The hypoxia-reoxygenation stress in plants.

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Highlight: Plant responses to hypoxia and subsequent reoxygenation are implemented through an intricately network of processes involving oxygen sensing, RNA function, chromatin remodeling, gene expression, and protein synthesis. All processes together allow plants to either escape or tolerate the stress condition.
Abstract

Plants are very plastic in adapting growth and development to changing adverse environmental conditions. This feature will be essential for plants to survive climate changes characterized by extreme temperatures and rainfall. Although plants require molecular oxygen (O$_2$) to live, they can overcome transient low O$_2$ conditions (hypoxia) until return to standard 21% O$_2$ atmospheric conditions (normoxia). After heavy rainfall, submerged plants in flooded lands undergo transient hypoxia until water recedes and normoxia is recovered. The accumulated information on the physiological and molecular events occurring during the hypoxia phase contrasts with the limited knowledge on the reoxygenation process after hypoxia, which has been often overlooked in many studies in plants. Phenotypic alterations during recovery are due to potentiated oxidative stress generated by simultaneous reoxygenation and reillumination leading to cell damage. Besides processes like N-degron proteolytic pathway-mediated O$_2$ sensing, or mitochondria-driven metabolic alterations, other molecular events controlling gene expression have been recently proposed as key regulators of hypoxia and reoxygenation. RNA regulatory functions, chromatin remodeling, protein synthesis and post-translational modifications must all be deeply studied in the next years to improve our knowledge on hypoxia-reoxygenation transition in plants, a topic with relevance in agricultural biotechnology in the context of global climate change.

Key words: development, flooding, hypoxia, mitochondria, nitric oxide, oxidative stress, oxygen sensing, phytohormones, reillumination, reoxygenation, submergence, waterlogging
Abbreviations: ERFVII, group VII of the Ethylene Response Factor family; NO, nitric oxide; ROS, reactive oxygen species
Introduction

Global climate change during the last decades is characterized by extreme temperatures and the onset of water-related opposite stress conditions such as drought and flooding. The Food and Agriculture Organization of the United Nations (FAO) has estimated losses around 19 billion dollars in developing world agriculture (2005-2015) due to floods (http://www.fao.org/news/story/en/item/1106977/icode/). An effective strategy for risk reduction in agriculture must be grounded on a better knowledge of plant adaptation to climate change and the elucidation of key processes involved in plant stress responses. Adverse effects may be different depending on the flooding condition, affecting only the roots (waterlogging), or both roots and shoots (partial or full plant submergence) (Sasidharan et al., 2017). In flooded plants, oxygen depletion due to less availability in water compared to air restrains growth and causes cell damage. These effects increase with duration of submergence period and with high temperatures as oxygen consumption due to plant respiration increase (Deutsch et al., 2015). Besides, the developmental stage of the submerged plants is critical for the damage extension, with developmental transitions, such as seed germination and early post-germinative growth or flowering, being markedly sensitive to low oxygen availability (Considine et al., 2017; Le Gac and Laux, 2019). Moreover, some of the developmental transitions are intrinsically associated to hypoxic conditions in certain organs or tissues that undergo exposure to low oxygen even in the absence of stress. Flooding also causes crop losses due to reduced nitrogen availability from soil because of enhanced denitrification under anaerobic conditions (Sjøgaard et al., 2018; Yu et al., 2019). In addition to abiotic factors, flooding favors the development of many plant pathogens, so crops suffer increased disease problems after floods (Gravot et al., 2016). These detrimental effects can be sometimes counteracted through hypoxia-triggered expression of genes coding for proteins that promote immunity (Hsu et al., 2013).

Hypoxic episodes experienced by living organisms are always transient or intermittent, and after that they undergo a reoxygenation process that brings them back to standard oxygen conditions. The hypoxia-reoxygenation process has a decisive impact on human health, from cardiological and neurological damage by intermittent hypoxia (Mallet et al., 2018), to ischemia-reperfusion during surgery or in transplanted organs (Granger and Kviety, 2015). Although this topic has been extensively studied in animal models, much less is known on this transition in plants. Due to the sessile nature of plants, which grow firmly anchored to the ground through their roots, they have developed strategies allowing survival
under submergence conditions in flooded lands after heavy rainfall (Phukan et al., 2016). Plants also sense the subsequent transition to normoxia when water recedes (Tamang and Fukao, 2015). While many studies have been performed in plants during the hypoxic phase, much less is known about the physiological and molecular events that occur during reoxygenation after hypoxia. It is worth mentioning that most of the studies on hypoxia caused by plant submergence have been performed under complete darkness. This approach has the advantage of minimizing the endogenous production of $O_2$ by photosynthesis, thus ensuring the environmentally imposed hypoxia is not counteracted. However, this experimental approach has also some drawbacks. In nature, submerged plants are usually exposed to lower light intensity not to darkness, so this experimental design does not fit to naturally occurring hypoxic conditions. Moreover, the subsequent reoxygenation after hypoxia is usually performed under standard light conditions, which is closer to natural recovery after flooding. The recovery process thus involves not only reoxygenation but also a darkness to light transition, causing light-induced reduction in photosynthetic capacity by photoinhibition that is accompanied by the production of reactive oxygen and cell damage (see Yeung et al., 2019 for a complete review on post-flooding responses involving reoxygenation and reillumination stresses). Enhanced survival potential in the light is likely due to increased rates of photosynthesis that leads to greater carbohydrate and molecular oxygen production (Mommer and Visser, 2005). These effects explain why plant submerged under light display higher survival than those submerged under darkness.

Diverse conditions causing hypoxia and downstream responses

Living organisms sometimes undergo low $O_2$ availability conditions that do not prevent but alter life. When plants are in excessively wet environment such as flooded lands, the excess of water surrounding roots and/or shoots severely hampers $O_2$ diffusion. The water excess also causes flooding of the cell apoplast that remains even after water recedes, thus causing the so-called hyperhydricity characterized by several morphological abnormalities linked to a severe impairment in gas exchange (van den Dries et al., 2013). Independently of the conditions causing low oxygen availability (Loreti and Perata, 2020), plants respond to hypoxic stress essentially through two alternative strategies (Fig. 1A). Wetland plants tolerate longer and stronger hypoxic conditions than terrestrial plants through combination of escape strategies, promoting growth of certain organs to reach normoxic status, and quiescence
strategies, slowing growth and saving metabolic resources (Nakamura and Noguchi, 2020). Both strategies differ in terms of phytohormone signaling involvement as well as N source utilization, and determine the degree of tolerance to hypoxia in wetland plants (Nakamura and Noguchi, 2020). In rice plants under partial submergence, the escape strategy seems to require a metabolic reprogramming that involves central carbon and amino acid metabolism (Fukushima et al., 2020). In turn, most terrestrial plants including several model plants such as Arabidopsis, tomato and maize can survive under short-term hypoxia stress but cannot survive long-term O₂ deficiency and severe anaerobic conditions. Plants of Brassicaceae species efficiently cope with the energy crisis caused by low-oxygen stress by tightly controlling their energy metabolism, thus enhancing tolerance and adaption (Hwang et al., 2020). In tomato plants, which are susceptible to flooding stress, several adaptive responses help to mitigate the deleterious effects of hypoxia in roots. Among them, the ethylene-mediated aerenchyma formation, the stem hypertrophy and the formation of adventitious roots facilitate oxygen transport and may act as an escape mechanism enabling hypoxia tolerance (Mignonli et al., 2020). Genes coding for proteins with a potential role in aerenchyma formation have been identified using an RNA-Seq approach in tomato roots under hypoxia (Safavi-Rizi et al., 2020).

Plants experience hypoxia also throughout development under non-stress environmental conditions (Fig. 1B). Although stress-induced hypoxia is, by far, more extensively studied than developmental-related hypoxia responses, low oxygen availability has emerged as an important developmental cue, essential for meiosis (Kelliher and Walbot, 2012), seed germination (Gibbs et al., 2014) and photomorphogenesis (Abbas et al., 2015). It seems also important in regulating developmental transitions by preserving genome integrity through maintaining quiescence within meristem cell niche (Considine et al., 2017). Proliferating and undifferentiated cells in meristems operate in chronic hypoxic niches where oxygen availability determines active growth (Weits et al., 2020). For instance, oxygen-dependent signaling seems to control the timing and effective coordination for bud burst in grapevine (Meitha et al., 2018). Besides the potential roles in developmental phase transitions, hypoxia is a natural condition for some plant storage tissues or organs such as fruits (Rolletschek et al., 2002; Cukrov, 2018; Xiao et al., 2018). Multiple metabolic evidence supports the development of hypoxic niches in diverse organs/tissues in plants (Armstrong et al., 2019). Fruits do not have an active O₂ transport mechanism allowing its even distribution to cells within, and are often covered by low-permeability layers, thus
causing a steep gradient from outside to inside (Ho et al., 2011). Hypoxic niches develop also in the tip and the stele of roots (Armstrong and Beckett, 1987; Gibbs et al., 1998). Sometimes, features of hypoxic metabolism occur within the tissues/organs even when surrounded by air. This is the case of germinating seeds of several species (Al-Ani et al., 1985; Raymond et al., 1985). Pollen seems to have also anaerobic metabolism under normoxic environmental conditions, thus suggesting it may experience hypoxia (Scott et al., 1995). However, it has been reported that O₂ readily entered the pollen, so that anaerobic metabolism would be controlled not by oxygen availability, but rather by sugar supply (Tadege and Kuhlemeier, 1997), therefore remaining unclear whether pollen could be considered as a true hypoxic core in a normoxic plant. It has been proposed that signaling from hypoxic niches to the surrounding tissues is required to achieve acclimation-induced tolerance of the organ or even the whole plant to hypoxic conditions (Armstrong et al., 2019). Several signaling pathways have been reported to be involved in hypoxia/anoxia-triggered responses including those involving NO and ROS (Pucciariello and Perata, 2017), ethylene (Voesenek and Sasidharan, 2013), and cytosolic Ca²⁺ (Igamberdiev and Hill, 2018).

**Oxygen sensing in plants largely depends on the N-degron pathway-mediated degradation of ERFVIIs but alternative sensing mechanisms exist**

Hypoxia-reoxygenation triggered responses require that plant cells sense changes in the levels of O₂. The way plant cells sense O₂ levels largely relies on the control of the stability of transcription factors of the group VII of the Ethylene Response Factor family (therein ERFVIIs). Among five ERFVIIs in Arabidopsis, three of them, Related to AP2 RAP2.2, 2.3 and 2.12, are constitutively expressed (Papdi et al., 2015; Bui et al., 2015), and two of them are induced under low oxygen conditions, Hypoxia Responsive HRE1 and 2 (Licausi et al., 2010; Yang et al., 2011; Park et al., 2011). In submerged Arabidopsis, ERFVIIs may act as either positive regulators of the hypoxic response or as repressors of oxidative-stress related genes, depending on the developmental stage (Giuntoli et al., 2017). Accumulated information during the last ten years points to the N-terminal modifications of the ERFVII proteins, through the N-degron pathway (formerly called N-end rule pathway), and the subsequent proteasomal degradation as key oxygen sensing mechanism in plants (Gibbs et al., 2011; Licausi et al., 2011; Sasidharan and Mustroph, 2011; Holdsworth et al., 2020). As summarized in Figure 2, N-terminal modifications of ERFVIIs occur through the Cys/Arg-
branch of the general N-degron pathway. It requires the oxidation of the N-terminal Cys2, resulting after removal of the initial Met residue by methionine aminopeptidases, from thiol to sulphinic acid. This reaction is catalyzed by a family of dioxygenases called Plant Cysteine Oxidases (PCO) directly enabling further arginyl transferase (ATE)-catalysed arginylation of N-degron pathway targets (Weits et al., 2014; White et al., 2017; 2018). PCO family comprises five members with different substrate specificities (White et al., 2018). Two of them PCO1 and 2 are hypoxia-inducible and they are conserved in plants and animals (Masson et al., 2019). It has been reported that plant PCOs have the kinetic and substrate specificities required to act as oxygen sensors (White et al., 2018). This strategy to sense oxygen by plants is like that for animals since both are based on the O2-dependent proteolysis of constitutively expressed factors that differ in different organisms (Licauisi et al., 2020). Although Cys2 oxidation-mediated degradation of ERFVIIs has been reported to require both O2 and NO in Arabidopsis (Gibbs et al., 2014), the ERFVII N-degron-based degradation of this factors in yeasts does not require NO (Puerta et al., 2019). Noteworthy, PCO1 and PCO2 genes are strongly up regulated by NO (Castillo et al., 2018). However, the nature and site of NO action in this process in Arabidopsis remains to be identified. Nevertheless, the N-degron pathway-mediated degradation of ERFVIIs determines the levels of these transcription factors. Stabilization during hypoxia leads to high levels whereas proteolytic degradation during reoxygenation decreases them (Fig. 2). Since ERFVIIs regulate a wide array of physiological processes including seed germination, aerial growth, stomata aperture, apical hook formation and photosynthetic competence, oxygen availability greatly determines plant performance.

Oxygen is involved in many enzyme-catalyzed redox reactions and redox chemistry is an essential feature for life on Earth (Dietz, 2003). Any enzyme catalyzing redox reactions might, in principle, act as an oxygen sensor when oxygen levels change below the affinity constant of the enzyme for that substrate (Wang et al., 2017; Schmidt et al., 2018a; Iacopino and Licausi, 2020). Multiple sensing mechanisms would allow the activation of different low oxygen-triggered responses in specific spatial and temporal patterns in distinct cells or even organelles inside the cells, tissues, organs, or parts of the plant. This multiplicity of sensing mechanisms can definitely be advantageous in waterlogged plants to orchestrate different responses in the submerged and aerial parts of the plants. Moreover, the existence of oxygen sensing mechanisms of high and low affinity allows also discriminating between responses in extreme or moderate low oxygen environments, which may happen even in different
subcellular locations of the cells. Oxidative protein folding in the endoplasmic reticulum (ER) relies on the activities of protein disulfide isomerase (PDI) and thiol oxidase, which transfers electrons from PDI to molecular oxygen (Aller and Meyer, 2013). When oxygen levels decrease below the constant affinity of ER thiol oxidase this enzyme could be functionally impaired and might act as sensors for low-oxygen conditions (Schmidt et al., 2018a). Several plasma membrane and tonoplast ion channels have been also proposed to play oxygen-sensing functions (Wang et al., 2017). In roots, the Hydraulic Conductivity of Root 1 (HCR1) protein has been proposed to sense both K⁺ and O₂ availability to control water transport, and it may represent another hypoxia signaling pathway in plants (Shahzad et al., 2016). The identification of novel oxygen sensors will likely provide new insights into oxygen-sensing origins and mechanisms in eukaryotes (Gibbs and Holdsworth, 2020). The link between oxygen availability and chromatin methylation status has emerged recently both in plants and animals (Gibbs et al., 2018; Batie et al., 2019; Chakraborty et al., 2019), thus pointing to chromatin modifications and remodeling as a relevant regulation level in hypoxia-related gene expression, but also as a potential mechanism to transduce information derived from oxygen sensing events. This sort of connection between oxygen sensing and chromatin modifications may have an important relevance not only to integrate different sensor mechanisms, but also to prepare plants for subsequent hypoxia stress onslaughts or even to transmit a primed hypoxia tolerance status to the progeny through epigenetic regulation.

Control of responses to hypoxia by regulatory RNAs

During the onset of hypoxia-triggered responses, RNAs of different sizes and origins as well as RNA-related molecular processes seem to play key regulatory roles. Hypoxia-responsive microRNAs, trans-acting small interfering RNAs and natural antisense short interfering RNA (natsiRNA) have been all reported to regulate responses to hypoxia (Moldovan et al., 2010a, b). Long non-coding RNAs are differentially expressed upon waterlogging stress (Yu et al., 2020), and they also seem to regulate plant tolerance to hypoxia (Song and Zhang, 2017). The hypoxia-responsive and salicylic acid (SA)-induced AtR8 IncRNA seems to be involved in activating Nonexpressor of Pathogenesis-Related Gene 1 (NPR1)-mediated and Pathogenesis-Related Proteins 1 (PR-1)-independent defense and root elongation through functional interaction with WRKY53/WRKY70 transcription factors (Li et al., 2020). This may represent a link between IncRNAs and lipid signaling in hypoxia-triggered responses, as
alterations in the levels of VLCFA during hypoxia were also involving NPR1-mediated signaling (Xie et al., 2015). Moreover, the participation of SA-related regulatory factors and cellular processes, such as cell death, in hypoxia responses strongly suggests the existence of further connections between hypoxia and defense against pathogens. In fact, submergence strongly induces the transcription of many defense genes in Arabidopsis (Hsu et al., 2013). Whether these non-coding RNA-mediated processes are relevant in driving plant responses to hypoxia must be further substantiated with more work.

The generation of noncanonical mRNA isoforms is an important feature of the hypoxia stress response (de Lorenzo et al., 2017). During hypoxia, plants retain poly(A) RNA in the nucleus as a survival strategy (Niedojadło et al., 2016), and it has been reported the involvement of Oligouridylate Binding Protein 1 in dynamic and reversible aggregation of translationally repressed mRNAs during hypoxia (Sorenson and Bailey-Serres, 2014). Macromolecular RNA-protein complexes contribute to the preferential translation of stress-responsive gene transcripts during hypoxia (Lee and Bailey-Serres, 2020). Post-transcriptional alternative splicing is also a key process in rice germination under hypoxic conditions (Chen et al., 2019). Moreover, RNA signaling controls hypoxia-induced gene regulation in Arabidopsis through convergence of ARGONAUTE1 (AGO1) signaling with the AGO4-dependent RNA-directed DNA methylation pathway (Loreti et al., 2020). All together these data point to a relevant RNA-mediated regulation of plant responses during hypoxia. However, to our knowledge, no data on the specific involvement of regulatory RNAs or RNA-related processes on the reoxygenation after hypoxia has been reported.

Carbon and nitrogen metabolism during hypoxia and reoxygenation

Mitochondria orchestrate changes at the transcriptomic, proteomic, metabolomic and enzyme activity levels not only during the hypoxic phase but also during reoxygenation (Shingaki-Wells et al., 2014). A large proportion of those changes are related to primary carbon metabolism. A homeostatic mechanism, detecting sugar starvation, dampens the hypoxia-dependent transcription to reduce energy consumption and preserves carbon reserves for regrowth when oxygen availability is restored (Cho et al., 2019a). Ethanol fermentation is one of the main metabolic adaptations to ensure energy production under hypoxic conditions in higher plants. Fermentation consumes NADH and requires pyruvate decarboxylation followed by reduction to ethanol, catalyzed by pyruvate decarboxylases (PDC) and alcohol
dehydrogenases (ADH), respectively. This process is largely conserved in land plants from different phyla as an adaptive mechanism to hypoxia, but its regulation and catalysis seem to have evolved during evolution (Bui et al., 2019). PDC and ADH conservation has made them good markers of hypoxia conditions, and accordingly they have been extensively used in the studies of low oxygen-related process in plants.

Pyruvate may be competitively used by the alanine aminotransferase/glutamate synthase cycle instead of PDCs, then leading to alanine accumulation and NAD⁺ regeneration during hypoxia. This represents a functional link between C, N metabolism and hypoxia-triggered responses, and constitutes a potential mechanism to save carbon resources in a nitrogen store instead of being lost through ethanol fermentative pathway (Diab and Limami, 2016). Wheat root nitrogen uptake and translocation to the shoots is severely reduced under O₂ restriction, thus causing reduced shoot growth and grain yield (Herzog et al., 2016). Under hypoxia, wheat roots accumulate high amounts of γ-aminobutyrate and lactate, whereas alanine accumulate in both roots and shoots (Mustroph et al., 2014). During the reoxygenation after hypoxia, the alanine aminotransferase/glutamate dehydrogenase cycle may reverse the process yielding pyruvate and NADH that can be directed to the TCA cycle fully functional during normoxic conditions. Regarding this C-N interaction, nitrate nutrition increases energy efficiency under hypoxia in Arabidopsis (Wany et al., 2019). Nitrate-supplied but not ammonium-supplied plants display high levels of nitrate reductase activity, NO, phytoglobin, and ERFVII transcription factor gene expression, thus enhancing energy yield under hypoxia (Wany et al., 2019). Nitrite, which is the product of the photosynthetic nitrate reduction, has an important role in maintaining mitochondrial function through the reduction of nitrite to NO by the mitochondrial electron transport chain under hypoxia (Gupta et al., 2017).

In Arabidopsis, sucrose catabolism required for the sucrose-ethanol metabolic transition under hypoxia might be dependent on the function of hypoxia-inducible sucrose synthases SUS1 and SUS4 (Bieniawska et al., 2007). However, it has been later reported that the sucrose synthase pathway is not the preferential route for sucrose metabolism under hypoxia (Santaniello et al., 2014). Instead, starch seems to be required for plants to survive under submergence as well as for ensuring the rapid induction of genes encoding enzymes required for anaerobic metabolism (Loreti et al., 2018). Moreover, sugar starvation effects on hypoxia-responsive gene expression occurs downstream of the hypoxia-dependent
stabilization of ERFVIIIs and independently of the energy sensor SNF1-related kinase 1.1 (SnRK1.1) protein (Loreti et al., 2018).

O₂ availability severely determines metabolism in all living organisms. Actually, it has been recently proposed that O₂, rather than glucose, NAD(P)H, or ATP, is the molecule that provides the most energy to animals and plants and is crucial for sustaining large complex life forms (Schmidt-Rohr, 2020). In plants, oxygen availability and biomass production are ensured by active photosynthesis (Stirbet et al., 2020). Oxygen acts as an efficient acceptor of the mitochondrial electron transport chain, which is coupled to the generation of ATP and reducing power, both essential for functional metabolism. As mentioned above, O₂ can be replaced by nitrite under hypoxia, thus maintaining ATP production and electrochemical gradient by coupling its reduction to the translocation of protons from the inner side of mitochondria (Gupta et al., 2020). As summarized in Figure 3, mitochondria seem to act as organelles involved in NO generation under hypoxia but also as a target of NO regulatory actions (Igamberdiev et al., 2014). Nitrite-dependent NO production in mitochondria is facilitated by the function of the Alternative Oxidase (AOX) complex in hypoxia but, in turn, minimizes NO synthesis, ROS, peroxynitrite formation and tyrosine nitration under normoxia (Kumari et al., 2019). Therefore, AOX might function as a key switch in the hypoxia-reoxygenation transition by regulating oxidative and nitrosative triggered protein modifications during re-aeration of plants (Fig. 3). A recent report pointed to AOX as a relevant factor in preventing nitro-oxidative stress during the reoxygenation period, thereby allowing the recovery of energy status following hypoxia (Jayawardhane et al., 2020).

In poplar trees, hypoxia led to reduced N uptake and N content together with a significant reduction in root biomass thus decreasing the root-to-shoot ratio (Liu et al., 2015). In contrast, root hypoxia up-regulates the enzymes involved in nitrogen assimilation in tomato plants (Horchani and Aschi-Smiti, 2010). Hypoxia also alters the transport of nitrogen-containing molecules from roots to shoots, and it has been proposed that foliar nitrate assimilation helps to improve the tolerance of roots to low oxygen conditions (Oliveira et al., 2013). Nitrogen metabolism under hypoxia favors the formation of NO, which can be synthesized as a result of a side-reaction of nitrate reductase activity (Lozano-Juste and León, 2010; Chamizo-Ampudia et al., 2017) in the cytoplasm, or as a by-product of the mitochondrial electron transport chain functioning with nitrite as electron acceptor (Gupta and Igamberdiev, 2011). However, the actual levels of NO inside cells are not only controlled...
by oxygen availability (Pucciariello and Perata, 2017), but largely reduced by scavengers. Among them, phytoglobins strongly modulate NO-regulated responses to hypoxia (Fig. 3), but also function as an energy saving system under low oxygen conditions (Vishwakarma et al., 2018). Overexpression of phytoglobins attenuates the responses of plants to hypoxic and anoxic conditions (Cochrane et al., 2017; Fukudome et al., 2019; Andrzejczak et al., 2020). Moreover, the overexpression of phytoglobins in hypoxic domains of the elongation zone of corn roots activates the fermentation pathway to sustain metabolism and production of ATP (Youssef et al., 2019).

**Lipid metabolism as cause and target of hypoxia-reoxygenation responses**

A large body of evidence already exists to demonstrate that lipids act both as triggering factors and as targets of hypoxia-reoxygenation responses. Hypoxia stress lowers the content of total lipids by inhibiting lipid biosynthesis and stimulating lipid degradation, thus leading to the accumulation of free fatty acids (Xu et al., 2020). Regarding lipid metabolism as triggering factor for low oxygen-related responses, the key functions exerted by ERFVII in hypoxia-triggered responses depend on the release of ERFVII from the complexes with membrane-associated Acyl-CoA Binding Proteins ACBP3 and 2 (Li and Chye, 2004; Kosmacz et al., 2015; Schmidt and van Dongen, 2019). An ATP-dependent shift in the levels of oleoyl-CoA and linoleyl-CoA seems to be relevant for the dynamics of ERVII-mediated hypoxia-triggered responses in Arabidopsis (Schmidt et al., 2018b; Zhou et al., 2020). Another signaling-related link between hypoxia and lipid metabolism in plants comes from the hypoxia-regulated production of calcium and ROS, which is triggered by D type phospholipases (PLDs)-mediated release of phosphatidic acid (Lindberg et al., 2018; Premkumar et al., 2019). Wheat plants tolerate hypoxia stress by regulating lipid remodeling causing multiple changes in the endogenous levels of lipids (Xu et al., 2019). Regarding lipids as targets, hypoxia caused the down regulation of cuticular lipid synthesis genes and the increased cuticle permeability in Arabidopsis (Kim et al., 2017), thus enhancing water entry, hyperhidricity, and displacing air from the apoplast (Lee et al., 2020; Xie et al., 2020). Moreover, suberin biosynthesis seems to be also involved in waterlogging-triggered responses in pedunculate oak roots (Le Provost et al., 2016). Suberin seems to be involved in the formation of hypertrophied lenticels in stems through the hypertrophy of secondary
aerenchyma, thus sealing the stem, limiting the radial diffusion of oxygen, and enabling oxygen transport down to the roots (Shimamura et al., 2010).

Very Long Chain Fatty Acids (VLCFAs) are direct precursors for the biosynthesis of cuticular lipids and sphingolipids, the latter being precursors in the formation of ceramides, which serve as both intermediates for turnover of sphingolipids and backbones for synthesis of more complex sphingolipids. The unsaturation of VLCFA-derived ceramides is a protective strategy for hypoxic tolerance in Arabidopsis that seems to be exerted through the modulation of ethylene signaling (Xie et al., 2015a, b). The sensitivity of plants to hypoxic stress seems to be negatively correlated with the rosette hydrogen peroxide levels, so that the hypoxia-activation of VLCFAs as well as VLCFA-derived ceramides may enhance plant survival during hypoxic stress by modulating the cellular homeostasis of ROS (Xie et al., 2015a, b). Moreover, elongation of VLCFAs and derivatives further influences cuticular lipid biosynthesis, so that they play crucial roles in cuticle formation and their potential functions as barriers in gas exchange processes.

In contrast to known functions of lipids during the hypoxia responses, much less known is the involvement of lipids during the subsequent re-aeration phase. During re-aeration, plant reoxygenation leads to the production of ROS and the activation of antioxidative systems (Biemelt et al., 1998; Garnczarska et al., 2004). It has been reported in hypoxia-pretreated lupin roots that reoxygenation causes a strong induction of oxidative stress and antioxidant systems that is accompanied by the accumulation of lipid peroxides (Garnczarska et al., 2004). Lipid peroxidation that occurs when hypoxic cells are re-aerated seem to be a key process for the destabilization of membranes leading to cell damage (Rawyler et al., 2002). In Arabidopsis, jasmonates, which are lipids with a specialized signaling function, restricts root elongation under low oxygen conditions (Shukla et al., 2020), and are also key regulators of the transcriptional activation of antioxidant systems, acting through the attenuation of oxidative damage during the reoxygenation response after hypoxia (Yuan et al., 2017). In rice, jasmonates also contribute to enhance ROS detoxification but at the same time promote chlorophyll catabolism and senescence (Fukao et al., 2012), which are key processes during the recovery after hypoxia.
Hormone-regulated responses to hypoxia-reoxygenation

As mentioned above for the lipid phytohormone jasmonates, other plant hormones such as ethylene and ABA play crucial roles in the genetically controlled survival of plants to hypoxia (Fig. 4) under waterlogging or submergence (Phukan et al., 2016). Ethylene has been extensively characterized as a key hormone in hypoxia-triggered responses (Perata, 2020), and it is essential for the recovery after hypoxia in Arabidopsis (Tsai et al., 2014). Ethylene and hydrogen peroxide coordinately control the hypoxia-triggered up regulation of the inducible ERFVII member AtERF73/HRE1 (Yang, 2014). Ethylene was also shown to accelerate and enhance the hypoxic response through Phytoglobin 1 (GLB1)-mediated NO depletion and the subsequent ERFVII stabilization, thus pre-adapting plants to survive the subsequent hypoxia (Hartman et al., 2019a; b). Phytoglobins also protect root apical meristems from hypoxia-induced cell death triggered by nitric oxide and mediated by ethylene and ROS (Mira et al., 2016). The effect of phytoglobins on hypoxic maize root tissues likely occurs upstream of ROS and ethylene production since hypoxia-triggered responses on growth can be alleviated by either constitutive expression of phytoglobins or inhibiting ethylene perception or ROS production. In turn, the scheme proposed by Hartman et al. (2019a; b) involves the same regulators but functioning in a different order. Ethylene triggers the synthesis of phytoglobins that scavenge NO, stabilizes ERFVIIIs and allow their translocation to the nucleus where they regulate gene expression only in limited oxygen levels. This represents an ethylene-triggered preadaptation mechanism to hypoxic conditions. On the other hand, phytoglobin regulatory functions are also connected to other hormones. The constitutive expression of GLB1 resulted in enhanced growth and increased number of laterals roots but reduced number of root hairs under normoxic conditions (Hunt et al., 2002). The establishment of hypoxic niches in the developing lateral root primordia contributes to shutting down key auxin-induced genes and regulating the production of lateral roots (Shukla et al., 2019; Labandera et al., 2020). Moreover, hypoxia triggers an escape response of the primary root causing bending that is controlled by ERFVII activity and mediated by auxin signaling in the root tip (Eysholdt-Derzsó and Sauter, 2017).

Besides ethylene, ABA also plays a relevant function in regulating hypoxia-reoxygenation responses. Regulation exerted by ABA is often performed in coordination with ethylene and other hormones. Hypoxia increases embryo sensitivity to ABA and interferes with ABA metabolism (Benech-Arnold et al., 2006). It has been reported that an enhancement of stem elongation and suppression of petiole growth is regulated by ABA but
not by ethylene or gibberellins in submerged watercress (Müller et al., 2019). Although the elongation rate during the first hours of the night period were much faster in submerged plants than in non-submerged plants, authors conclude that enhanced stem elongation, which occurs mostly during the night, was not linked to hypoxic conditions (Müller et al., 2019). In turn, hypoxia inhibits root water transport and triggers stomata closure (Fig. 4) through a process requiring the function of aquaporins and the hormones ethylene and ABA (Tan et al., 2018). A regulatory network involving ROS, ABA and ethylene as well as the Respiratory Burst Oxidase Homolog D (RBOH D), the Senescence-Associated Gene113 (SAG113) and ORESARA1 proteins control ROS homeostasis, stomata aperture, and chlorophyll degradation during submergence recovery (Yeung et al., 2018) (Fig. 4). In Arabidopsis, both RBOH D and F are also required for activating responses to hypoxia (Liu et al., 2017).

Ethylene and RBOHD are involved in regulating seed germination and post-germination stages under normoxic conditions, and in modulating seedling root growth, leaf chlorophyll content, and hypoxia-inducible gene expression under low oxygen availability (Hong et al., 2020). The high tolerance to low oxygen conditions is dependent on the high ABA level and the ABA-mediated antioxidant capacity in rice roots, through a process requiring proline accumulation (Cao et al., 2020).

Hypoxia triggers the accumulation of auxins, whereas the subsequent reoxygenation rapidly reduces their levels to that of normoxic plants (Yemelyanov et al., 2020). Increases in endogenous auxin levels are required to produce a long coleoptile phenotype of rice plants under submergence (Nghi et al., 2020). Moreover, the increase in auxin levels either by exogenous treatment or enhanced biosynthesis led to an improvement of tolerance to oxygen deprivation (Yemelyanov et al., 2020). A transcriptional rewiring of several components of IAA and ABA signaling accompanied by increases in the content of fatty acids and related lipids, organic acids, amino acids and secondary metabolites with antioxidant activity have been reported to occur during partial reoxygenation of apple fruits after hypoxic storing conditions (Brizzolara et al., 2019). The involvement of other phytohormones in the hypoxia-reoxygenation responses is less well documented but it has been also reported that brassinosteroids induce protection against damage triggered by waterlogging (Pereira et al., 2020). Transient accumulation of cytokinins were reported in embryogenic tissue of Picea abies and wheat under hypoxic conditions (Kvaalen and Emstsen, 1993). Moreover, the overexpression of the IPT gene coding for the cytokinin biosynthesis rate limiting step in Arabidopsis and wheat led to enhanced tolerance to hypoxia (Zhag et al., 2000; Tereshonok...
et al., 2010; Vartapetian et al., 2014). Down regulation of brassinosteroid, auxin and gibberellin biosynthesis genes in waterlogged plants followed by transcriptional activation and repression of gibberellin biosynthetic and metabolic genes, respectively, during recovery (Ruperti et al., 2019) seems to also support a role for gibberellins in the signaling, metabolic, and hormonal changes transduced from waterlogged grapevine rootstocks to the above ground plant. In Arabidopsis, DELLA proteins interact with the ERFVII DNA-binding domain, thus disrupting their binding to the promoters of target genes (Marín-de la Rosa et al., 2014). Therefore, changes in the levels of gibberellins during hypoxia and subsequent reoxygenation are likely relevant to control plants responses during the hypoxia- reoxygenation transition through gibberellin-induced degradation of DELLA proteins and the subsequent relieve of the repression of ERFVII-mediated gene expression. The regulation of submerged organ growth through an ethylene-driven and gibberellin-enhanced process seems to be in the basis of a general survival strategy that connects waterlogged hypoxic parts to aerial normoxic organs of plants (Voesenek and Bailey-Serres, 2015).

Dehydration, chlorophyll catabolism and senescence are paramount processes during post-hypoxia recovery

Plant exposure to low-oxygen conditions such as submergence has a great impact on physiology and metabolism, and during the post-hypoxia recovery phase, the simultaneous reoxygenation and reillumination imposes additional stress. Post-hypoxic plants display alterations in the capacity of roots to absorb water. The regulation of hydraulic conductivity in roots seems to be exerted by a protein kinase that links oxygen and potassium sensing in soils thus modulating tolerance to hypoxia (Shahzad et al., 2016). The potential reduction in hydraulic conductivity during post-submergence remains to be demonstrated in different plants but it certainly would lead to dehydration and leaf wilting in shoots (Striker et al., 2017; Yeung et al., 2018), symptoms that are likely due to the inability to efficiently close the stomata (Postiglione and Muday, 2020). Although stomata closure can prevent water loss by transpiration, it also limits carbon dioxide uptake and thus photosynthesis, so this process should be tightly regulated during the post-hypoxia recovery (Fig. 4).

Another effect caused by simultaneous reoxygenation, reillumination and oxidative stresses during recovery after hypoxia is the chlorosis in leaves due to accelerated chlorophyll degradation (Fukao et al., 2011; Alpuerto et al., 2016; Yeung et al., 2018) that leads to leaf
senescence. The degradation of chlorophyll begins during the hypoxic phase and is visible after prolonged submergence in rice and Arabidopsis (Fukao et al., 2012; Lee et al., 2011). In rice, these physiological alterations are restrained by the ERF domain-containing transcription factor submergence tolerance regulator SUBMERGENCE1A (SUB1A) that enhance tolerance to prolonged periods of submergence by attenuating leaf senescence (Fukao et al., 2006). Enhanced tolerance to waterlogging was also reported for barley RNAi plants defective in HvPRT6 (Mendiondo et al., 2016). In Arabidopsis, leaf senescence strongly progresses during the post-hypoxia recovery though a process involving ROS and the hormones abscisic acid and ethylene (Yeung et al., 2018). Whether leaf senescence during reoxygenation recovery represents a mechanism of nutrient reallocation, useful for the progression of new organs and thus useful for survival, remains to be further studied. Nevertheless, any positive effects of nutrient reallocation on growth would be counteracted by the loss of chlorophyll-mediated photosynthesis that harms and represents a direct threat for the entire plant.

Plant responses to reoxygenation seems to be orchestrated through light- and O2-driven changes in the regulatory effects exerted by hormones including ethylene, ABA and JA as well as ROS, which together regulates root and shoot processes such as water balance and transport, stomata closure, chlorophyll degradation and leaf senescence (Fig. 4).

**Post-hypoxia reoxygenation triggered changes at the transcriptome, epigenome at metabolic levels**

Plant tolerance to low oxygen is highly dependent on the ability to adapt growth and development to transient anaerobic conditions and the subsequent recovery under normoxic conditions. Only those processes specifically occurring during the reoxygenation and not during hypoxic phases should be considered as specific reoxygenation-triggered responses. However, processes specifically occurring during hypoxia may critically affect the reoxygenation-triggered responses. As an example, Brassica seeds cannot germinate in an oxygen-free atmosphere (Park and Hasenstein, 2016) but keep germination potential so that, after being subsequently transferred to air, a significant proportion of seeds germinate, and their roots grow transiently longer than those from seeds germinated under normoxic conditions (Park and Hasenstein, 2016). In turn, rice seeds can germinate even under anoxic conditions (Miro and Ismail, 2013), and the alcohol dehydrogenase 1 (ADH1)-regulated
carbohydrate metabolism in the embryo and endosperm is critical for coleoptile growth and survival after seed germination in flooded lands (Takahashi et al., 2014). The tolerance of rice to low oxygen conditions has made this plant an excellent model to study not only the hypoxia-related but the specific reoxygenation-related processes. Specific transcriptome, DNA methylation and metabolic changes during hypoxia and the subsequent reoxygenation have been reported in rice (Narsai et al., 2009; 2017). The analysis of the selective mRNA translation in anoxia-intolerant Arabidopsis seedlings subjected to hypoxia and subsequently re-aerated, reveals that transcripts encoding proteins involved in cell wall formation, transcription, signaling, cell division, hormone metabolism and lipid metabolism are translationally repressed under hypoxia but relieved after 1 h of reoxygenation (Branco-Price et al., 2008). Moreover, comparison of hypoxia-triggered responses in plant species with different levels of tolerance to hypoxia suggest that metabolic changes do not correlate with the degree of tolerance. However, regulation of these processes at the transcriptional level varied between species (Narsai et al., 2011). The fact that a large proportion of Arabidopsis genes strongly induced upon hypoxia do not significantly decrease after reoxygenation (Branco-Price et al., 2008), suggests that some hypoxia-induced transcripts are important for reoxygenation. Alternatively, the identification of a cluster of Arabidopsis genes that are induced during hypoxia, but which only associate with ribosomes during reoxygenation (Branco-Price et al., 2008), suggests that delaying polysome dissociation under hypoxic conditions might represent an evolutionary benefit (Shingaki-Wells et al., 2014).

The identification of VERNALIZATION INSENSITIVE 3 (VIN3) and VERNALIZATION 2 (VRN2) relationship with hypoxia (Bond et al., 2009a, b; Gibbs et al., 2018; Labandera et al., 2020) allows proposing a functional link between low oxygen-and low temperature-triggered processes with the epigenetic regulation of the corresponding stress responses. The reoxygenation of anaerobically grown rice seedlings results in rapid transcriptomic changes in DNA methylation that did not correlate with actual changes in DNA methylation (Narsai et al., 2017). Reversion of the DNA methylation state upon reoxygenation may represent a way to reset and prepare the plant for the rapid molecular changes occurring during cell division. However, the role of the epigenetic regulation on the responses during the hypoxia-reoxygenation transition remains mostly unknown. Additional work will be needed to address the function of chromatin modification and remodeling as well as DNA methylation in controlling responses to transient hypoxia and the subsequent reoxygenation recovery. A recent integrative analysis of the epigenome and translatome in
Arabidopsis in response to hypoxia and reoxygenation showed that upregulation of hypoxia-responsive gene transcripts and their preferential translation are generally accompanied by increased chromatin accessibility, RNA-Polymerase II (RNAPII) engagement, and reduced Histone 2A.Z association, whereas progressively up regulated and growth-associated gene transcripts are rapidly mobilized to ribosomes upon reaeration (Lee and Bailey-Serres, 2019).

Among processes occurring during hypoxia, cells undergo extensive degradation of intracellular components through autophagy, which is a highly regulated vacuolar degradation pathway for recycling cytosolic components with essential functions in metabolic adaptation to various biotic and abiotic stresses (Li and Vierstra, 2012). Increased ROS generation by hypoxia-reoxygenation stress contributes to induction of autophagy that attenuates oxidative stress (Pérez-Pérez et al., 2012), thus representing a regulatory loop. Submergence-induced autophagy modulates salicylic acid-mediated cellular homeostasis (Chen et al., 2015) and attenuates the effects on root cell death (Guan et al., 2019) during hypoxia in Arabidopsis. Moreover, under hypoxia S-nitrosylation induces the selective autophagy of the Arabidopsis S-nitrosoglutathione reductase GSNOR1, which regulates intracellular levels of S-nitrosoglutathione (GSNO) and indirectly also of protein S-nitrosylation (Jahnová et al., 2019), thus establishing a molecular link between low oxygen levels, NO signaling and autophagy (Zhan et al., 2018). Most of these processes are required to supply material components and energy necessary for resuming growth upon reoxygenation and are thus accompanied by metabolic rearrangements. The restriction in ATP production through mitochondrial respiration (Wagner et al., 2018) is likely one of the most influencing metabolic processes for subsequent plant performance during reoxygenation. Decreased ATP is associated with increased cytoplasmic acidity potentially hindering recovery upon reoxygenation (Felle, 2005). Plants need to produce energy based on processes different than Tricarboxylic acids (TCA) cycle under oxygen limitation. This is likely articulated by ethylene-regulated expression of genes coding for enzymes, such as pyruvate phosphate dikinase and glutamate dehydrogenase, essential for TCA cycle replenishment during the hypoxia-reoxygenation transition (Tsai et al., 2016). Besides, ethanol produced during anaerobiosis is oxidized to acetaldehyde during reoxygenation and its quick metabolism by aldehyde dehydrogenase is essential for plant recovery (Tsuji et al. 2003). Several other metabolites, including arabinose and trehalose, accumulate also during reoxygenation (Narsai et al., 2009; Shingaki-Wells et al., 2011), whereas alanine accumulates during hypoxia and it is quickly metabolized during reoxygenation (de Sousa and Sodek,
2003), thus likely contributing to a better recovery after hypoxia (Rocha et al., 2010). Several other mitochondrial metabolic processes, including polyamine production based on basic amino acid metabolism, respiratory chain function and alternative oxidase-based alternative respiration, seem to be relevant to ensure plant recovery after transient hypoxic conditions (for a complete review see Shingaki-Wells et al., 2014). Results from a proteomic approach with soybean seedlings suggest that alteration of cell structure through changes in cell wall metabolism and cytoskeletal organization may be also involved in post-flooding recovery processes (Salavati et al., 2012).

Conclusions and perspectives

Intensive work performed during the last 30 years allowed us to know in great detail many of the physiological and biochemical events occurring when plants experience low oxygen conditions. However, our current knowledge of the molecular processes underlying the onset of tolerance mechanisms to hypoxia in plants have been based on the work performed in the last 5 to 10 years, mainly due to the application of omics techniques and also the discovery of hypoxia sensing mechanisms. Significant advances in transcriptome and epigenome analyses have helped us to understand the involvement of basic processes including chromatin modification and remodeling, transcription, and translation on determining plant responses especially during the hypoxic phase. However, these analyses should be also implemented during the reoxygenation recovery to better understand this process, often overlooked but of relevance for plant survival under transient low oxygen environmental conditions. Moreover, our knowledge on the proteome changes during the hypoxia-reoxygenation transition is very scarce, and even more, very little is known about post-translational modifications. New approaches and wide proteomic analyses should be performed in the next few years that will help us to better understand changes in enzymes and transcriptional regulators involved in well-known metabolic and regulatory processes occurring during hypoxia-reoxygenation.

On the other hand, although plants and animals are quite different in triggering responses to hypoxia and subsequent reoxygenation, plant researchers should take advantage of the extensive knowledge accumulated in the hypoxia-reoxygenation transition in animal models. Comparative analyses will allow finding new components involved in key processes such as oxygen sensing, redox regulation of oxidative and nitrosative stress, lipid signaling, and intracellular trafficking between endomembranes, which will open new paths for the study of plant responses to transient responses to hypoxia, and also to know how plants deal
with the subsequent transition to normoxic conditions enabling full recovery. In particular, the identification of plant ion channels and transporters with roles in oxygen sensing through ion (Ca$^{2+}$, K$^+$, Na$^+$)-triggered signaling as well as proteins with oxygen-sensing domains will be crucial to understand the hypoxia-reoxygenation transition in plants. Other membrane-related process such as endomembrane protein trafficking or autophagy and the corresponding components involved should be also extensively studied in plants, with emphasis on the analysis of post-translational modifications that likely represent a relevant level of regulation in hypoxia and post-hypoxia. This information will not only be of interest for basic science but will also have a tremendous impact on potential biotechnological applications for future agriculture in an environmental frame of acute climate change.
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Author contributions

JL wrote the article. MCC and BG had an equal contribution in collecting information. JL conceived the project and supervised co-authors draft writing, and agrees to serve as the author responsible for contact and ensures communication. The authors declare no competing interest.
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**Figure legends**

**Figure 1.** Diverse hypoxic conditions followed by re-oxygenation. (A) Stress-activated hypoxia responses and the subsequent recovery during re-oxygenation follow an escape strategy, characterized by increased metabolism and growth, or a quiescence process, which slow metabolism, stop growth, and enhanced tolerance. (B) Developmentally controlled hypoxic niches along plant lifespan occur in seeds, root and shoot apical meristems, and fruits.

**Figure 2.** Oxygen sensing through regulation of ERFVII stability by the Cys/Arg branch of the N-degron pathway and proteasome-mediated proteolysis. N-containing metabolites (green) produced NO either from nitrate assimilation pathway involving nitrate reductase (NR) and nitrite reductase (NiR), or from mitochondrial electron transport chain (mitETC). Under high O\(_2\) levels (left side) the N-degron pathway is activated to degrade MC-X protein substrates by the successive action of MAP, methionine amino peptidase; PCO, Plant cysteine oxidase; ATE, arginyl transferase; PRT6, Proteolysis 6 E3 ubiquitin ligase; and the 26 proteasome acting on polyubiquitinated (Ubq-Ubq…Ubq) proteins. Under low O\(_2\) levels (right side), the N-degron pathway is blocked (purple crosses) at the level of C oxidation (C\(_{ox}\)) by PCOs thus enabling the stabilization of MC-X protein substrates that regulates the diverse box-enclosed processes.

**Figure 3.** Alternative oxidase modulates N metabolism and phytoglobin cycle in mitochondria during hypoxia and subsequent reoxygenation. Under low oxygen conditions (left side) alternative oxidase (AOX) and complex IV of mitochondria use nitrite (NO\(_2^-\)) as acceptor of the electron transport chain thus enhancing NO production. In parallel, electrons from the ubiquinone (Q), besides being delivered to AOX, are also delivered to complex III allowing the production of superoxide anion (O\(_2^-\)). NO and O\(_2^-\) react to form the nitrating agent peroxinitrite (ONO\(_2^-\)). Both NO and ONO\(_2^-\) trigger post-translational modifications (PTMs) such as cysteine S-nitrosylation and tyrosine nitration. During the reoxygenation after hypoxia (right side), both AOX and complex IV use O\(_2\) as electron acceptor and Q delivers electrons mainly to AOX and marginally to complex III, thus attenuating O\(_2^-\) production. Besides, the residual AOX-catalyzed conversion of nitrite to NO is attenuated by coupling to the phytoglobin (PGB) cycle with NO-dioxygenase activity that converts NO back to nitrate (NO\(_3^-\)), which is incorporated to nitrate assimilation pathway.
Figure 4. Different levels of ROS and phytohormones orchestrate changes in roots and shoots that affect water transport, stomata closure and chlorophyll degradation in Arabidopsis experiencing transition from hypoxia/darkness to reoxygenation/light. Abscisic acid (ABA); Ethylene (C$_2$H$_4$); Jasmonic acid (JA); Nitric oxide (NO); Reactive Oxygen Species (ROS).
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