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REVIEW

Stress signalling dynamics of the mitochondrial electron transport chain and oxidative phosphorylation system in higher plants

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• **Background** Mitochondria play a diversity of physiological and metabolic roles under conditions of abiotic or biotic stress. They may be directly subjected to physico-chemical constraints, and they are also involved in integrative responses to environmental stresses through their central position in cell nutrition, respiration, energy balance and biosyntheses. In plant cells, mitochondria present various biochemical peculiarities, such as cyanide-insensitive alternative respiration, and, besides integration with ubiquitous eukaryotic compartments, their functioning must be coupled with plastid functioning. Moreover, given the sessile lifestyle of plants, their relative lack of protective barriers and present threats of climate change, the plant cell is an attractive model to understand the mechanisms of stress/organelle/cell integration in the context of environmental stress responses.
• **Scope** The involvement of mitochondria in this integration entails a complex network of signalling, which has not been fully elucidated, because of the great diversity of mitochondrial constituents (metabolites, reactive molecular species and structural and regulatory biomolecules) that are linked to stress signalling pathways. The present review analyses the complexity of stress signalling connexions that are related to the mitochondrial electron transport chain and oxidative phosphorylation system, and how they can be involved in stress perception and transduction, signal amplification or cell stress response modulation.
• **Conclusions** Plant mitochondria are endowed with a diversity of multi-directional hubs of stress signalling that lead to regulatory loops and regulatory rheostats, whose functioning can amplify and diversify some signals or, conversely, dampen and reduce other signals. Involvement in a wide range of abiotic and biotic responses also implies that mitochondrial stress signalling could result in synergistic or conflicting outcomes during acclimation to multiple and complex stresses, such as those arising from climate change.

Key Words: Mitochondria, abiotic stress, biotic stress, mitochondrial stress, mitochondria-derived signalling, retrograde signalling, interorganellar signalling, reactive oxygen species, programmed cell death.

INTRODUCTION

Mitochondria are present in all plant cells, where they carry out vital functions of nutrition, metabolism and biosynthesis. Plant mitochondria present various biochemical peculiarities, such as cyanide-insensitive alternative respiration mediated by alternative oxidase (AOX) (Elthon and McIntosh, 1987), and, besides integration with ubiquitous eukaryotic compartments, their functioning is coupled with plastid functioning, whether in photosynthetic or non-photosynthetic tissues, and whether under light, shade or dark conditions. Their electron transport chain (ETC) and oxidative phosphorylation system (OXPHOS) provide the necessary energy for survival and development of the plant in spatial or temporal collaboration with photosynthetic processes (Schwarzländer and Finkemeier, 2013; Wurzinger *et al.*, 2018). Given their strong involvement in energy homeostasis, mitochondria are key organelles for plant responses to environmental stresses (Crawford *et al.*, 2018). Moreover, they function through an important surface of contact and strong biochemical exchanges with the cytosol, and thus, directly or indirectly, with all of the cell compartments. Environmental stresses can directly affect mitochondrial activities, thus leading to situations of mitochondrial perturbation or stress. Conversely, perturbations and stresses that affect other cell compartments can reach and modify mitochondrial functioning (Van Aken *et al.*, 2016). The involvement of mitochondria in the integration of plant cell responses to stresses entails a complex network of signalling which has not been fully elucidated, given the great diversity of mitochondrial constituents (metabolites, reactive molecular species, structural and regulatory

biomolecules) that are linked to stress and programmed cell death (PCD) signalling pathways (Møller, 2001; Mittler *et al.*, 2004; Gupta *et al.*, 2011; Jacoby *et al.*, 2012; Mano, 2012; Schwarzländer and Finkemeier, 2013; Hildebrandt *et al.*, 2015; Welchen and Gonzalez, 2016; Wang *et al.*, 2018; Cui *et al.*, 2019; Huang *et al.*, 2019). The present review analyses this complexity of mitochondrial stress signalling connexions through the specific cases of ETC and OXPHOS. Drawing on different examples of abiotic and biotic stresses, we discuss how mitochondrial ETC and OXPHOS can be involved in stress perception and transduction, stress signal amplification, or cell stress response modulation

SIGNALLING DYNAMICS OF MITOCHONDRIAL ENERGY METABOLISM

Signalling energy metabolites

The ETC and OXPHOS sustain the major mitochondrial function of ATP generation, in relation to the metabolic dynamics of tricarboxylic acids (TCAs), acetyl-CoA, ADP, oxidized (NAD^+) or reduced (NADH) β-nicotinamide adenine dinucleotide, oxidized (FAD) or reduced ($FADH_2$) flavin adenine dinucleotide (Bohovych and Khalimonchuk, 2016). The NAD^+/NADH and FAD/$FADH_2$ equilibria are maintained through the TCA cycle, the ETC and OXPHOS (Bohovych and Khalimonchuk, 2016). Because of these strong connections with central metabolites, mitochondria can be key organelles for the perception of stresses harmful to the plant (Crawford *et al.*, 2018). Environmental stresses can directly or indirectly disrupt ETC and OXPHOS activity and perception of the disturbance can be transduced to the nuclear genome with consequent regulation of metabolism- and stress-related genes (Che-Othman *et al.*, 2017). Under conditions that lead to mitochondrial dysfunctioning or damage, decrease in ATP production can lead to depletion of ATP levels and increase in ADP and AMP (Bailey-Serres *et al.*, 2011; Pedrotti *et al.*, 2018). Situations where carbohydrates are limiting or eventually run out, such as the end of night during night–day cycles, or extended darkness, result in energy limitation or starvation (Baena-González and Sheen, 2008; Pedrotti *et al.*, 2018). The resulting decrease in ATP levels can induce retrograde signals from mitochondria to the genome, resulting in the induction of alternative respiratory pathways such as amino acid and fatty acid catabolism (Schwarzländer and Finkemeier, 2013; Hildebrandt *et al.*, 2015). Furthermore, fluctuations in the ATP level can indirectly act on other metabolites, and these metabolites can themselves mediate retrograde signalling. It has thus been established or hypothesized that acetyl-CoA, TCA cycle intermediates and NADH may act as retrograde signals from the mitochondria to the nucleus (Schwarzländer and Finkemeier, 2013; Ashrafi *et al.*, 2018; Wagner *et al.*, 2018). This may lead to the hypothesis that the efficiency of the stress response may depend on the quantity and diversity of mitochondrial stress signals.

Metabolic energy sensors

The plant sucrose-non-fermenting (SNF)-related kinase 1 (SnRK1) is a central metabolic sensor that belongs to a highly conserved eukaryotic protein kinase family (Crozet *et al.*, 2014). Sensing of variations in adenylate nucleotide and sugar levels by the SnRK1 sensor provides the cell with information on energy and nutritional status and on the necessary adjustments for stress tolerance (Baena-González and Sheen, 2008). SnRK1 functions closely with TOR (target of rapamycin) kinase, another sugar sensor inducing antagonistic growth-related responses (Baena-González and Sheen, 2008). SnRK1 and TOR kinase therefore function as hubs for energy, growth and stress sensing. Interplay between soluble sugar fluctuations, SnRK1 and TOR kinase results in large-scale transcriptome reprogramming that contributes to homeostasis restoration, cell survival, autophagy regulation and adaptive responses (Baena-González and Sheen, 2008; Janse van Rensburg *et al.*, 2019). The regulatory properties of SnRK1 imply that it can perceive variations in adenylate nucleotide levels as well as those in several other metabolites, such as sucrose, glucose, trehalose-6-P, glucose-1-P or glucose-6-P (Crozet *et al.*, 2014). Although the links between SnRK1 and the different cellular compartments, especially mitochondria and plastids, are not fully elucidated, its cytoplasmic localization implies that it can integrate the perception of metabolic cues originating from or regulated by different sources (Crozet *et al.*, 2014; Wurzinger *et al.*, 2018). The regulation of SnRK1 in response to stress and metabolic changes can result in transcriptional regulation of stress-related genes or in post-translational phosphorylation regulation of key metabolic enzymes (Broeckx *et al.*, 2016; Nukarinen *et al.*, 2016; Wurzinger *et al.*, 2018). Unexpectedly, phosphorylation regulation also affects some mitochondrial proteins (Wurzinger *et al.*, 2018), thus suggesting regulatory loops between mitochondrial retrograde AMP/ADP/ATP signals, cytoplasmic SnRK1, mitochondrial functioning and mitochondrial metabolites (acetyl-CoA, TCA cycle intermediates, NADH) that are themselves candidate retrograde signals (Schwarzländer and Finkemeier, 2013; Ashrafi *et al.*, 2018; Wagner *et al.*, 2018). However, in contrast to the characterization of SnRK1 as a metabolic sensor of adenylate nucleotides and carbohydrates, the mechanisms of retrograde signalling by mitochondrial metabolites are not yet fully elucidated. Citrate may act through specific receptors or transporters, as is the case in bacteria (Schwarzländer and Finkemeier, 2013), or through epigenetic modifiers, in association with acetyl-CoA, as is the case in animal cells (Shaughnessy *et al.*, 2014).

MITOCHONDRIAL REACTIVE OXYGEN AND NITROGEN SPECIES

Dynamics of electron fluxes and reactive oxygen species

The flux of electrons through the ETC and oxygen reduction can produce partially reduced reactive oxygen species (ROS), such as superoxide ion and hydrogen peroxide (Møller, 2001; Murphy, 2009). ETC complexes I, II and III (Fig. 1) are major sites of ROS production (Gleason *et al.*, 2011; Andreyev *et al.*, 2015). On the one hand, superoxide and hydrogen peroxide are continuously produced by natural ETC functioning. On the other hand, several metabolic and stress situations lead to a more reduced state of the ETC and increased ROS production (Møller, 2001). This occurs for instance under situations of

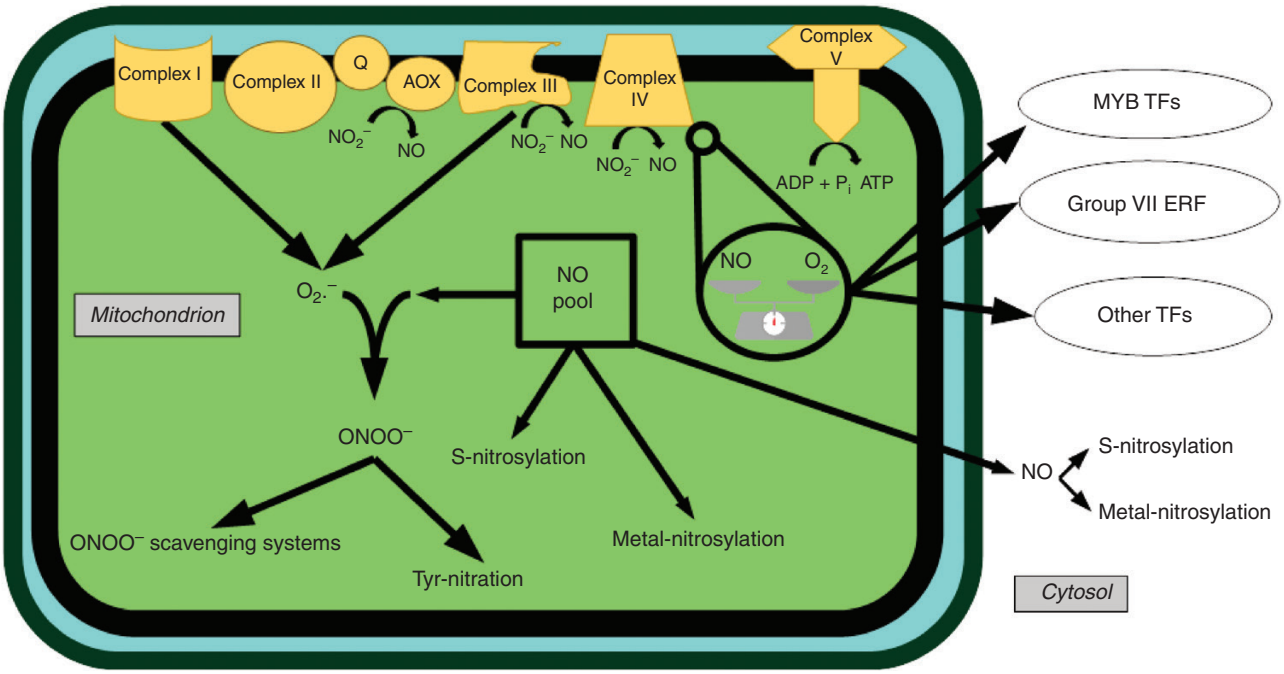

FIG. 1. Mitochondrial dynamics and cellular effects of NO. Nitric oxide can be produced at different levels of the ETC (PLANCHET *ET al.*, 2005; Castello *et al.*, 2006; Gupta and Igamberdiev, 2011; Alber *et al.*, 2017; Vishwakarma *et al.*, 2018). A balance between NO and O_2 exists in the mitochondria (Vieira and Kroemer, 2003; Amirsadeghi *et al.*, 2007). Nitric oxide can lead to the formation of peroxynitrite (Radi *et al.*, 2002; Gupta *et al.*, 2011). The balance between NO and O_2 may act as a hypoxic signal involving several classes of transcription factors (Castello *et al.*, 2006; Gibbs *et al.*, 2015). Q, quinone pool; TF, transcription factor.

ETC inhibition or ETC slow-down, whenever ADP availability is reduced by stress. Thus, respiratory inhibitors can inhibit ETC complexes, and induce over-reduction of various parts of the ETC, thus leading to superoxide overproduction (Li *et al.*, 2003; Schwarzländer *et al.*, 2009). Stress-induced alterations of mitochondrial ultrastructure, as occur for instance during salt stress, can directly affect or damage ETC and OXPHOS functioning (Garcia de la Garma *et al.*, 2015).

Abiotic stresses usually lead to superoxide overproduction in mitochondria (Basu *et al.*, 2001; Dixit *et al.*, 2002), and the action of superoxide dismutases (SODs) generates hydrogen peroxide from superoxide (Turrens, 2003). Whereas superoxide has a very short half-life, hydrogen peroxide has a longer half-life and can cross membranes through aquaporins (Bienert *et al.*, 2007), thus potentially serving as a signal linking mitochondria to other cell compartments (Bienert *et al.*, 2007; Bohovych and Khalimonchuk, 2016).

This ROS-based dynamics from the mitochondria has been associated with ROS signalling mechanisms (Møller and Sweetlove, 2010; Ng *et al.*, 2014; Noctor and Foyer, 2016) that involve oxidized intermediates, Ca^{2+} and phosphorylation processes (Møller and Sweetlove, 2010; Ng *et al.*, 2014) and with transcriptional and post-transcriptional alterations of cell functioning that can lead to regulation of growth and development programmes, including PCD (Gao *et al.*, 2008; Liu *et al.*, 2014; Wu *et al.*, 2015; Singh *et al.*, 2016; Cui *et al.*, 2019). Mitochondrial ROS signalling and mitochondrial perturbation signalling are linked to developmental processes regulated by auxins (Kerchev *et al.*, 2014; Yang *et al.*, 2014; Wang and Auwerx, 2017). In *Arabidopsis FtsH4* mutants, which are affected in a mitochondrial protein-processing protease, accumulation of mitochondrial hydrogen peroxide is associated with deregulation of auxin homeostasis, cell cycle dysregulation and impairment of meristem activity (Zhang *et al.*, 2014; Dolzblasz *et al.*, 2018). Mutation of the ABA-overly-sensitive-8 (ABO8) splicing factor, which is necessary for correct expression of the NAD4 component of complex I, results in increased mitochondrial ROS production, abscisic acid (ABA) hypersensitivity, reduced auxin accumulation/signalling and reduced meristem activity (Yang *et al.*, 2014). This cross-talk between mitochondrial ROS, hormones and development shows that mitochondrial ROS signalling may be mediated, at least in part, by hormone signalling pathways.

Under conditions of biotic stress, PCD is part of the hypersensitive response (HR) that decreases the growth and development of biotrophic pathogens (Dangl and Jones, 2001). This HR is related to an increase in ROS levels (Mur *et al.*, 2007). Besides plasma-membrane-localized NADPH oxidases (Suzuki *et al.*, 2011), mitochondria are also an important source of ROS (Møller, 2001) for pathogen-defence oxidative bursts and HR (Allan and Fluhr, 1997; Cvetkovska and Vanlerberghe, 2012*a*; Cvetkovska *et al.*, 2013). Characterization of the *Arabidopsis mosaic-death-1* (*mod1*) mutant (Wu *et al.*, 2015) has shown that PCD could be triggered by higher ROS production resulting from the destabilization of ETC complex I. Interestingly, in the *mod1* mutant the destabilization of ETC complex I is due to chloroplastic fatty acid biosynthesis deficiency, thus emphasizing that ROS-based mitochondrial signalling could link perturbation in another type of subcellular compartment with PCD induction.

Moreover, ROS-based mitochondrial signalling appears to involve multiple mechanisms and multiple levels of regulation.

Stress-induced PCD involves two phases of ROS induction. The first phase is immediately triggered after stress perception, while a second phase appears a few hours after stress perception. The initial ROS phase may be related to mitochondrial permeability transition. Mitochondrial membrane permeability is tightly regulated, but during stress-induced PCD mitochondrial membranes become permeable to bigger solutes, which modifies normal functioning and leads to ETC inhibition, ROS overproduction and PCD induction (Rostovtseva *et al.*, 2005; Scott and Logan, 2008; Van Aken and Van Breusegem, 2015). This multi-step induction has been demonstrated by sequential hydrogen peroxide treatments (Murik *et al.*, 2014). ETC-related increases in ROS production can reinforce mitochondrial dysfunction, which, in turn, can enhance ROS production, thus generating a self-amplifying loop of ROS dynamics in the mitochondria (Amirsadeghi *et al.*, 2007). Under conditions of biotic stress, such amplifying loops can be triggered by plant growth regulators, such as salicylate, by pathogenic toxins, such as harpin (Krause and Durner, 2004) or victorin (Yao *et al.*, 2002), and by virulence (Amirsadeghi *et al.*, 2007).

Proline regulation of ROS dynamics

In plant cells, proline is a multi-usage amino acid with implications in growth and development as well as in stress responses (Szabados and Savouré, 2010). Proline is generally synthesized in the cytosol from glutamate under the control of pyrroline-5-carboxylate synthetase (P5CS) and pyrroline-5-carboxylate reductase (P5CR). Its oxidative degradation leading to glutamate production occurs in mitochondria through a two-step mechanism that involves proline dehydrogenase (ProDH) and pyrroline-5-carboxylate dehydrogenase (P5CDH). A variety of stress situations (drought, high temperature, low temperature, heavy metal, pathogen infection, anaerobiosis, nutrient deficiency, atmospheric pollution, UV irradiation) lead to proline accumulation resulting from upregulation of P5CS (proline synthesis) and downregulation of ProDH (proline catabolism) (Verbruggen and Hermans, 2008). Alternatively, other stress situations are associated with ProDH (proline catabolism) upregulation in parallel with proline accumulation (Verslues et Sharma, 2010; Garcia de la Garma *et al.*, 2015).

Proline dehydrogenase is localized at the inner face of the mitochondrial inner membrane in association with the ETC (Cabassa-Hourton *et al.*, 2016). As a flavoenzyme, ProDH can feed electrons to the ETC (Rasmusson and Møller, 2011; Schertl and Braun, 2014), but whenever stress-related perturbations lead to ETC over-reduction, reduced $FADH_2$ in ProDH can directly reduce oxygen to superoxide and hydrogen peroxide, thus contributing to mitochondrial ROS production (Liang *et al.*, 2013). The presence of proline and the activity of ProDH therefore interact with the optimal or stressed status of ETC, with ROS production and redox status as biochemical and signalling outputs (Rasmusson and Møller, 2011). This ROS production from proline/P5C conversion through ProDH activity plays an important role in PCD and HR induction under conditions of biotic stress (Monteoliva *et al.*, 2014). Proline mitochondrial metabolism has thus been shown to contribute significantly to oxidative bursts involved in pathogen defence (Verslues and Sharma, 2010). Moreover, proline-based ROS production shows links with the functioning of plasma-membrane-localized respiratory burst NADPH oxidase homologue D (RBOHD) (Fabro *et al.*, 2016). Under conditions of biotic stress, RBOHD provides apoplastic ROS involved in oxidative bursts and in pathogen-triggered immunity (Fabro *et al.*, 2016). Weaker immune responses and a decrease in ROS generation by RBOHD were observed in *prodh* mutants, and ProDH activation or inhibition treatments showed that ProDH activity modulated RBOHD activity (Fabro *et al.*, 2016). Given the importance of RBOHD for systemic ROS and Ca^{2+} wave signalling through the plant (Gilroy *et al.*, 2014), the relationship between ProDH, mitochondrial ROS production and RBOHD shows potential links between the stress status of mitochondria and systemic signalling. Moreover, the ProDH/PC5CDH pathway is involved in the regeneration of glutamate and may thus contribute to the dynamics of the glutamate pool (Schertl and Braun, 2014). Glutamate has been associated with signalling processes involving glutamate-receptor-like channels (Forde and Roberts, 2014; Toyota *et al.*, 2018) and with systemic Ca^{2+} responses to wounding and pathogens (Forde and Roberts, 2014; Hilleary and Gilroy, 2018; Toyota *et al.*, 2018). Glutamate may thus mediate another level of interaction between mitochondrial proline dynamics and systemic signalling.

On the other hand, involvement in senescence processes (Cecchini *et al.*, 2011; Zhang and Becker, 2015) strongly suggests that the roles of proline-based ROS production are much wider than the biotic stress context. Overexpression of heat-shock factors has thus been shown to improve heat tolerance and to increase salt sensitivity through alterations of ProDH activity and proline catabolism (Wu *et al.*, 2018). Moreover, the regulation of *ProDH* gene expression under conditions of abiotic (Wu *et al.*, 2018) or biotic (Monteoliva *et al.*, 2014) stresses indicates that control of mitochondrial proline catabolism may be important for stress acclimation.

Dynamics of electron fluxes and nitric oxide

Nitric oxide (NO) has been shown to be involved as a reactive nitrogen species (RNS) and through its signalling properties in multiple mechanisms and physiological processes from seed germination to flowering and senescence, whether under optimal conditions or under conditions of abiotic and biotic stress (Gupta *et al.*, 2011). Nitric oxide can reach and affect multiple targets in different subcellular compartments. At protein level, NO has three main modalities of action (Fig. 1): S-nitrosylation, metal-nitrosylation and tyrosine nitration (Besson-Bard *et al.*, 2008). S-Nitrosylation consists in the addition of an NO group to cysteine residues. Targeted proteins are connected to a wide range of functions, such as metabolism, signalling, stress responses, redox homeostasis and cellular architecture (Astier *et al.*, 2011). S-Nitrosylation can alter transcription factors, such as MYB or group VII ethylene response factors (ERFs) (Dubos *et al.*, 2010; Bailey-Serres *et al.*, 2011; Gibbs *et al.*, 2015), thus leading to differential gene expression, which shows the importance of NO as a signalling molecule. Metal-nitrosylation affects major proteins such as haemoglobins, aconitases, lipoxygenases, catalases, cytochrome

c oxidase and ascorbate peroxidases by binding to the haem structure (Besson-Bard *et al.*, 2008). Tyrosine nitration results from the reactivity of peroxynitrite ($ONOO^-$), which leads to the addition of a nitronium (NO_2^+) group to tyrosine residues and generally to loss of protein function (Besson-Bard *et al.*, 2008; Astier *et al.*, 2011). Through these multiple biochemical actions, NO is also connected to other secondary messengers, such as Ca^{2+}. Elicitation of tobacco cells induces the mobilization of intracellular Ca^{2+} through modifications of Ca^{2+} channels by NO (Lamotte *et al.*, 2004).

Mitochondria play a major role in NO synthesis and dynamics and therefore in the control of NO effects on cellular functions (Fig. 1). Whereas the existence of a mitochondrial isozyme of NO synthase is not established, mitochondria possess a wide range of NO sources (Moreau *et al.*, 2008). Nitric oxide can be produced at different steps of the ETC (Castello *et al.*, 2006; Gupta and Igamberdiev, 2011; Alber *et al.*, 2017). Complex III is involved in NO production by nitrite reduction (Alber *et al.*, 2017). Complex IV cytochrome c oxidase (COX), especially under conditions of anoxia or hypoxia, shows significant nitrite reductase activity and can thus represent one of the most important sources of NO in the cell (Castello *et al.*, 2006). Finally, ETC inhibition studies have suggested that AOX may also carry out reduction of nitrite to NO (Planchet *et al.*, 2005). Moreover, the work of Vishwakarma *et al.* (2018) indicates that such AOX-dependent NO production preferentially occurs under anoxia or hypoxia conditions. Nitric oxide plays an important role at the mitochondrial ETC level, as it can inhibit OXPHOS (Yamasaki *et al.*, 2001) and COX (Vieira and Kroemer, 2003; Amirsadeghi *et al.*, 2007). Inhibition of COX leads to an increase in O_2 concentration in the vicinity of COX (Vieira and Kroemer, 2003; Amirsadeghi *et al.*, 2007). A balance between NO and O_2 therefore exists in the mitochondria and may act as a hypoxic signal (Fig. 1), involving several classes of transcription factors, such as MYB transcription factors and group VII ERFs (Castello *et al.*, 2006; Bailey-Serres *et al.*, 2011; Gibbs *et al.*, 2015). As soon as COX produces NO, complete depletion of O_2 in the mitochondria is avoided, and NO production triggers the induction of hypoxia-responsive genes. Alternatively, NO can react with other ROS, thus leading to the formation of peroxynitrite, which can trigger its own regulatory pathways (Gupta and Igamberdiev, 2011). This balance between NO, O_2 and peroxynitrite plays important roles not only in abiotic stresses, such as hypoxia, but also in biotic stresses. Under conditions of biotic stress, oxidative bursts consume O_2 in the vicinity of COX, which leads to NO synthesis and activation of the HR (Modolo *et al.*, 2005) and induction of pathogenesis-related genes (Parani *et al.*, 2004). Moreover, the balance between NO, O_2 and peroxynitrite results not only from NO synthesis mechanisms, but also from NO scavenging systems, some of which are mitochondrial (Fig. 1). Complexes I and III of the mitochondrial ETC are important producers of the anion superoxide (Andreyev *et al.*, 2015). Peroxynitrite that results from NO and superoxide reaction can be scavenged by specific mechanisms (Radi *et al.*, 2002). A potential NO-scavenging mechanism involving superoxide formation and Ca^{2+}-dependent external NAD(P)H dehydrogenases has also been reported (de Oliveira *et al.*, 2008). Finally, since NO can bind to and inhibit COX, and since S-nitrosylation can be passive, mitochondrial structures are an important pool of immobilized NO. The respective activities of all of these mechanisms of synthesis, immobilization and scavenging contribute to maintain NO at a setpoint that prevents NO-dependent nitrosative damage.

Alternative oxidase as an ROS and RNS signalling rheostat

The AOX terminal oxidase of plant mitochondria (Elthon and McIntosh, 1987) exists as different isoforms encoded by a small multigene family that is differentially regulated (Ho *et al.*, 2008; Giraud *et al.*, 2009; Hanqing *et al.*, 2010). Unlike the COX pathway, AOX does not pump protons and therefore does not contribute to the proton motive force (McIntosh, 1994; Finnegan *et al.*, 2003; Millenaar and Lambers, 2003). On the other hand, by preventing over-reduction of ETC, AOX can regulate the generation of ROS (Maxwell *et al.*, 1999), especially under stress conditions (Vanlerberghe *et al.*, 2009). As an example, in the case of heavy metal stress, overexpression of AOX facilitates stress tolerance, whereas wild-type plants are affected by reduced respiration, increased ROS production and decreased cell viability (Liu *et al.*, 2014).

Various signals can modulate AOX expression. Besides its inhibitory effects on mitochondrial COX (Vieira and Kroemer, 2003; Amirsadeghi *et al.*, 2007), NO increases the expression of AOX (Huang *et al.*, 2002; Gupta *et al.*, 2012). Jasmonate, ethylene and salicylate induce the increase in AOX transcription (Fung *et al.*, 2006; Wang *et al.*, 2010; Zhang *et al.*, 2012). Expression of *AOX1* can also be induced by ABA and hydrogen peroxide in *Arabidopsis* (Ho *et al.*, 2008; Giraud *et al.*, 2009). Cvetkovska and Vanlerberghe (2012*a*, 2013) highlight that, according to the nature of the pathogen, *Nicotiana tabacum* is able to regulate differentially the expression of AOX, thus modulating the production of mitochondrial ROS, the mitochondrial oxidative burst and therefore HR. *Pseudomonas syringae* pv. *maculicola* triggers an HR reaction with no parallel induction of AOX. In contrast, *P. syringae* pv. *phaseolica* induces pathogen defences without HR in parallel with an increase in AOX and MnSOD proteins. The plant is thus able to downregulate AOX despite the presence of AOX-inducing regulators (Cvetkovska *et al.*, 2013). Moreover, AOX seems to play different roles depending on the type of pathogen. Silencing of AOX causes increased susceptibility of *Nicotiana attenuata* to a piercing–sucking insect and accelerated cell death against pathogenic *P. syringae* pv. *tomato*, but this AOX regulation was not involved in responses to attacks by chewing herbivores (Zhang *et al.*, 2012). Given its implications in ETC functioning (McIntosh, 1994; Finnegan *et al.*, 2003; Millenaar and Lambers, 2003) and in NO production (Planchet *et al.*, 2005), and given its stress-dependent regulation (Ho *et al.*, 2008; Giraud *et al.*, 2009), AOX may therefore be considered as an ETC-related rheostat for mitochondrial ROS and RNS dynamics and therefore for mitochondrial ROS and RNS signalling (Cvetkovska and Vanlerberghe, 2012*b*; Kumari *et al.*, 2019). More generally, as shown by mitochondrial biogenesis mutants (Yang *et al.*, 2014; Zhang *et al.*, 2014; Dolzblasz *et al.*, 2018), the developmental and hormonal context controls and determines the level of expression of mitochondrial components, such as ETC

components, thus specifying a setpoint for the capacity to generate ROS and RNS.

SIGNALLING DYNAMICS OF MITOCHONDRIAL SUPRAMOLECULES

Proteome and metallome dynamics

The abundance of metal-containing proteins in the ETC implies that mitochondria possess an important metallome, including in particular Cu and Fe (Tan *et al.*, 2010; Jacoby *et al.*, 2012). Under conditions of direct or indirect oxidative stress, metal-containing proteins are affected in their conformation, in their electrophilicity, in protein–protein interactions and in protein–membrane interactions. Oxidative-stress-mediated damage can thus trigger the release of metals from mitochondrial proteins (Fig. 2). Metal release can directly affect biological activity and therefore ETC and mitochondrial homeostasis in relation to the ROS-amplifying loop described above (Amirsadeghi *et al.*, 2007; Tan *et al.*, 2010). Excess Cu or Fe has thus been shown to stimulate ROS production in mitochondria and affect mitochondrial respiration (Keunen *et al.*, 2011). Moreover, released metals can act as the catalysts of metal-catalysed oxidation affecting oxidation-prone amino acid residues, such as arginine, lysine, proline, cysteine and histidine, in susceptible proteins (Møller *et al.*, 2011; Jacoby *et al.*, 2012), with potential triggering of the mitochondrial dysfunction/ROS-amplifying loop. Resulting damaged proteins tend to aggregate, which again is likely to disturb mitochondrial homeostasis (Jacoby *et al.*, 2012). Finally, the release of metal catalysts in an oxidative environment including superoxide and hydrogen peroxide activates the Haber–Weiss reaction or the Fenton reaction, which lead to hydroxyl radical ($HO^{\cdot}$) production (Mittler *et al.*, 2004). This highly reactive compound adds another level to ROS damage (Fig. 2) that can affect lipids and proteins and contribute to the ROS- and metal-amplifying loops described above.

Lipid peroxides and reactive carbonyl species

The hydroxyl radical described above (Fig. 2) is a strong inducer of lipid peroxidation and therefore tightly linked to membrane dynamics. Resulting lipid peroxides or lipid peroxidation end products are reactive carbonyl species (RCS) with highly electrophilic groups that can actively react with other molecules as they are negatively charged (Møller *et al.*, 2011; Jacoby *et al.*, 2012). Cascades of reactions lead to the formation of derived RCS, such as acrolein and 4-hydroxy-2-nonenal (HNE) (Mano, 2012). Acrolein and HNE can form Michael adducts on thiol and amino groups of proteins (Mano, 2012); HNE can thus inhibit several enzymes involved in TCA cycle and respiration, such as malate dehydrogenase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase (Fig. 2). HNE also has an inhibitory impact on ETC proteins, including AOX (Winger *et al.*, 2005, 2007). However, through signalling mechanisms, this inhibition can also induce the activation of *AOX* gene expression and AOX protein synthesis, in parallel with the induction of other stress-related genes (Winger *et al.*, 2007). Finally, HNE

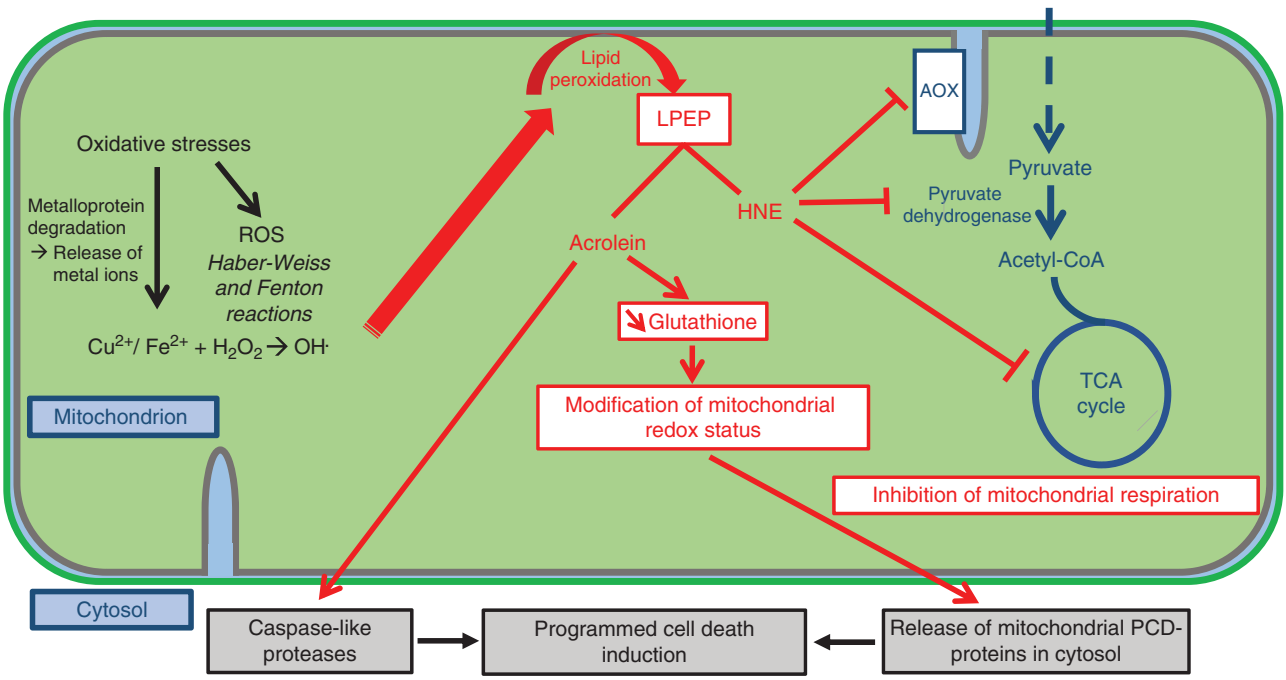

FIG. 2. Mechanisms of mitochondrial oxidative stress sensing through metallome and lipid peroxidation dynamics. Oxidative-stress-mediated damage triggers the release of metals from mitochondrial proteins and the released metals are the catalysts of metal-catalysed oxidation (MØLLER *ET AL.*, 2011; Jacoby *et al.*, 2012). Cascades of reactions lead to the formation of lipid peroxidation products, such as acrolein and 4-hydroxy-2-nonenal (HNE), with wide-ranging effects on metabolism, redox status and programmed cell death (Winger *et al.*, 2005, 2007; Mano, 2012; Biswas and Mano, 2015, 2016). LPEP, lipid peroxidation end products.

can modify, through formation of Michael adducts, the interactions between glyceraldehyde-3-phosphate dehydrogenase and mitochondria (Winger *et al.*, 2007).

Mitochondria are therefore directly involved in cascades of biochemical events that link environmental constraints acting on mitochondrial ETC functioning (Amirsadeghi *et al.*, 2007), ROS and metal dynamics (Jacoby *et al.*, 2012), RCS (Mano, 2012) and post-translational modifications of cell functioning, including further disruption of mitochondrial respiration (Winger *et al.*, 2005, 2007). Such cascades of events involving RCS can lead to PCD regulation. Accumulation of acrolein can activate caspase-like proteases, which play a major role in the induction of PCD (Biswas and Mano, 2015, 2016). Acrolein increase also leads to decrease in glutathione, which modifies the redox status of mitochondria. The altered redox status and inactivation of pyruvate dehydrogenase (Fig. 2) can affect mitochondrial membranes through formation of pores through which PCD-signalling proteins can exit the mitochondrion (Biswas and Mano, 2015).

Finally, the impact of RCS such as HNE on differential gene expression indicates that RCS could be involved in ROS signalling and act as retrograde signals from the mitochondria to the nucleus (Møller and Sweetlove, 2010; Schwarzländer and Finkemeier, 2013). Further work would be required to determine whether this RCS retrograde signalling includes direct biochemical modifications of DNA.

Cardiolipin and cytochrome c

Functioning of mitochondrial ETC and OXPHOS requires correct protein–protein and protein–membrane interfaces. As a small haem protein located in the mitochondrial intermembrane space and carrying electrons between complex III and complex IV, cytochrome c plays important roles in these interfaces. Moreover, differential expression of cytochrome c-encoding genes under conditions of abiotic (cold, heat, UV-B) and biotic stress suggests that cytochrome c dynamics is involved in stress responses (Welchen *et al.*, 2009; Welchen and Gonzalez, 2016). In particular, cytochrome c plays a major role in PCD responses, through triggering pro-apoptotic routes and inhibiting pro-survival factors (Kobylińska *et al.*, 2017). The mechanisms of cytochrome c involvement in apoptosis have been thoroughly described in mammalian cells (Kagan *et al.*, 2009), but the mechanisms of its implication in plant PCD remain to be fully elucidated.

Plant responses to pathogens (Krause and Durner, 2004) and to abiotic stresses, such as heat stress (Vacca *et al.*, 2006), have been associated with release of cytochrome c from the outer face of the inner mitochondrial membrane into the cytoplasm and triggering of PCD (Fig. 3). This release occurs in two steps, consisting in initial dissociation from cardiolipin followed by formation of the permeability transition pore in the outer mitochondrial membrane. Cytochrome c interacts electrostatically with cardiolipin, which anchors it to the outer face of the mitochondrial inner membrane (Vacca *et al.*, 2006; De Paepe *et al.*, 2014). *Arabidopsis* mutants lacking cardiolipin show an increased sensitivity to PCD induction (Pineau *et al.*, 2013; De Paepe *et al.*, 2014). Moreover, mammalian cell studies suggest that several post-translational modifications of cytochrome c play a role in its interaction with cardiolipin. Thus, nitration can trigger cytochrome c degradation (Díaz-Moreno *et al.*, 2011). As described above, under conditions of mitochondrial dysfunctioning or damage, decrease in ATP production can lead to depletion of ATP levels and increase in ADP and AMP (Bailey-Serres *et al.*, 2011; Pedrotti *et al.*, 2018). In the case of mammalian cells, it has been shown that such ATP depletion can cause cytochrome c dephosphorylation, which in turn can induce cardiolipin peroxidation and the detachment of cytochrome c from the inner mitochondrial membrane (Yu *et al.*, 2008; Kagan *et al.*, 2009; Sanderson *et al.*, 2013).

Heat stress responses also show a link between cytochrome c release and Ca^{2+} dynamics. Heat stress induces increases in cytosolic and mitochondrial Ca^{2+} concentrations that are mediated by influxes from apoplastic and intracellular compartments (Rikhvanov *et al.*, 2014). Among several channels and transporters of Ca^{2+}, voltage-dependent anion channels in the outer mitochondrial membrane and the mitochondrial calcium uniporter in the inner mitochondrial membrane are involved in Ca^{2+} influx into mitochondria (Li *et al.*, 2013; Rikhvanov *et al.*, 2014; Wagner *et al.*, 2015, 2016). This accumulation of Ca^{2+} in the mitochondrial matrix as well as ROS formation can induce a decrease in the size of the transmembrane electrical potential (Gao *et al.*, 2008), which is linked to the formation of permeability transition pores (Vianello *et al.*, 2012; Zancani *et al.*, 2015). Altered redox status can also affect mitochondrial membranes through formation of pores (Biswas and Mano, 2015). In other words, release of cytochrome c from the outer face of the inner mitochondrial membrane occurs in a context of permeabilization of the outer mitochondrial membrane that promotes the release of cytochrome c and other factors into the cytosol (Petrosillo *et al.*, 2003; Vianello *et al.*, 2012; Zancani *et al.*, 2015).

In the cytosol, cytochrome c can interact with several partners (Martínez-Fábregas *et al.*, 2013): a nucleosome assembly protein-related protein involved in DNA dynamics, a transcriptional coactivator-like protein involved in mRNA metabolism, a translation initiation factor, a glyoxylase involved in oxidative stress, glyceraldehyde-3-phosphate dehydrogenase, and a cysteine protease involved in PCD. Thus, sequences of events that lead to the release of cytochrome c can be initiated (Figs 1–3) by ETC dysfunction, ATP depletion and phosphorylation dynamics, oxidative processes, NO dynamics, metal ion dynamics, glutathione and redox status, lipid peroxidations or Ca^{2+} dynamics. Such perturbations and different combinations thereof are known to occur in response to a variety of environmental and climate change stresses, such as hypoxia (Bailey-Serres *et al.*, 2011), carbohydrate limitation (Pedrotti *et al.*, 2018), heat (Vacca *et al.*, 2006; Rikhvanov *et al.*, 2014), salinity (Biswas and Mano, 2015) or pathogenic toxins (Krause and Durner, 2004). On the other hand, given the diversity of the retrograde targets of cytochrome c (Fig. 3), it can be speculated that variable combinations of triggering events, variable intensities of cytochrome c release, and variable levels of targets, depending on cell type and developmental stage, can yield different outcomes (regulation, survival or PCD) (Vianello *et al.*, 2012; Welchen and Gonzalez, 2016).

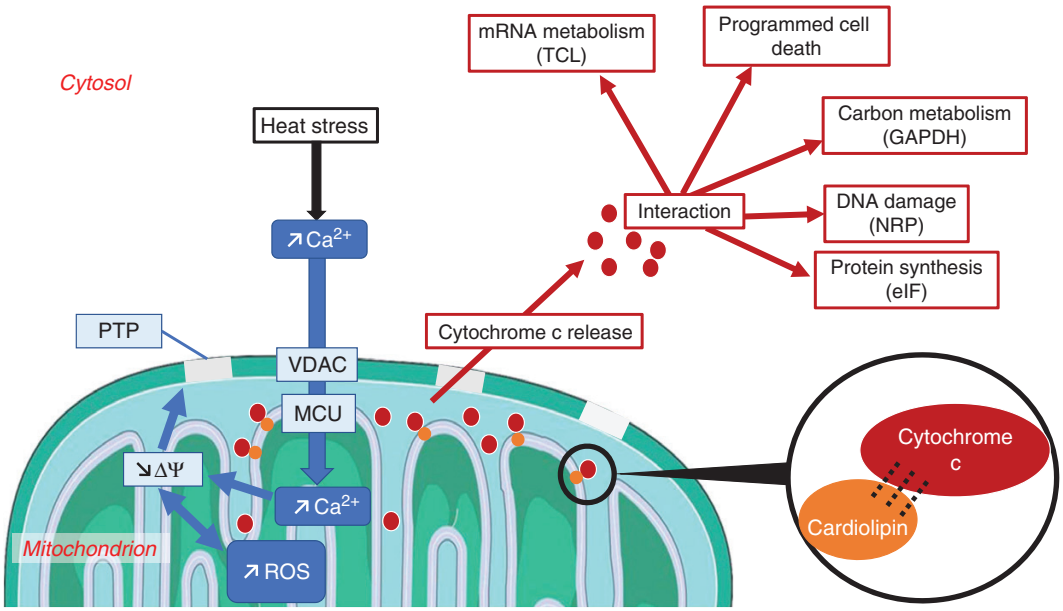

FIG. 3. Mechanisms of cytochrome c release in mitochondria under heat stress conditions. Increase in cytosolic Ca^{2+} can cause Ca^{2+} influx into the mitochondria through the outer and inner mitochondrial membranes, with the involvement of voltage-dependent anion channels (VDAC) and of the mitochondrial calcium uniporter (MCU) (LI *ET al.*, 2013; Rikhvanov *et al.*, 2014; Wagner *et al.*, 2015, 2016). Ca^{2+} influx into the matrix can lead to dissipation of the transmembrane potential and ROS production, thus enabling the formation of permeability transition pores (PTP) and cytochrome c release (Gao *et al.*, 2008; Vianello *et al.*, 2012; Zancani *et al.*, 2015). Cytochrome c release involves mechanisms of destabilization of cytochrome c–cardiolipin interactions (Vacca *et al.*, 2006; Pineau *et al.*, 2013; De Paepe *et al.*, 2014). In the cytosol, cytochrome c interactions can affect nucleic acid and protein dynamics, carbon metabolism and regulation of programmed cell death (Martínez-Fábregas *et al.*, 2013). Blue and red arrows respectively indicate mitochondrial and cytochrome c-dependent processes. Δψ, transmembrane potential; eIF, translation initiation factor; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; NRP, nucleosome assembly protein-related protein; TCL, transcriptional coactivator-like.

MITOCHONDRIAL CROSSTALK SIGNALLING AND INTERORGANELLAR STRESS INTEGRATION

Transcriptional and post-translational interorganellar stress integration

The different mechanisms of mitochondria–nucleus retrograde signalling (Schwarzländer and Finkemeier, 2013; Ashrafi *et al.*, 2018; Wagner *et al.*, 2018) are essential for the coordination of stress responses in eukaryotic cells (De Souza *et al.*, 2017; Crawford *et al.*, 2018). Moreover, in the plant cell the activities of mitochondria and plastids must be tightly coordinated in order to integrate stress-related carbon, energy and redox requirements (Crawford *et al.*, 2018). This coordination includes the multiple sensing and signalling activities associated with mitochondria and plastids (Foyer and Noctor, 2003). The importance of mitochondria–nucleus and chloroplast–nucleus retrograde signalling emphasizes the coordinating role of nuclear transcriptional regulation (Crawford *et al.*, 2018). However, the timescale of transcriptional responses suggests that rapid stress acclimation must also involve post-translational crosstalk between mitochondria and chloroplasts.

Gene expression regulation

Chloroplasts and mitochondria present distinct sets of retrograde signals. Chloroplast retrograde signalling is mediated by ROS and metabolites including β-cyclocitral, 2-C-methyl-D-erythritol-2,4-cyclodiphosphate (MecPP), 3′-phosphoadenosine 5′-phosphate (PAP) and intermediates of the tetrapyrrole biosynthesis pathway (Crawford *et al.*, 2018). The retrograde signals of mitochondria include energy metabolites, cytochrome c, ROS and PAP (Møller and Sweetlove, 2010; Møller, 2016; de Souza *et al.*, 2017; Van Aken and Pogson, 2017; Waszczak *et al.*, 2018). Stress conditions modulate the levels of all of these retrograde signals, including ROS and PAP, which are common to chloroplasts and mitochondria (Estavillo *et al.*, 2011; Chan *et al.*, 2016*a*, *b*).

Stress-related perturbations of the mitochondrial ETC are associated with superoxide and hydrogen peroxide accumulation (Basu *et al.*, 2001; Dixit *et al.*, 2002; Bienert *et al.*, 2007). Longer half-life allows hydrogen peroxide to move into the cytosol (Bienert *et al.*, 2007). Hydrogen peroxide can interact with the endoplasmic reticulum and induce post-translational modifications of *ARABIDOPSIS* TRANSCRIPTION ACTIVATION FACTOR/CUP-SHAPED COTYLEDON (ANAC) transcription factors ANAC013 and ANAC017 (De Clercq *et al.*, 2013; Ng *et al.*, 2013; Meng *et al.*, 2019). Hydrogen peroxide-induced modifications are associated with the release of transcription factors from the endoplasmic reticulum. ANAC017 has been shown to contain, in addition to its C-terminal transmembrane region, a rhomboid protease cleavage site that needs to be cleaved to induce transcription factor release from the endoplasmic reticulum (Ng *et al.*, 2013). Action of ANAC017 and ANAC013 on the nuclear genome activates a wide range of genes. ANAC017 induces the expression of *AOX1a*, *ANAC013*, *WRKY*, *DRE2B* and *RAP2* genes (Ng *et al.*, 2013). ANAC013 interacts with mitochondrial dysfunction domain-containing

promoters of mitochondrial dysfunction genes, such as *AOX1a* (De Clercq *et al.*, 2013). Besides ANAC013 and ANAC017, WRKY15/WRKY40/WRKY63 (Vanderauwera *et al.*, 2012; Van Aken *et al.*, 2013) and ABSCISIC ACID INSENSITIVE4 (ABI4) (Giraud *et al.*, 2009) transcription factors have been identified as additional downstream regulators of mitochondrial retrograde signalling. Moreover, ANAC017, WRKY40 and ABI4 are also involved in chloroplast retrograde signalling (Koussevitzky *et al.*, 2007; Shang *et al.*, 2010; Van Aken *et al.*, 2013, 2016), thus demonstrating the convergence of retrograde signalling cascades between mitochondria and chloroplasts (Schwarzländer and Finkemeier, 2013; Wagner *et al.*, 2018). The involvement of ANAC017 in both mitochondrial and chloroplast retrograde signalling suggests the possible convergence of mitochondria-derived (Møller, 2016) and chloroplast-derived (Maruta *et al.*, 2012) hydrogen peroxide signals. Differential gene induction under different modalities of hydrogen peroxide production and of abiotic stresses (Maruta *et al.*, 2012; Ng *et al.*, 2013; Van Aken *et al.*, 2016), however, indicates that hydrogen peroxide-dependent convergence is a complex regulatory process rather than the result of mere signalling overlapping.

3′-Phosphoadenosine 5′-phosphate originates from the cytosolic degradation of 3′-phosphoadenosine 5′-phosphosulphate (Bohrer *et al.*, 2015), and can accumulate in mitochondria and chloroplasts. In chloroplasts, its levels are controlled by the activity of SAL1 PAP phosphatase, which catalyses its conversion into AMP and Pi (Estavillo *et al.*, 2011). Under stress conditions, increased levels of hydrogen peroxide decrease SAL1 activity, thus resulting in higher levels of PAP, which can be exported from the chloroplast to the cytosol and the nucleus (Chan *et al.*, 2016*a*, *b*). Besides its localization in chloroplasts, SAL1 undergoes alternative targeting to mitochondria (Estavillo *et al.*, 2011; Van Aken and Pogson, 2017). The combination of PAP accumulation, SAL1 targeting and ROS dynamics is likely to be the basis for the involvement of PAP dynamics in mitochondria–cytosol–nucleus communication, but the export of PAP from mitochondria to the nucleus remains to be characterized. PAP is involved in the transcriptional regulation of stress-response genes (Estavillo *et al.*, 2011). Moreover, within the nucleus, PAP inhibits the RNA-degrading activity of 5′-3′exoribonucleases, thus resulting in a regulation of RNA processing (Estavillo *et al.*, 2011). Interestingly, PAP and ANAC017 are involved in overlapping retrograde signalling pathways that control similar sets of genes (Van Aken and Pogson, 2017). Moreover, PAP, ANAC013 and ANAC017 signalling pathways are all negatively regulated by the transcriptional hub protein RADICAL-INDUCED CELL DEATH1 (Waszczak *et al.*, 2018). As is the case for hydrogen peroxide signalling, these relationships highlight the interactions between mitochondrial and chloroplastic signalling pathways.

Glutathione post-translational interactions

Mitochondria and chloroplasts are connected by biochemical links and physical contacts (Foyer *et al.*, 2009; Pérez-Sancho *et al.*, 2016), which may be the basis for post-translational interorganellar crosstalk, as in the case of glutathione. Glutathione is synthesized in the cytosol and chloroplasts (Noctor *et al.*, 2012). Glutathione is then distributed between the cytosol, chloroplasts, mitochondria and peroxisomes (Zechmann *et al.*, 2008; Noctor *et al.*, 2012), thus reflecting the importance of glutathione production and allocation within the plant cell. The ATP requirement for glutathione synthesis (Noctor *et al.*, 2012) may be modulated by ATP availability from mitochondria and chloroplasts, in relation to metabolic energy sensing (Baena-González and Sheen, 2008; Janse van Rensburg *et al.*, 2019). Glutathione is mostly found in its reduced form (GSH) which is oxidized by ROS, including hydrogen peroxide, to its disulphide form (GSSG). GSH can then be regenerated from GSSG by reductive processes. These interconversions of GSH and GSSG are carried out by sets of cytosolic, chloroplastic and mitochondrial enzymes (Mittler *et al.*, 2004). Glutathione is therefore important for the control of ROS and redox homeostasis, at the overall plant cell level (Schwarzländer *et al.*, 2008; Noctor *et al.*, 2012; Attacha *et al.*, 2017) and in the mitochondria (Schwarzländer *et al.*, 2008; Passaia *et al.*, 2013; Attacha *et al.*, 2017). Reciprocal changes of the GSH:GSSG ratio reflect the dynamics of ROS production, which, in the case of mitochondria, is tightly linked to ETC and OXPHOS functioning (Basu *et al.*, 2001; Dixit *et al.*, 2002; Turrens, 2003). The highly reduced glutathione redox potential (E_{GSH}) that derives from the GSH:GSSG ratio (Meyer *et al.*, 2007; Meyer, 2008; Schwarzländer *et al.*, 2008) can therefore act as a sensitive sensor of oxidative homeostasis and stress, and of ETC and OXPHOS functioning, in the mitochondria. Global accumulation of GSSG has been shown to induce an increase in total glutathione in the cell both through gene expression regulation and through post-translational effects (Noctor *et al.*, 2012). Decrease in GSH concentration in mitochondria and modifications of mitochondrial redox status are related to induction of PCD processes (Fig. 2). Because of interconnections of glutathione synthesis and allocation within the plant cell, it could also be hypothesized that the fluctuations of glutathione in the mitochondria could induce glutathione-related responses in the cytosolic and plastidial compartments.

Through glutathionylation, which forms a disulphide bond between GSH and cysteine residues, GSH is able to mediate post-translational modifications of proteins (Noctor *et al.*, 2012; Zaffagnini *et al.*, 2012). This post-translational modification prevents permanent oxidation of protein thiols by ROS and changes protein conformation, thus affecting protein dynamics and activity (Zaffagnini *et al.*, 2012). Important targets of glutathionylation include proteins that are found both in mitochondria and in chloroplasts, including the redox regulatory proteins thioredoxins (TRX) and peroxiredoxins (PRX) (Rouhier *et al.*, 2008; Martí *et al.*, 2011; Liebthal *et al.*, 2018; Thormählen *et al.*, 2018). Thioredoxins are disulphide reducers widely involved in redox signalling and ROS protection (Geigenberger *et al.*, 2017). Although mostly described in plastids, TRX systems are also present in mitochondria (Balmer *et al.*, 2004; Martí *et al.*, 2011; Yoshida *et al.*, 2013; Daloso *et al.*, 2015; Geigenberger *et al.*, 2017). Thus, in pea leaves, the mitochondrial TRXo1 isoform is involved in protection from oxidative stress (Martí *et al.*, 2011). Peroxiredoxins are thiol-peroxidases acting in antioxidant mechanisms and redox signalling (Liebthal *et al.*, 2018). Like TRXs, PRXs are cysteine

proteins that can undergo glutathionylation. Hyperoxidation of plastidial PRX leads to inactivation of peroxidase activity, thus resulting in hydrogen peroxide increase (Liebthal *et al.*, 2018). Thioredoxins and PRXs interact with and potentially regulate myriad target proteins related to carbon, nitrogen and ATP metabolisms, including carbon assimilation, mitochondrial respiration and AOX (Geigenberger *et al.*, 2017; Liebthal *et al.*, 2018). This complexity of interactions and their localization in both mitochondria and plastids suggest that TRXs and PRXs play an important role at the interface between mitochondria and chloroplasts (Geigenberger *et al.*, 2017). The crosstalk that is required for integrative functioning of TRXs and PRXs between mitochondria and chloroplasts has been ascribed to various metabolites, such as NAPDH, dihydroxyacetone phosphate, malate and glycolate (Balmer *et al.*, 2004; Geigenberger *et al.*, 2017). However, through its interactions with ETC functioning and through glutathionylation, glutathione may also be an important post-translational signal between mitochondria and chloroplasts.

Ascorbate post-translational interactions

Ascorbate is widely present in the plant cell, in the cytosol, in chloroplasts and in mitochondria (Smirnoff and Wheeler, 2000; Smirnoff, 2018). It is a key antioxidant molecule for detoxifying ROS produced under stress conditions (Smirnoff, 2018). Biosynthesis in plant cells involves the D-mannose/L-galactose (Smirnoff–Wheeler) pathway, where the final step consists in the oxidation of L-galactono-1,4-lactone to L-ascorbate (Smirnoff, 2018). While the initial steps occur in the cytosol, the last step is specifically carried out by L-galactono-1,4-lactone dehydrogenase (GalDH) associated with complex I of the mitochondrial ETC (Bartoli *et al.*, 2000; Smirnoff and Wheeler, 2000; Schertl *et al.*, 2012; Venkatesh and Park, 2014; Smirnoff, 2018). This association of ascorbate synthesis with the mitochondrial ETC is both structural and functional. GalDH forms part of subcomplexes of complex I and GalDH activity donates electrons to the ETC (Bartoli *et al.*, 2000; Schertl *et al.*, 2012; Smirnoff, 2018). From the site of production at the outer face of the inner mitochondrial membrane, ascorbate must then be allocated to the different cell compartments (Smirnoff, 2018).

Ascorbate is directly involved in antioxidant defence and ROS scavenging in all the different compartments where it is found (Smirnoff, 2018). Removal of hydrogen peroxide relies on ascorbate peroxidases catalysing the oxidation of ascorbate to monodehydroascorbate and reduction of hydrogen peroxide to H_2O. The unstable monodehydroascorbate yields dehydroascorbate. Reduction of monodehydroascorbate and dehydroascorbate to ascorbate is carried out by monodehydroascorbate reductases and GSH-dependent dehydroascorbate reductases (Mittler *et al.*, 2004). Oxidized glutathione (GSSG) is recycled to GSH through NADPH-dependent glutathione reductases, thus sustaining the ascorbate–glutathione cycle (Noctor and Foyer, 1998; Mittler *et al.*, 2004).

Mitochondria are the site of active ascorbate dynamics through direct involvement in its synthesis providing the necessary pool for subcellular allocation and through utilization of the ascorbate–glutathione cycle for removal of hydrogen peroxide, whose production is tightly linked to ETC and OXPHOS functioning (Basu *et al.*, 2001; Dixit *et al.*, 2002; Turrens, 2003). This ascorbate dynamics is thus linked to various mitochondrial signals that have been described above, such as hydrogen peroxide and glutathione. The influence of this dynamics on allocation of ascorbate to the chloroplasts may also have an impact on chloroplast-derived signals such as hydrogen peroxide (Estavillo *et al.*, 2011; Chan *et al.*, 2016*a*, *b*). Moreover, ascorbate itself is thought to play a signalling role in cell division and embryo development (Gallie, 2013).

Stress-related perturbations are bound to act on mitochondrial ascorbate dynamics through their effects on mitochondrial ETC and on superoxide and hydrogen peroxide accumulation (Basu *et al.*, 2001; Dixit *et al.*, 2002; Bienert *et al.*, 2007). Mitochondrial ascorbate dynamics is therefore likely to be involved in signalling interactions between stresses and plant cell acclimation. Moreover, the D-mannose/L-galactose pathway of ascorbate synthesis in the mitochondria is regulated by a number of stress-related mechanisms, involving activation by high light, ethylene and ROS treatment and inhibition by prolonged darkness (Wang *et al.*, 2013). Such mechanisms suggest that maintenance or adjustment of the ascorbate pool size may be important for stress acclimation, whether in terms of biochemical action or in terms of signalling impact (Stevens *et al.*, 2018).

MITOCHONDRIAL PROCESSING AND DYNAMICS OF STRESS HORMONE INFORMATION

Under conditions of abiotic or biotic stress, mitochondrial functioning occurs in a cellular context where stress regulators and hormones, such as ABA, cytokinins, ethylene, salicylate and jasmonate, accumulate (Koornneef and Pieterse, 2008; Wang *et al.*, 2010; Verslues, 2016; Zhu, 2016), which can directly interact with mitochondrial functions. At low concentrations, salicylate acts as an uncoupling agent, but at higher concentrations, salicylate can act on complexes I and III of the mitochondrial ETC (Norman *et al.*, 2004; Czarnocka and Karpinski, 2018). Different molecular forms of cytokinins and of cytokinin analogues can interfere with mitochondrial respiration (Miller, 1982; Alberto *et al.*, 2017). ABA may interfere with ATP/ADP exchanges between mitochondria and cytosol transport through inhibition of mitochondrial adenine nucleotide translocators (ANTs) (Kharenko *et al.*, 2011; Berkowitz *et al.*, 2016). The affinity of ANTs for ATP is higher than their affinity for ABA, but under stress conditions increased ABA levels may inhibit ADP/ATP exchange (Kharenko *et al.*, 2011), thus leading to decreases in ATP transfer to the cytosol or of ADP replenishment to the mitochondria (Fig. 4). This direct link between ABA and ATP dynamics was characterized by *in vitro* studies (Kharenko *et al.*, 2011). Its relevance to *in vivo* cell functioning, which must depend on the relative *in vivo* concentrations of ATP, ADP and ABA, remains to be validated.

Decrease in ADP availability in mitochondria leads to accumulation of electrons in the ETC (Møller, 2001). All of these interactions, with mitochondrial respiration or with ATP/ADP dynamics, are therefore associated with the activation of ROS production (Basu *et al.*, 2001; Møller, 2001; Dixit *et al.*, 2002; Li *et al.*, 2003; Turrens, 2003). Enhanced ROS production in

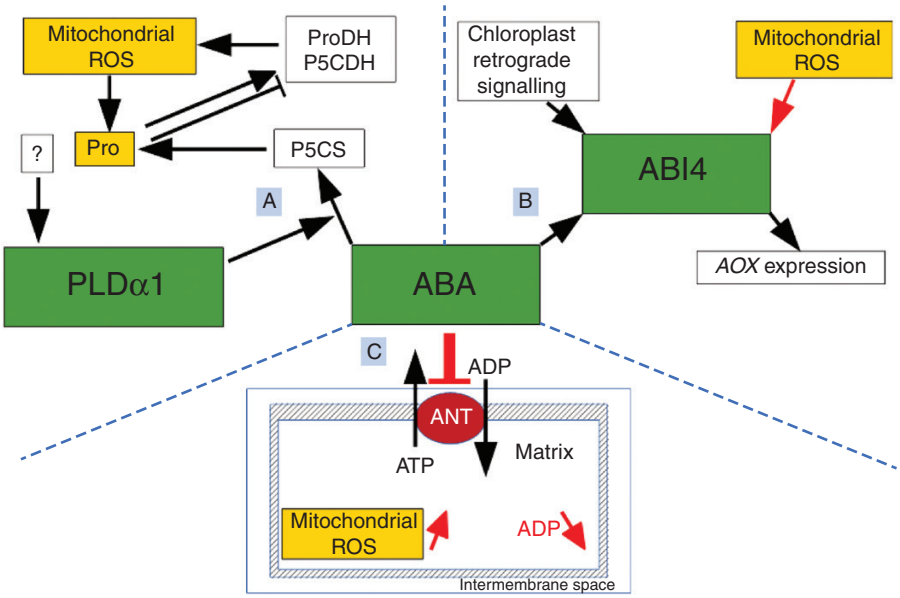

FIG. 4. Signalling interactions between ABA and mitochondrial ROS. (A) Under salt stress conditions, proline (Pro) and mitochondrial ROS are involved in regulatory loops involving ABA pathway phospholipase Dα1 (PLDα1) (POKOTYLO *ET al.*, 2012; Garcia de la Garma *et al.*, 2015). Depending on stress conditions, proline dehydrogenase (ProDH) can be downregulated (Verbruggen and Hermans, 2008) or upregulated (Verslues et Sharma, 2010; Garcia de la Garma *et al.*, 2015) by proline. Phospholipase Dα1 appears to be regulated by stress-related factors that remain to be identified (Garcia de la Garma *et al.*, 2015). (B) The ABA-insensitive-4 (ABI4) transcription factor integrates mitochondrial retrograde signals, in particular ETC-derived ROS (Schwarzländer and Finkemeier, 2013; Waszczak *et al.*, 2018), with chloroplast retrograde signals and ABA signalling (Koussevitzky *et al.*, 2007; Giraud *et al.*, 2009; Zhang *et al.*, 2013). (C) According to *in vitro* studies, ABA may act on ATP/ADP and ROS dynamics through inhibition of mitochondrial adenine nucleotide translocator (ANT) (Kharenko *et al.*, 2011; Berkowitz *et al.*, 2016). Decrease in ADP availability in mitochondria is associated with the activation of ROS production (Basu *et al.*, 2001; Møller, 2001; Dixit *et al.*, 2002; Li *et al.*, 2003; Turrens, 2003). P5CS, pyrroline-5-carboxylate synthetase; P5CDH, pyrroline-5-carboxylate dehydrogenase.

the mitochondria is associated with transcriptional and post-translational regulation, with hydrogen peroxide retrograde signalling, with membrane permeability modifications and cytochrome c release (Fig. 3), and with PCD induction (Gao *et al.*, 2008; Liu *et al.*, 2014; Wu *et al.*, 2015; Carraro and Bernardi, 2016; Cui *et al.*, 2019). In parallel, modifications of ATP synthesis or of ATP/ADP exchange can be sensed by the SnRK1 metabolic sensor, with subsequent effects of transcriptional regulation of stress-related genes or post-translational phosphorylation regulation of key metabolic enzymes (Broeckx *et al.*, 2016; Nukarinen *et al.*, 2016; Wurzinger *et al.*, 2018). Consequently, salicylate, cytokinins and ABA are likely to influence directly mitochondrial ROS signalling, interorganellar stress integration and regulation of PCD induction. Mitochondria can therefore be considered as organellar transducers of stress hormone signalling and, given the convergence of action on ROS and ATP/ADP ratios, as organellar integrators of multiple stress hormone signals.

Abscisic acid signalling is thought to be involved in feedback regulation of mitochondrial ROS signalling during salt stress (Pokotylo *et al.*, 2012; Garcia de la Garma *et al.*, 2015). Salt stress response is associated with induction of ROS production in mitochondria (Garcia de la Garma *et al.*, 2015). In contrast with other stress situations, this salt-stress-induced ROS production in turn enhances proline accumulation and activation of mitochondrial ProDH and P5CDH activities (Garcia de la Garma *et al.*, 2015). Proline accumulation and enhanced proline catabolism activate electron fluxes through the mitochondrial ETC, thus exacerbating mitochondrial ROS production (Liang *et al.*, 2013; Schertl and Braun, 2014; Garcia de la Garma, 2015). Through unknown mechanisms, this stress-related regulatory loop appears to be connected to phospholipase D (PLD) α1 (Fig. 4), which is involved in activation of ABA signalling and enhancement of *P5CS* expression in relation to proline biosynthesis (Garcia de la Garma *et al.*, 2015). On the one hand, this regulation of ROS amplification can lead to PCD (Figs 2 and 3). On the other hand, although its exact role remains to be elucidated, PLDα1 is related to enhanced salt tolerance (Garcia de la Garma *et al.*, 2015). Moreover, besides transducing information from the canonical ABA signalling pathway (Zhang *et al.*, 2013), the ABI4 transcription factor integrates mitochondrial and chloroplast retrograde signals (Koussevitzky *et al.*, 2007; Giraud *et al.*, 2009). This convergence (Fig. 4) affects in particular the regulation of mitochondrial AOX expression (Giraud *et al.*, 2009), and is therefore related to the rheostat functions of AOX in mitochondrial ROS and RNS dynamics (Cvetkovska and Vanlerberghe, 2012*b*; Kumari *et al.*, 2019). Several ETC-related mitochondrial stress signals therefore depend on pathways that mobilize stress hormone signalling mechanisms, especially ABA signalling. Conversely, such interactions can be seen as interferences with hormone-signalling pathways, and therefore as mechanisms of mitochondrial modulation of hormone signalling.

CONCLUSIONS

Plant mitochondria are endowed with a diversity of multi-directional hubs of stress signalling (Bohovych and

Table 1. *Examples of involvement of mitochondrial ETC- and OXPHOS-related signalling in environmental stress responses*

Environmental stress	Mitochondrial signals	Stress response	Reference
Drought	Proline	Redox regulation	Liang *et al.* (2013)
ABA	ATP/ADP	Not characterized	Kharenko *et al.* (2011)
Cold	Ca^{2+}	Not characterized	Li *et al.* (2013)
Heat	Ca^{2+}, cytochrome c	PCD	Rikhvanov *et al.* (2014)
Heat, salinity	Redox potential	PCD regulation	Schwarzländer *et al.* (2009)
Salinity	Proline, ROS	ABA response	Garcia de la Garma *et al.* (2015)
Darkness	ATP/ADP	Alternative respiratory pathways	Pedrotti *et al.* (2018)
High light	Ascorbate	Heat-shock response	Stevens *et al.* (2018)
Hypoxia	NO	Ethylene response	Gibbs *et al.* (2015)
Experimental oxidative stress	RCS	PCD, redox regulation	Winger *et al.*(2005, 2007)
Lead	ROS, cytochrome c	PCD regulation	Kobylińska *et al.* (2017)
Chromium	ROS	Redox regulation	Dixit *et al.* (2002)
Xenobiotics	ATP/ADP	Alternative respiratory pathways	Alberto *et al.* (2017)
Piercing–sucking insects	AOX	Resistance	Zhang *et al.* (2012)
Pseudomonas spp.	AOX	Resistance	Zhang *et al.* (2012)
Flagellin	Proline	Immunity	Fabro *et al.* (2016)
Toxins	ROS	PCD	Yao *et al.* (2002)

Khalimonchuk, 2016; Welchen and Gonzalez, 2016). These mitochondrial stress signalling hubs are involved in the responses to a wide range of abiotic stresses (cold, drought, extended darkness, heat, heavy metals, high light, hydrogen peroxide, hypoxia, salinity, UV-B, xenobiotics), biotic stresses (piercing–sucking insects, *Pseudomonas* spp., toxins) and developmental, nutritional and hormonal perturbations (ABA, carbohydrate starvation, ethylene, jasmonate, nitrogen starvation, PCD, salicylate). Table 1 highlights the diversity of environmental stresses, signals and responses that are related to mitochondrial ETC and OXPHOS. Most of these stresses, with various degrees of frequency and intensity, play a role in the combination of climate change drivers affecting plant communities (Komatsu *et al.*, 2019).

It can therefore be assumed that, as multi-stress signalling hubs related to energy and redox balance, mitochondria could function as integrators of multiple climate change signals and be involved in acclimation to climate change (Munné-Bosch *et al.*, 2013). However, involvement in such a wide range of responses also implies that mitochondrial stress signalling could lead to synergistic or conflicting outcomes during acclimation to multiple and complex stresses, such as those arising from climate change.

The mechanisms of these mitochondrial stress signalling hubs involve regulatory loops and regulatory rheostats, whose functioning can amplify and diversify some signals or, conversely, dampen and reduce other signals. As emphasized in the present review, ETC and OXPHOS are centrally involved in this network of mitochondrial signals. Moreover, expression levels of ETC and OXPHOS components are controlled by the developmental and hormonal context, thus implying that ETC and OXPHOS stress signalling dynamics can function at different setpoints of respiratory activity, ATP production and ROS production. However, the involvement of other mitochondrial structures and processes, such as membrane contacts or Ca^{2+} dynamics, that are also connected to signalling mechanisms should be further investigated. Moreover, mitochondrial signalling hubs may involve not only functioning and perturbations of functioning, but also biogenetic processes such as protein import and supramolecular assembly. Thus, ETC and OXPHOS homeostasis is likely to act not only on respiration and energy functioning, but also on the correct assembly of ETC and OXPHOS complexes. Finally, further research should be carried out on the potential links between the mitochondrial signalling hubs, nuclear epigenetic regulation (Shaughnessy *et al.*, 2014) and mitochondrial epigenetics (van der Wijst and Rots, 2015). Understanding these links should bring new insights into the involvement of mitochondria in the processes of stress memory and priming (Hilker and Schmülling, 2019).

The regulation of mitochondrial respiration and of mitochondria/cell crosstalk has been recognized to be a major determinant of plant vigour and crop productivity (Amthor *et al.*, 2019). The objective of decreasing respiratory carbon loss for improvement of crop productivity will depend on the identification of relevant genetic and physiological targets (Amthor *et al.*, 2019). However, the search for such targets should not be confined to metabolic and biosynthetic processes, and should take into account signalling interactions that are likely to sustain integrative and adaptive responses, and thus especially mitochondria-related signalling.

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