACO) in a reaction requiring oxygen. Both ACS and ACO belong to large multigene families and are regulated by various external and internal cues to control ethylene production. In cells of flooded organs, endogenous ethylene levels increase rapidly, mainly due to hampered diffusion to the surrounding water. Ethylene accumulates to high physiologically saturating levels in several plant species in flooded shoots and roots (Voesenek and Sasidharan, 2013). Ethylene can reach levels that are 20-fold (1 μL L^{-1}) higher than nonsubmerged tissue within 1 h (Fig. 1). Upon soil flooding, root ethylene levels were variable across species, as determined by production rates and diffusion capacity. Wetland species possessing aerenchymatous tissue could vent entrapped ethylene and had lower accumulated ethylene in flooded roots (Visser and Pierik, 2007). An overview of ethylene concentrations in various plant species and organs upon flooding can be found in the study of Voesenek and Sasidharan (2013). Ethylene accumulation is not known to be affected directly by changes in light levels during flooding. Thus, unlike oxygen and CO_2 levels, which can be highly variable and influenced by several

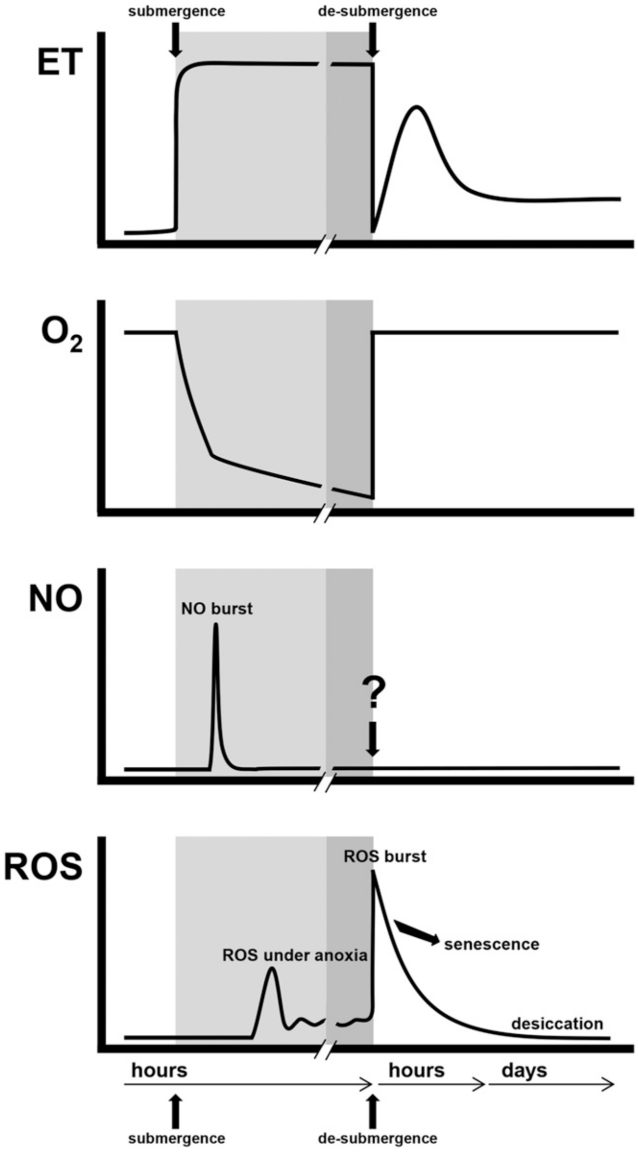

Figure 1. Signal dynamics during a typical light-limited flooding event. During early submergence (light gray shading), ethylene accumulates rapidly while oxygen levels decline gradually. Upon hypoxia, NO and ROS bursts occur. Upon recovery from prolonged submergence (dark gray shading), there is transient ethylene (ET) production while oxygen levels return to normal. NO dynamics upon desubmergence are unknown, but a strong ROS burst likely occurs. The schematic conveys general trends based on current knowledge and is intended to show that flooding signals can display strong variability during different phases of the flooding event. Furthermore, these signal dynamics are strongly dependent on flood conditions, plant species, and the organ and tissues affected.

factors, high ethylene concentrations are the most consistent, pervasive, and reliable signal conveying early flooding (Voesenek and Sasidharan, 2013; Sasidharan and Voesenek, 2015). Since ACC conversion to ethylene requires oxygen, ethylene production cannot occur under true anoxic conditions; therefore, it is not a signal in these extreme situations.

NO Metabolism

NO is a short-lived, highly reactive molecule regulating several plant developmental and stress responses (Astier et al., 2011; Manjunatha et al., 2012; Farnese et al., 2016). Plants regulate endogenous NO levels via the control of biosynthesis and scavenging. The regulation of NO biosynthesis in plants is poorly understood. Several studies suggest that the main source of NO production is via enzymatic and nonenzymatic reduction of nitrite (Planchet et al., 2005; Mur et al., 2013; for review, see Chamizo-Ampudia et al., 2017). Nitrite production is highly dependent on nitrate reductase (NR) activity. The dependency of NO production on nitrite availability makes NR the major player in NO production (Magalhaes et al., 2000; Gupta and Kaiser, 2010; Gupta et al., 2011; Chamizo-Ampudia et al., 2017) The removal of synthesized NO can occur via multiple reactions. NO can react chemically with oxygen to produce nitrite and NO_3^- or with ROS to form additional reactive nitrogen species (Delledonne et al., 2001; Chamizo-Ampudia et al., 2017). NO can be scavenged by glutathione to produce *S*-nitrosylated glutathione (Wilson et al., 2008; Frungillo et al., 2014). Finally, phytoglobins (previously called class I nonsymbiotic hemoglobins; Voesenek et al., 2016) use oxygen to dioxygenate NO in the plant cell to form nitrate (Hebelstrup et al., 2006, 2012; Hill, 2012).

There are limited and contrasting data regarding temporal and spatial NO dynamics in flooded plants. In Arabidopsis and cotton (*Gossypium hirsutum*), NO emissions declined in the aerial plant tissues, while emissions increased in three waterlogged deciduous tree species (Magalhaes et al., 2000; Copolovici and Niinemets, 2010; Zhang et al., 2017). However, NO dynamics under hypoxia have been studied more extensively. Both cellular and exogenous NO levels increased in various plant species during hypoxia (Planchet et al., 2005; Mugnai et al., 2012; Gupta and Igamberdiev, 2016). This NO burst during hypoxia is thought to result from enhanced NR activity and nitrite accumulation, providing a substrate for NO production (Planchet et al., 2005; Mugnai et al., 2012; Gupta and Igamberdiev, 2016). In roots, NO bursts could be specific to the transition and division zone and dependent on hypoxia sensing in the root apex (Mugnai et al., 2012; Fig. 1). Posttranslational modification of NR via phosphorylation effectively inactivated NO synthesis in tobacco (*Nicotiana tabacum*; Lea et al., 2004), and this phosphorylation may be impaired under hypoxic conditions, leading to higher NR activity. NR activity also is lowered under reduced light conditions (Nemie-Feyissa et al., 2013), with potential implications for NR activity during submergence in turbid waters. In conclusion, the temporal and spatial dynamics of NO, and therefore its effects, are likely dependent on the conditions of flooding.

ROS Metabolism

ROS are highly reactive, chemical species formed by the stepwise reduction of molecular oxygen. ROS include superoxide ($O_2^{\cdot -}$), singlet oxygen, hydrogen peroxide (H_2O_2), and the hydroxyl radical (Demidchik, 2015; Mittler, 2017). ROS are by-products of various metabolic pathways and are produced enzymatically or nonenzymatically. Nonenzymatic ROS production can occur in chloroplasts and mitochondria via electron transport chains (ETCs). In both organelles, the occasional leakage of electrons to oxygen during electron transport can result in the partial reduction of oxygen, generating $O_2^{\cdot -}$, which subsequently gives rise to other more reactive ROS (Møller, 2001; Asada, 2006). Enzymatic ROS production can occur at several sites within the cell, including peroxisomes, cell walls, plasma membrane, and apoplast (Mignolet-Spruyt et al., 2016). Peroxisomes are the site of several oxidative metabolic processes that can generate ROS, such as β-oxidation of fatty acids and photorespiration (Del Río and López-Huertas, 2016). In the peroxisome, $O_2^{\cdot -}$ is formed by xanthine oxidase (Bolwell and Wojtaszek, 1997), while glycolate oxidase catalyzes H_2O_2 generation (Del Río and López-Huertas, 2016). Another enzymatic ROS source is plasma membrane-bound NADPH oxidases, or respiratory burst oxidase homologs (RBOHs). RBOHs reduce extracellular oxygen to $O_2^{\cdot -}$ using cytosolic NADPH (Møller, 2001). Plants counter excessive ROS production with an efficient scavenging machinery. This consists of ROS-scavenging enzymes like superoxide dismutase, ascorbate peroxidase (APX), catalase (CAT), and glutathione peroxidase and antioxidant molecules like glutathione, ascorbic acid, and α-tocopherol (Mittler et al., 2004; Steffens et al., 2013).

Considering that ROS originate from oxygen, it is expected that, under flooding-induced hypoxic conditions, ROS production also is restricted. However, several studies report increased ROS accumulation under hypoxia/anoxia (Fig. 1; Chang et al., 2012; Pucciariello et al., 2012; Paradiso et al., 2016). Under oxygen deprivation, ROS production likely still occurs in the mitochondria, chloroplasts, and peroxisomes. Anoxia inhibits the mitochondrial ETC, resulting in the formation of mitochondrial ROS (Chang et al., 2012), and chloroplastic ROS generation might occur via a similar process. ROS also could be formed by peroxisomes during flooding in light. When terrestrial plants photosynthesize underwater, photorespiration rates can increase (Mommer and Visser, 2005). Photorespiration is one route via which peroxisomal H_2O_2 production can be boosted (Del Río and López-Huertas, 2016).

Furthermore, the antioxidant system can be negatively affected by hypoxia (Lasanthi-Kudahettige et al., 2007), disrupting the tightly regulated balance between scavenging and production. During flooding and hypoxia, ROS also is produced in a regulated manner via RBOHs. In Arabidopsis, *RBOHD* is up-regulated specifically during flooding and hypoxia and is one of the core hypoxia genes (Mustroph et al., 2009; Pucciariello et al., 2012; Yao et al., 2017). ROS signaling via regulated ROS production is considered an important component of hypoxia signaling and adaptive responses to flooding (Pucciariello et al., 2012; Steffens et al., 2012; Yamauchi et al., 2014; Gonzali et al., 2015; Yamauchi et al., 2017).

SIGNAL INTERACTIONS

Ethylene and Hypoxia Signaling Interact with NO

The interplay between ethylene and NO has often been described but has rarely been investigated mechanistically. However, chemical or genetic impairment of one of these pathways often affects the other and impacts plant responses (Magalhaes et al., 2000; Manjunatha et al., 2012; Asgher et al., 2017). Like ethylene, NO also could accumulate to higher concentrations in flooded tissues due to restricted gas diffusion. However, since NO is highly reactive and short-lived, accumulation is likely limited without the additional hypoxic NO burst described earlier. Accordingly, waterlogged Arabidopsis and cotton plants showed elevated ethylene emission and signaling, respectively, but declining NO emission from aerial tissues (Magalhaes et al., 2000; Zhang et al., 2017). In addition, exogenous NO application increased ethylene production in various plant species, possibly via enhanced ACO activity (Magalhaes et al., 2000; Manac'h-Little et al., 2005). On the other hand, NO levels declined in ethylene-deficient or constitutive mutants (Magalhaes et al., 2000; Liu et al., 2017). Thus, both gases may affect each other under the conditions that vary over the course of a flooding event.

The NO-scavenging phytoglobins could potentially facilitate cross talk between NO and ethylene. However, conclusive mechanistic evidence is lacking. Phytoglobin mRNA levels increased under waterlogging and hypoxic conditions in multiple plant species (Hebelstrup et al., 2012; van Veen et al., 2013; Mira et al., 2016). Phytoglobin silencing in Arabidopsis and maize (*Zea mays*) increased ethylene and NO emissions and up-regulated ethylene biosynthesis and signaling genes (Hebelstrup et al., 2012; Mira et al., 2016). Interestingly, NO also enhanced phytoglobin mRNA abundance in rice, cotton, and spinach (*Spinacia oleracea*; Ohwaki et al., 2005; Qu et al., 2006; Bai et al., 2016), hinting at a feedback mechanism. In the wetland species *Rumex palustris*, phytoglobin transcript levels increased following a short ethylene treatment and could potentially reduce NO in these tissues (van Veen et al., 2013). Taken together, phytoglobins modulate NO and ethylene levels, while these gases in turn also affect phytoglobin abundance.

Cross talk and feedback loops between NO and ethylene also may occur at the level of ERFVIIs. ERFVII stability and action depend strongly on NO and oxygen levels (Gibbs et al., 2011, 2014; Licausi et al., 2011). When either the NO or oxygen concentration declines, ERFVIIs accumulate and facilitate downstream target gene transcription. Interestingly, ERFVII-regulated genes that contain the hypoxia-responsive promoter element include multiple ethylene signaling genes and the NO-scavenging phytoglobin, HEMOGLOBIN1 (Gasch et al., 2016). In addition, the expression of several ERFVIIs also is regulated by ethylene (Chang et al., 2013). In conclusion, ERFVII abundance is regulated by NO, oxygen, and possibly ethylene, while ERFVII action, in turn, can induce positive feedback loops for ethylene biosynthesis and NO scavenging (Gasch et al., 2016).

The Functional Role of NO

While exact NO dynamics in flooded plants remain vague, it is clear that an NO upsurge during hypoxia has functional implications for survival (Mugnai et al., 2012; Gupta and Igamberdiev, 2016; Mira et al., 2016). For instance, chemically blocking the hypoxia-induced NO burst at the onset of hypoxia strongly impaired hypoxia survival in maize root tips (Mugnai et al., 2012). In addition to its role in regulating ERFVII abundance, NO also may exert a regulatory role during flooding or hypoxia, by posttranslational modification of proteins via *S*- or metal-nitrosylation and Tyr nitration (for review, see Astier et al., 2011; León et al., 2016). Exogenous NO application in Arabidopsis effectively *S*-nitrosylated proteins involved in respiration, metabolism, signaling, and stress responses (Lindermayr et al., 2005; Astier et al., 2011; León et al., 2016). *S*-Nitrosylated proteins potentially involved in flooding signaling and adaptation include ERFVIIs, cytochrome *c* oxidase (COX), aconitase, phytoglobins, and the H_2O_2 scavenger APX1 (Millar and Day, 1996; Perazzolli et al., 2004; Gupta et al., 2012; Gibbs et al., 2014; Begara-Morales et al., 2016). Indeed, some reports indicate that an NO burst may inhibit COX activity (Millar and Day, 1996; Brown, 2001). On the other hand, *S*-nitrosylation and, therefore, inhibition of aconitase leads to enhanced alternative oxidase (AOX) activity under hypoxia in Arabidopsis (Gupta et al., 2012). This altered bioactivity of COX and AOX by NO suggests a role in the tight regulation of respiration and oxygen consumption in plant mitochondria during hypoxia.

Phytoglobins mediate $NAD(P)^+$ regeneration under hypoxia via the so-called phytoglobin/NO cycle (Perazzolli et al., 2004; Igamberdiev et al., 2005; Gupta and Igamberdiev, 2016). In the absence of oxygen, plant mitochondria can keep the electron transport functional using nitrite as the electron acceptor (Gupta et al., 2005; Gupta and Igamberdiev, 2011). This nitrite reduction to NO in the ETC recycles NAD(P)H to $NAD(P)^+$ and leads to some ATP production. This process, in addition to the ATP generated by fermentation, retains the energy status of cells as long as sugar availability is sufficient. The NO produced can be scavenged by phytoglobins via *S*-nitrosylation, and this is thought to contribute to the regeneration of $NAD(P)^+$ and nitrate, in turn fueling glycolysis and ATP production. The observed induction of phytoglobin transcripts by ethylene might enhance this process in some plant species when submerged (van Veen et al., 2013). Finally, the importance of phytoglobins for hypoxia acclimation is highlighted in various studies. Phytoglobin-impaired mutants showed reduced hypoxia tolerance, while overexpression enhanced tolerance in multiple plant species (Dordas et al., 2003; Mira et al., 2016). In conclusion, the phytoglobin/NO cycle shows a crucial strategy of adaptation leading to a retained energy status under hypoxia.

ROS-Mediated Hypoxia Acclimation

ROS production and signaling during hypoxia are considered essential for stress acclimation. In hypoxic Arabidopsis seedlings, *RBOHD* mRNA levels are strongly up-regulated (Pucciariello et al., 2012; Yang and Hong, 2015). Elevated H_2O_2 levels in Arabidopsis seedlings shortly after the imposition of anoxia (Baxter-Burrell et al., 2002; Pucciariello et al., 2012) are linked to RBOH-mediated electron flow from NADPH to oxygen, resulting ultimately in H_2O_2 generation. Accordingly, this hypoxic H_2O_2 increase is absent and survival is compromised in *rbohD* seedlings or upon chemical inhibition of RBOH activity. RBOH activity and, therefore, H_2O_2 production during oxygen deprivation is regulated by the activity of at least two other hypoxia-inducible proteins: HYPOXIA RESPONSIVE UNIVERSAL STRESS PROTEIN1 (HRU1) and RHO (Ras homologous)-RELATED PROTEIN FROM PLANTS2 (ROP2; Baxter-Burrell et al., 2002; Gonzali et al., 2015).

Hypoxic conditions convert ROP2 to its active form GTP-ROP2 and activate RBOH-mediated H_2O_2 production. The subsequent ROS burst triggers the expression of downstream beneficial targets, including fermentation genes (e.g. *ALCOHOL DEHYDROGENASE* [*ADH*]) required for hypoxia acclimation. However, ROP2-triggered H_2O_2 signaling also up-regulates *ROP GUANOSINE TRIPHOSPHATASE-ACTIVATING PROTEIN4* (*ROPGAP4*), a negative regulator of ROP2. ROPGAP4-mediated inactivation of ROP2 consequently dampens RBOHD-mediated ROS production. In *ropgap4* mutants or in lines expressing a constitutively active form of ROP2, *ADH* expression and activity were increased but tolerance was reduced (Baxter-Burrell et al., 2002). Thus, negative feedback inhibition of ROP2 and the tight regulation of ROS production play a role in preventing oxidative stress and improving hypoxia tolerance.

Another hypoxia-inducible gene and ERFVII target regulating RBOH-mediated ROS production is *HRU1*. HRU1 interacts with ROP2-GTP and RBOHD both in vitro and in vivo, and *hru1* mutants lack the hypoxic H_2O_2 burst observed in wild-type Arabidopsis seedlings. HRU1 can exist as cytosolic HRU1-HRU1 dimers or monomers that can take another interacting protein partner. The balance between these dimers and monomers is essential for the control of ROS production. A shift in balance toward HRU1 monomers might be favored during hypoxia, because, under these conditions, HRU1 translocation to the plasma membrane was observed. Here, it may form an HRU1-ROP2-RBOHD complex and influence ROS production (Gonzali et al., 2015). Together, these findings indicate that apoplastic ROS production is a tightly regulated process involving multiple protein interactions and is essential for hypoxia acclimation and survival.

Functional ROS-Ethylene Interactions

Plants growing in flooded environments use morphological adaptations to improve internal aeration and avoid flooding-induced hypoxia. These traits include the formation of gas-filled voids or aerenchyma in existing roots/shoots or shoot-borne, aerenchyma-rich adventitious roots. Aerenchyma, either constitutive or induced, improve gas diffusion between flooded and nonflooded plant parts and permit aerobic respiration to continue in affected organs (Voesenek and Bailey-Serres, 2015). Several studies have revealed that interactions between ROS and ethylene signaling regulate lysigenous (formed by regulated cortical cell death) aerenchyma development and adventitious roots (Steffens et al., 2012; Yamauchi et al., 2014, 2017).

Ethylene-induced formation of lysigenous aerenchyma under oxygen-deprived conditions, via the control of ROS production, has been demonstrated in species such as rice, wheat (*Triticum aestivum*), and maize (Yamauchi et al., 2014, 2017; Takahashi et al., 2015). Stem aerenchyma in deepwater rice internodes required ethylene-mediated ROS accumulation to induce parenchymal cell death (Steffens et al., 2012). In rice adventitious roots, stagnant flooding increased ethylene levels due to a combination of restricted diffusion and enhanced biosynthesis. This increased transcript abundance and, subsequently, the activity of *RBOHH*. Interestingly, the strongest *RBOHH* expression was in the root cortical cells and corresponded with ROS accumulation and programmed cell death (PCD) only in these cells. Accordingly, in adventitious roots of CRISPR/Cas9 *RBOHH* knockouts, H_2O_2 and aerenchyma were reduced significantly under stagnant conditions (Yamauchi et al., 2017). Considering that ethylene accumulates in all cells, the question arises of how cellular specificity is achieved for ROS generation and subsequent cell death. The answer might lie in the distinct characteristics (thinner cell walls, higher ROS, and low starch) and higher ethylene sensitivity of pre-aerenchymatous cells (Justin and Armstrong, 1991; Visser and Bögemann, 2006; Steffens et al., 2012). In situ staining of stagnant rice roots showed $O_2^{\cdot -}$ accumulation and a radial expansion of collapsed cells starting from the midcortical cells and spreading to the neighboring cells within the cortex. RBOHH-mediated $O_2^{\cdot -}$ could be the signal propagating cellular collapse to adjacent cells (Yamauchi et al., 2017). Such a systemic signaling role has been demonstrated in Arabidopsis, where RBOHD-generated H_2O_2 stimulated RBOHD activity in adjacent cells, resulting in an autopropagating wave of ROS production (Miller et al., 2009; Mittler et al., 2011). Whether such a systemic signal transmission occurs during aerenchyma formation has yet to be confirmed.

Interactions between ethylene and ROS signaling also regulate adventitious root growth and emergence in rice. Preceding adventitious root emergence, the epidermal cells overlying adventitious root primordia have to die (Steffens et al., 2012). Ethylene stimulates this epidermal cell death by promoting RBOH-mediated H_2O_2 accumulation. In epidermal cells that undergo PCD, ethylene also reduced the expression of *Metallothionein2b* (*MT2b*), a ROS scavenger (Steffens et al., 2012). Accordingly, enhanced constitutive epidermal cell death was observed in *MT2b* knockdown mutants, which also had high H_2O_2 levels. Ethylene and ROS signaling also mediate adventitious root growth regulation. Ethylene-induced adventitious root growth clearly requires ROS, since chemical manipulation of ROS levels clearly affected adventitious root formation. However, this was highly specific to the nature of ROS perturbation. For example, chemical inhibition of CAT and RBOH activity clearly restricted ethylene-induced adventitious root growth. In contrast, adventitious root growth was unaffected in *MT2b* knockdown lines with enhanced H_2O_2 (Steffens et al., 2012). Adventitious root growth and emergence needs to be coordinated precisely with epidermal cell death to protect the emerging root primordium. This requires accurate signaling of the location where cell death should occur. Ethylene and ROS alone could elicit local epidermal cell death only when a mechanical stimulus (the physical pressure of the emerging root) was also present. According to the current hypothesis, adventitious root formation requires ethylene-mediated ROS production in both the adventitious root primordium and the overlying epidermal cells. ROS accumulation in the adventitious root primordium promotes growth. The growing root exerts a mechanical force on specific epidermal cells above it, whereby mechanical signaling and ethylene-induced ROS signaling together trigger PCD (Steffens et al., 2012).

SIGNAL GENERATION AND INTERACTION UPON REAERATION

When floodwaters subside, submergence-mediated damage is compounded further. Plants are reexposed to higher oxygen concentrations and increased light intensity, resulting in further oxidative stress through a burst of ROS production (Fukao et al., 2011; Luo et al., 2012; Alpuerto et al., 2016; Fig. 1). Postsubmergence ROS damage is parallel to oxidative damage during hypoxic conditions, in which ROS disrupts the photosynthetic apparatus (Luo et al., 2011; Panda and Sarkar, 2012; Alpuerto et al., 2016) and, consequently, hinders photosynthetic recovery and the replenishment of carbohydrate reserves (Bhowmick et al., 2014; Gautam et al., 2016). During reoxygenation and reillumination, ROS and photoinhibition can further trigger desiccation stress (Setter et al., 2010), leaf senescence (Gautam et al., 2016; Liu and Jiang, 2016), and cell death (Tamang et al., 2014). Upon reoxygenation, ROS accumulation likely occurs due to a combination of reduced scavenging capacity and increased ROS production (Rhoads et al., 2006; Blokhina and Fagerstedt, 2010; Shapiguzov et al., 2012). Excessive ROS accumulation is associated with the high-energy demands of reactivated mitochondrial and photosynthetic metabolism due to reoxygenation and reillumination, causing electron leakage in ETCs and proton leakage in mitochondrial matrixes (Elstner and Osswald, 1994; Smirnoff, 1995; Roach et al., 2015). Excess oxygen reacting with ROS-related by-products produced during hypoxic conditions also can trigger additional ROS formation.

While ethylene is well established as a signal triggering adaptive responses during flooding, less is known of its role during flooding recovery. Several studies have reported increased ethylene biosynthesis and enhanced *ACS* and *ACO* expression in plants upon reoxygenation (Khan et al., 1987; Voesenek et al., 2003; García et al., 2014; Tsai et al., 2014; Ravanbakhsh et al., 2017). Anoxia limits ethylene biosynthesis, since ACO requires oxygen for ACC conversion to ethylene (Yang and Hoffman, 1984). However, reoxygenation may trigger increased ethylene biosynthesis, promoted by elevated levels of the rate-limiting ACC enzymes. The role of ethylene during reoxygenation could be distinct from its regulatory roles during flooding and hypoxia (Fukao et al., 2011; Tsai et al., 2014, 2016). In *R. palustris*, ethylene accumulation upon desubmergence correlated with increased ACC levels and its conversion to ethylene by increased ACO activity (Voesenek et al., 2003). This rapid induction of ethylene synthesis upon desubmergence promoted shoot elongation as a strategy to avoid complete submergence later (Voesenek et al., 2003). In addition, shoot elongation rates in *R. palustris* upon desubmergence was dependent on submergence duration, suggesting that time taken for ACC accumulation could be the rate-limiting determinant (Voesenek et al., 2003). Thus, the basal level of ACC biosynthesis could be critical for postsubmergence ethylene responses.

In Arabidopsis seedlings, ethylene signaling was important for limiting postanoxic injury (Tsai et al., 2014). Ethylene response transcription factor1 (ERF1), a marker of the ethylene transduction pathway, together with ERF2 were induced during reoxygenation. Moreover, two ethylene-insensitive mutants, *ein2-5* and *ein3eil1*, displayed increased chlorosis and cell damage upon reoxygenation compared with the wild type. Genes encoding heat shock factors, heat shock proteins, and antioxidants were enriched significantly, implying the potential challenges caused by reoxygenation. The activation of ROS amelioration genes suggests that ethylene could be important in eliminating ROS produced upon reaeration. However, ethylene accumulation under submergence negatively affected antioxidant levels upon desubmergence in intolerant rice cultivars (Kawano et al., 2002). This again suggests that regulatory roles of ethylene during hypoxia and reoxygenation could be different. In addition, comparison of the transcriptome of wild type and ethylene-insensitive Arabidopsis mutants also suggested that ethylene might be involved in regulating distinct pathways upon reoxygenation, such as jasmonate signaling, feedback inhibiting its own production, and suppressing dehydration via the inhibition of abscisic acid signaling (Tsai et al., 2014).

CONCLUSION

The energy and carbon crisis in flooded plants poses the largest threat to survival. Sometimes starvation is ameliorated through increasing gas exchange via aerenchyma and adventitious root development. However, a large majority of flooding responses, such as reduced protein synthesis and down-regulation of secondary metabolism, most likely are coordinated via elaborate sugar-sensing mechanisms. Although energy signaling is essential to plant survival, by itself it is not specific enough to reliably perceive flooding. However, a plant can utilize a variety of other cues to precisely gauge a flooding event.

Changes in the gases ethylene, oxygen, and CO_2 do not necessarily mean that plants use them to initiate adaptive responses. Ethylene is well established as an important signal triggering several flood-adaptive traits (e.g. adventitious root and escape growth; Sasidharan and Voesenek, 2015). Rapid ethylene accumulation regardless of the flooded conditions makes it a reliable signal, in contrast with oxygen levels that are highly variable. For a long time, it was unclear if oxygen sensing occurred through direct mechanisms or through an indirect effect of oxygen on metabolism. It is now evident that plants sense oxygen through the oxygen-dependent degradation of ERFVIIs (Gibbs et al., 2011; Licausi et al., 2011). Changes in CO_2 could potentially also act as a flooding signal. However, although several possible roles have been suggested (Greenway et al., 2006), currently, there is no evidence for a significant function in plant flooding responses (Voesenek et al., 1997; Colmer et al., 2006).

Plants have relatively little control over these signals, which, for a large part, result directly from the restriction of gas diffusion underwater. However, an adaptive down-regulation of oxygen consumption rate has been suggested (Zabalza et al., 2009). In this sense, ROS production during flooding is similar, since it also occurs in an unregulated process, mainly at the ETCs and peroxisomes. However, regulated ROS production via the RBOHs also occurs and is essential for hypoxia acclimation and survival (Loreti et al., 2016). In aerenchyma and adventitious root formation, a certain background level of unregulated ROS, together with ethylene-regulated scavenging, is required to induce cell death in specific cells (Steffens and Rasmussen, 2016). Taken together, rather than a cue to gauge flooding, ROS is a signaling intermediate in hypoxia sensing and ethylene-regulated root development.

NO dynamics during flooding remain unclear. However, an NO burst does occur upon hypoxia, linked to hypoxia-induced NR activity. This could make NO, unlike ROS, a possible signal to assess the flood event. However, NO is strongly regulated by phytoglobin, which is under both ERFVII and ethylene control (Fig. 2). Thus, NO also assumes the role of a signaling intermediate.

Although ethylene invariably accumulates upon flooding, a plant needs hypoxia sensing to activate fermentation pathways. That this metabolic adaptation is linked to oxygen-sensing ERFVIIs makes sense, as it prevents fermentation in shoots submerged under light conditions where not aerobic respiration but photosynthesis is impaired. Interestingly, oxygen availability seems of little importance in aerenchyma formation or adventitious root development (Fig. 2). Given that, even under drained soil conditions, roots experience hypoxia, this could mean that oxygen is not such a robust flooding signal for roots. Instead, ethylene is the key player mediating this plasticity in root development. These separate roles of ethylene and oxygen permit a response tailored to specific flooding conditions.

Little is known regarding oxygen and ethylene interactions. However, ethylene mutants have reduced hypoxic *ADH* up-regulation (Peng et al., 2001; Yang et al., 2011), ethylene-induced escape growth was enhanced under hypoxic conditions (Voesenek et al., 1997), and ethylene pretreatment can enhance anoxia tolerance (van Veen et al., 2013). Here, there is a potential role for ROS and NO. Both are affected by and have an impact on hypoxia and ethylene signaling. While NO destabilizes ERFVIIs, it is also scavenged by the ethylene-inducible and ERFVII target phytoglobin and provides a mechanistic link between ethylene and NO (Fig. 2). Similarly, ROS is part of both ethylene and ERFVII signaling pathways. However, it remains unclear whether ROS derived from either signal are interchangeable.

It is clear that plants use a multitude of signals to assess a flooding event and trigger appropriate responses that prolong survival (Fig. 2). Interestingly, the role of these signals changes through time, as is apparent from the distinct signal interactions during and after submergence (Fig. 1). Relatively little is known about signaling dynamics during recovery and how this links to responses initiated during flooding. Additionally, electrophysiological changes occur within

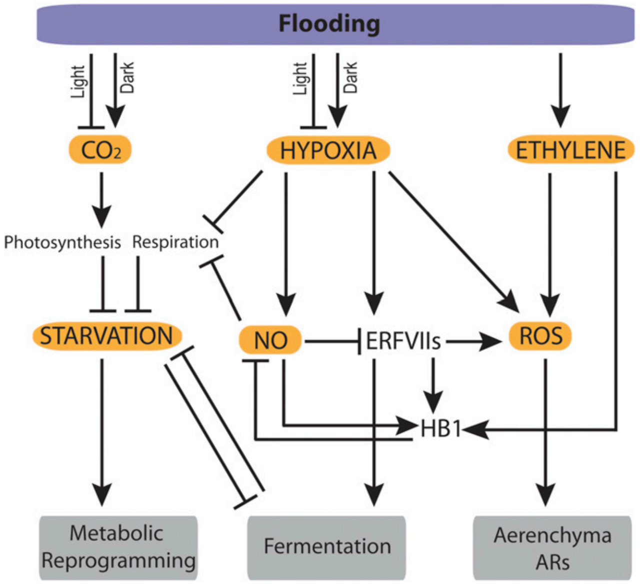

Figure 2. Overview of the major flooding signals (yellow boxes) and their interactions, leading to the regulation of major adaptive responses (gray boxes). Restricted gas exchange between the plant and its environment during flooding results in alterations in endogenous levels of CO_2, oxygen, and ethylene. These primary signals can further give rise to the secondary signals ROS, NO, and starvation. Changes in the availability of oxygen and CO_2 are the net result of production, consumption, and diffusion and, therefore, are highly dependent on light conditions during flooding. Changes in CO_2 likely influence flooding responses, due to its role as a substrate for photosynthesis. CO_2 limitation in the light leads to starvation and subsequent metabolic reprogramming via energy signaling mechanisms. A decline in oxygen levels limits aerobic respiration but also triggers downstream acclimation responses via the ERFVII transcription factors. Oxygen-dependent stabilization of ERFVIIs via the N-end rule enhances hypoxia-responsive gene expression, including the fermentation enzymes (e.g. *ADH*). However, an efficient transcriptional induction requires an ERFVII-dependent ROS burst through RBOHD. ROS also is formed nonenzymatically during hypoxia via the ETC. ERFVII degradation also is dependent on NO. Hypoxia induces NO accumulation, probably due to increased NR activity and subsequent nitrite reduction at the mitochondrial ETC. However, NO also is scavenged during hypoxia by hemoglobin (HB1), which, in turn, is induced by ERFVIIs. Oxygen levels also play an essential role in energy homeostasis, not just via their role as a substrate for respiration. The activation of fermentation through hypoxia-stabilized ERFVIIs boosts ATP production, diminishing starvation. At the same time, fermentation is highly dependent on sufficient sugar availability and, thus, is inhibited by starvation. Additionally, NO increase upon hypoxia is suggested to inhibit COX and the tricarboxylic acid cycle enzyme aconitase, altering efficient ATP generation via respiration. Ethylene biosynthesis rates can change upon flooding, but reduced gas exchange is the primary reason for ethylene accumulation to saturating levels. Ethylene accumulation plays a pivotal role in aerenchyma and adventitious root (AR) development mediated by interactions with ROS. PCD of epidermal cells covering AR primordia is required for penetration and is essential in the cortex for aerenchyma formation. Ethylene-mediated ROS accumulation occurs via RBOH activity or due to reduced ROS scavenging.

OUTSTANDING QUESTIONS

- How do the spatial and temporal responses to ethylene, O_2, ROS, and NO vary during flooding and subsequent recovery?
- To what extent are dynamics of ROS and NO observed in hypoxic systems relevant to actual flooded conditions?
- Do regulated and uncontrolled ROS or NO production have similar roles during flooding and recovery?
- What is the mechanism of ethylene and oxygen crosstalk?
- Is there variation across species in the ability to perceive and process flooding signals, and does this correspond with flooding tolerance?

minutes of hypoxia/anoxia, but their physiological role remains unestablished (Wang et al., 2017). Likewise, NO and ROS bursts occur within the first hours of hypoxia. It is unclear whether these bursts only push the plant into an altered physiological state that it can homeostatically maintain or whether they are recurring events during flooding. Too little is known of the temporal dynamics of flooding signals, and the future challenge lies in determining this to assess the relevant positive and negative regulatory feedback loops under actual flooded conditions and how they influence plant response and survival.

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