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# Plant mitochondria under pathogen attack: A sigh of relief or a last breath?

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ABSTRACT

Plants constitute excellent sources for pathogen nutrition and survival. To fight against pathogen attack, higher plants have developed a sophisticated immune system responsible for pathogen recognition and activation of downstream defense responses. After pathogen perception, mitochondria play an important role in the defense strategy of the plant cell, integrating and amplifying diverse signals such as salicylic acid, nitric oxide, reactive oxygen species (ROS) or pathogen elicitors. Signals perceived by mitochondria usually impact on their normal function, destabilizing the organelle, generating changes in respiration, membrane potential and ROS production. At this stage, mitochondria produce several signals influencing the redox state of the cell and promoting changes in the expression of nuclear genes by mitochondrial retrograde regulation. At more advanced stages, they promote programmed cell death in order to avoid pathogen propagation to the whole plant. Recent evidence indicates that plants and pathogens have evolved mechanisms to modulate the immune response by acting on mitochondrial functions. In this review, we summarize knowledge about the involvement of mitochondria in different aspects of the response of plants to pathogen attack.



## 1. Introduction

Plants represent an excellent source of water and nutrients for microbes that can easily enter plant tissues through wounds or natural entrances like hydathodes or stomata, remain in the apoplast and move through the xylem vascular system (Abramovitch et al., 2006). Plant–pathogen interaction is a complex process and the events triggered after the first recognition depend on many factors such as the type of microbe or pathogen (i.e. bacteria, viruses, fungi or insects), and the characteristics and health of the plant.

When a pathogen interacts with a plant cell, it induces a sophisticated immune response in the plant. The extent of the response depends on the pathogen characteristics and the mechanism used by the foreign organism to elude the plant defense system. Briefly, the plant immune system has two different branches: the basal defense or PTI/MTI (PAMP-triggered immunity or MAMP-triggered immunity) and the induced defense or ETI (effector-triggered immunity) (Dangl and Jones, 2001; Jones and Dangl, 2006). The first or basal defense barrier is raised when the extracellular part of plant cell membrane receptors, known as PRRs (Pattern Recognition Receptors), recognizes microbial or pathogen associated molecular patterns (MAMPs or PAMPs). PRRs are typical RLKs (receptor like kinases) and they are able to generate rapid transcriptional changes inside the plant cell (Fig. 1, #1–4). Many pathogens have evolved different strategies to elude the barrier imposed by PTI, by releasing effector molecules that can interfere with signal transduction between PRRs and the nucleus, leading to plant ETS (effector-triggered susceptibility). However, if pathogen-effectors are specifically recognized by R (Resistance) proteins of the plant cell, the second defense barrier known as ETI is raised. During ETI, pathogen effectors are recognized by intracellular receptors or NB-LRR (nucleotide binding-leucine rich repeat domain) proteins (Abramovitch et al., 2006; Jones and Dangl, 2006). ETI finally leads to HR (hypersensitive response) in the infection site. This response is a kind of plant programmed cell death (PCD) established in order to isolate pathogenic cells and confine

*Abbreviations:* AA, antimycin A; AOX, alternative oxidase; BA, Bongkrekic Acid; COX, cytochrome *c* oxidase; CsA, cyclosporine A; CypD, cyclophilin D; ETC, electron transfer chain; ETI, effector-triggered immunity; ETS, effector-triggered susceptibility; HR, hypersensitive response; IMM, mitochondrial inner membrane; MAMP, microbe-associated molecular pattern; MAPK, MAP kinase; mGDC, mitochondrial glycine decarboxylase; MMP, mitochondrial membrane potential; MnSOD, manganese superoxide dismutase; mROS, mitochondrial ROS; MTI, MAMP-triggered immunity; NB-LRR, nucleotide binding-leucine rich repeat domains; NO, nitric oxide; NOS1, nitric oxide synthase 1; $O_2^-$, superoxide; OMM, outer mitochondrial membrane; PAM16, pre-sequence translocase-associated protein import motor 16; PAMP, pathogen-associated molecular pattern; PCD, programed cell death; PPIX, protoporphyrin IX; PR, pathogenesis related; PRRs, Pattern Recognition Receptors; PTI, PAMP-triggered immunity; PTP, permeability transition pore; R proteins, resistance proteins; RBOH, respiratory burst oxidase homolog; RLK, receptor like kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SA, salicylic acid; SNC1, suppressor of NPR-1 constitutive 1; T3E, type III effector; T3SS, type III secretion systems; UCP, uncoupling protein.

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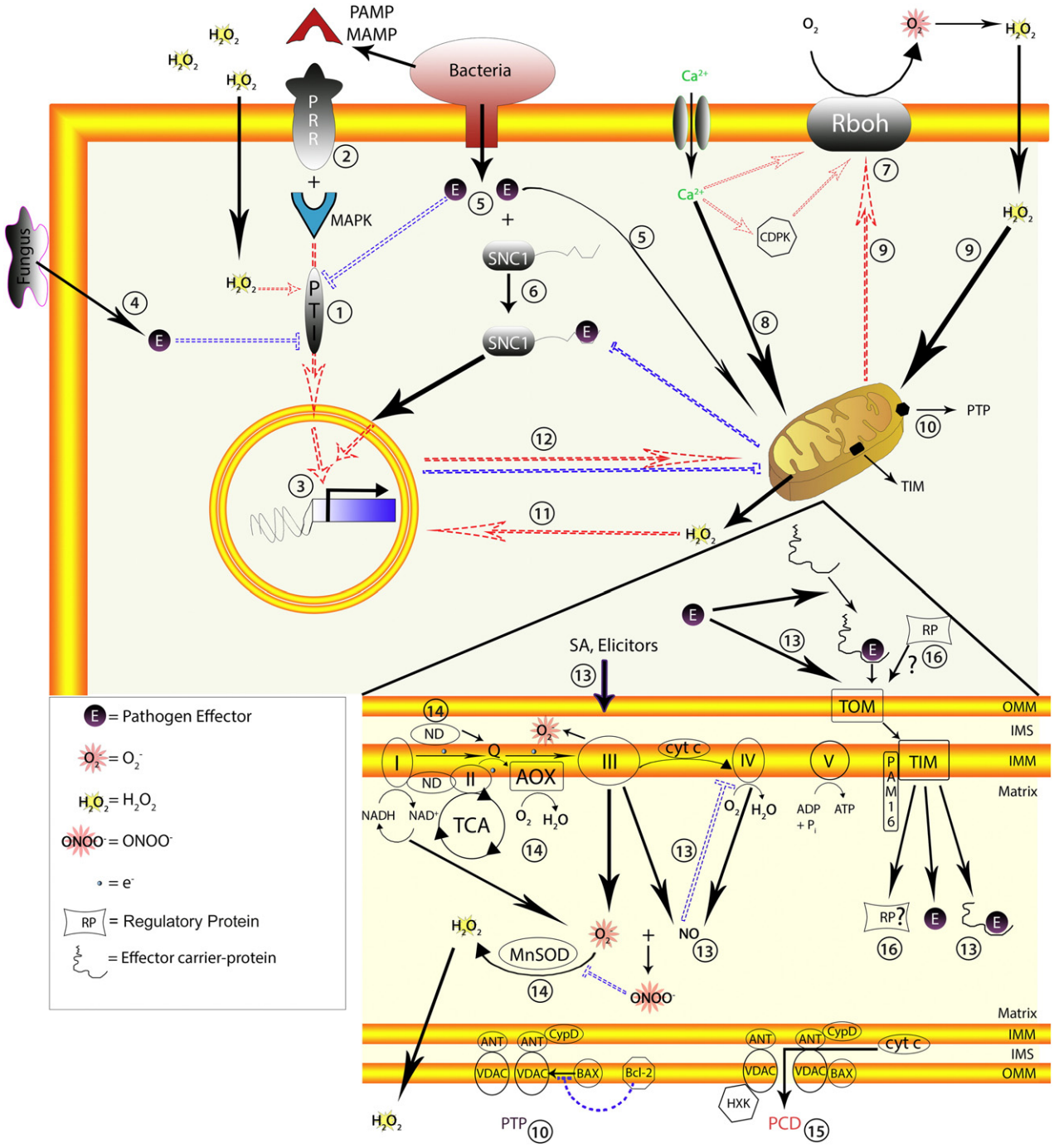


**Fig. 1.** The many roles of mitochondria in the response of plants to pathogens. Basal defense or PTI (1) is activated when extracellular plant cell membrane receptors (PRR, 2) recognize specific PAMPs or MAMPs and, through MAPK cascades, are able to generate rapid transcriptional changes in the nucleus of the plant cell (3). Many pathogens have evolved different strategies to elude the barrier imposed by PTI, thus releasing effector molecules (4, 5) involved in suppressing basal defense. Effector recognition by R proteins triggers the second defense barrier known as ETI. SNC1 is an example of a TIR NB-LRR R protein that would be responsible for recognition of unknown pathogen effectors (6). In addition, upon pathogen perception an oxidative burst takes place in the cell, promoted by RBOH-family proteins present in the plasma membrane (7). Mitochondria are deeply involved in the signaling networks related to pathogen attack. They modulate changes in cytoplasmic $Ca^{2+}$ and ROS related to activation of RBOH (8, 9). These events initiate a depolarization of the mitochondrial membrane which initiates the formation of the PTP (10). As a consequence of changes in respiratory activity and ROS production, mitochondria produce several signals that influence the expression of nuclear genes in a process known as mitochondrial retrograde regulation (11). Changes perceived in the nucleus, in turn, modify the expression of several mitochondrial proteins (12). Several compounds related with plant–pathogen interactions, like SA, pathogen elicitors, effectors and NO, impact on mitochondrial function (13). The activities of alternative NAD(P)H dehydrogenases (ND), AOX and MnSOD modulate the balance between different ROS, like $O_2^-$ and $H_2O_2$ (14). Under biotic stress conditions, mROS influence the behavior of the whole cell leading to diverse levels of responses that can culminate in the establishment of PCD (15). Recently, a protein connected with the TIM23 translocase, PAM16, was identified as a negative regulator of the immune response, suggesting the existence of regulatory proteins (RP) that are imported to mitochondria and impact on the development of ETI (16).

them at the site of infection, blocking their spread through the plant (Jones and Dangl, 2006; Lam et al., 2001) (Fig. 1, #5–7). Both PTI and ETI activate similar signaling pathways including MAP kinase (MAPK) cascades, calcium ion efflux, changes in transcriptional programs and hormone signaling, lignin and callose deposition at the cell wall and increase ROS production (Block and Alfano, 2011; Chisholm et al., 2006) (Fig. 1, #7–9, #11).

Upon pathogen recognition, an "oxidative burst" characterized by a rapid and transient apoplastic ROS (reactive oxygen species) production takes place. The sources for this apoplastic oxidative burst are plant

NADPH oxidases of the plasma membrane, also called RBOHs (respiratory burst oxidase homologs) (Bindschedler et al., 2006; Torres and Dangl, 2005) (Fig. 1, #9). However, besides this first apoplastic ROS production and depending on the extent of the infection, ROS produced from different organelles also act as signaling molecules, thus amplifying the initial response and acting as positive and also negative modulators in the spread of cell death (Torres, 2010). Among others, chloroplasts have an essential role in localized cell death produced by ROS (Zurbriggen et al., 2009).

Mitochondria also constitute an important source of ROS, like $O_2^-$ and $H_2O_2$, and RNS (reactive nitrogen species), which is conditioned by the mitochondrial membrane potential (MMP) and the reduction state of the ETC (electron transfer chain) (Møller, 2001). In the case of imbalances and alterations in respiration, a mitochondrial $O_2^-$ burst is produced, which is normally controlled by alternative pathways and scavenging systems present in the organelle (Gupta et al., 2011; Planchet et al., 2005; Vanlerberghe et al., 2009). However, under biotic stress, mROS (mitochondrial ROS) influence the behavior of the whole cell leading to diverse levels of responses that can culminate in the establishment of plant PCD (Cvetkovska et al., 2012; Krause and Durner, 2004; Solovieva et al., 2013; Torres, 2010; Vidal et al., 2007).

Mitochondria have been proposed as target sites for the action of signaling molecules generated during plant–pathogen interactions. Once perceived by the organelle, these signals generate a disruption of mitochondrial homeostasis and an oxidative burst of ROS and RNS that then act as new signaling molecules to establish defense mechanisms and modulate the immune response of the plant (Amirsadeghi et al., 2007; Cvetkovska and Vanlerberghe, 2013; Maxwell et al., 2002).

In this review, we discuss the role of mitochondria in different plant immune system barriers, as well as the role of mitochondria in the interface between PTI and ETI. We also mention the latest evidence regarding pathogen effectors targeting mitochondria and new components of the mitochondrial import machinery involved in negative regulation of plant cell immunity. Finally, we list the most relevant examples of mitochondrial proteins involved in the defense mechanisms elicited by the plant cell.

## 2. The role of mitochondria in defense against pathogen attack

### 2.1. Mitochondrial responses during the early infection stages

Plant mitochondria play a role in the response to biotic stress. It is generally assumed that PTI is a rapid response of the plant immune system and this first "cell reprogramming step" occurs during the first hour after plant–pathogen recognition. There are several evidences about the role of plant mitochondria during incompatible plant–pathogen interactions that include the perception of signals coming from the intercellular space or apoplast (Amirsadeghi et al., 2007). PAMPs like Flg22, harpin, lipopolysaccharides, fungal polygalacturonases and chitin are examples of molecules that induce high mitochondrial ROS production (Torres, 2010). ROS, salicylic acid (SA), nitric oxide (NO), bacterial elicitors and selective toxins are the signals perceived by the organelle in order to activate defense mechanisms (Krause and Durner, 2004; Laloi et al., 2004; Lam et al., 2001; Mur et al., 2006; Norman et al., 2004; Torres et al., 2006) (Fig. 1, #13, #14). In this sense, it is well known that SA impacts on mitochondrial functions in a dose dependent form, acting as uncoupler and inhibitor of ETC by interaction with Complexes I and II (Norman et al., 2004; Xie and Chen, 1999). Harpin also inhibits mitochondrial respiration in *Arabidopsis* cells, causing an increase in ROS and NO and originating a strong induction of small heat-shock proteins and the stress-responsive protein AOX (alternative oxidase) (Krause and Durner, 2004). Regarding NO, this molecule could be generated as a consequence of cellular dysfunction and decreased ATP production. Mitochondrial ETC is one of the sites for NO synthesis through nitrite reduction at the sites of complexes III, and IV and AOX, thus contributing to ATP production especially under hypoxic conditions (Modolo et al., 2005). During pathogen attack, when mitochondrial NO production is excessive, it serves as a nitrosylating agent, acting specifically at the level of complex I, promoting PCD (Gupta and Kaiser, 2010; Gupta et al., 2011). NO can reversely bind to cytochrome *c* oxidase (COX), markedly altering its activity and perturbing mitochondrial respiration (Amirsadeghi et al., 2007; Gardner, 2005). Moreover, NO mediates the inhibition of the mitochondrial glycine decarboxylase (mGDC) by nitrosylation, limiting the source of NADH for the mitochondrial respiratory chain, thus altering the redox status of the cell and promoting PCD (Gupta et al., 2011; Modolo et al., 2005).

Yao et al. (2002) showed that a burst of mROS occurs after treatment of *Avena sativa* leaves with the toxin victorin (a virulence factor synthesized by a pathogenic fungus). The increase in mROS production preceded a decrease in MMP. Later, Curtis and Wolpert (2004) demonstrated that victorin interacts with a cell surface protein to initiate the defense and originates a severe modification in MMP that ends in a PCD response. Once victorin gains access to the mitochondrial matrix through the permeability transition pore (PTP) (Fig. 1, #10), it binds two proteins (P- and H-proteins) of mGDC, which is important in the photorespiratory cycle. This leads to an accumulation of $H_2O_2$ within mitochondria that inhibits mGDC, altering mitochondrial functions in this way (Yao et al., 2002).

Zipfel et al. (2004) demonstrated a strong induction of several WRKY transcription factors, and of genes with an over-representation of WRKY binding sites (W-boxes) in their promoter regions, after a short time of treatment with Flg22, the elicitor epitope of flagellin. More recent studies driven by Van Aken et al. (2013) showed that many promoter regions of nuclear genes encoding proteins responsive to mitochondrial dysfunction contain the core motif of the W-box, TTGAC. By mutation of the W-boxes in the promoters of *AOX1a*, *NDB2* and *BCS1*, which encode stress-responsive mitochondrial proteins, the authors demonstrated the functionality of these boxes. Moreover, the importance of WRKY transcription factors in the regulation of the expression of these genes was studied after Flg22 application in 12 different WRKY mutant and overexpressor lines. WRKY40 was found to be a regulator of *BCS1* expression after Flg22 spraying, while wrky63 mutant plants showed reduced expression of *BCS1* and *AOX1a* even under control conditions (Van Aken et al., 2013). This study highlights the importance of mitochondria in basal responses and reinforces the notion of the existence of a cross-talk between the nucleus, chloroplasts and mitochondria, through a process known as retrograde signaling (Welchen et al., 2014) (Fig. 1, #11, #12).

All this information points at mitochondria as a target of signals transduced during PTI. Elicitors interact with PRR receptors in the cell surface; then, a MAPK cascade brings the signal to the nucleus where a set of transcriptional modifications takes place. Mitochondria are not only involved in the perception of the stress signal but are also responsible for signal transduction (Maxwell et al., 2002). There are several evidences supporting this hypothesis.

Defensive responses mediated by MAPK protein cascades and nuclear gene expression changes after antimycin A (AA), SA, and $H_2O_2$ treatments were inhibited by BA (Bongkrekic Acid), an agent that alters mitochondrial membrane permeability (Maxwell et al., 2002; Takahashi et al., 2003). In addition, peptides derived from proteolytic breakdown of mitochondrial proteins damaged after oxidative stress may act as specific secondary messengers to regulate specific subsets of genes (Møller and Sweetlove, 2010).

### 2.2. Mitochondria as the interface between PTI and ETI

Once plant cells trigger their first immune barrier, successful pathogens start their virulence programs. Phytopathogenic bacteria deliver different effectors or virulence proteins into host cells using type III secretion systems (T3SS) in order to block the PTI response (Alfano and Collmer, 2004) (Fig. 1, #5). This block can act at the PRR membrane receptor level, interfere with the MAPK cascade or prevent proteins

involved in PTI from reaching their targets in the cytoplasm of the host. The effectors delivered by bacteria (T3Es) promote virulence and pathogenicity by targeting the plasma membrane, mitochondria and chloroplasts of the host cells (Block and Alfano, 2011; Greenberg and Vinatzer, 2003). There are different T3E proteins with several enzymatic activities such as cysteine protease, ubiquitin-like protease, E3 ubiquitin ligase and protein phosphatase activity (Abramovitch et al., 2006; Block et al., 2008). They perform immune suppression using several strategies including inhibition of RNA metabolism, blocking of vesicle trafficking and interference with organelle functions (Block and Alfano, 2011). Effectors that enable pathogens to suppress PTI are known as avirulence (Avr) proteins when they are recognized by specific plant R proteins (Alfano and Collmer, 2004; Zipfel et al., 2004). In the "gene-for-gene" model *R* genes are effective if a specific *Avr* gene is present in the pathogen. When R proteins detect an Avr protein, the defense cascade triggers the HR (Jones and Dangl, 2006). Most R proteins contain NB-LRR motifs and although their activity is crucial for the regulation of immunity, it remains unclear as to how they are activated.

T3Es can be found in organelles like chloroplast and mitochondria (Block and Alfano, 2011). T3E Hopl1 targets chloroplasts and initiates a re-folding of host proteins and a decrease in the production of the hormone SA (Jelenska et al., 2010). Block et al. (2010) identified HopG1, the first T3E of the bacterial pathogen *Pseudomonas syringae* localized into mitochondria. HopG1 suppresses innate immunity and PTI by disrupting mitochondrial functions and promoting plant disease. Although the mechanism of action and specific target of HopG1 are unknown, it can lead to decreased oxygen respiration rate, enhanced basal level of ROS and altered *PR1* (*PATHOGENESIS RELATED 1*) and *WRKY22* expression after treatment with the Flg21 elicitor (Block et al., 2010). This is an indication that mitochondria are involved in PTI as well as ETI responses.

In a more recent study, Huang et al. (2013) reported the identification of negative regulators of the TIR-type NB-LRR R protein SNC1 (suppressor of NPR-1 constitutive 1) and ETI. An *Arabidopsis thaliana* SNC1 gain-of-function mutant conferring constitutive defense activated response (Fig. 1, #6) was initially used to identify *mos* (modifier of *snc1*) mutants that suppress the autoimmune phenotype. Huang et al. (2013) used *mos4 snc1* double mutants to screen for mutations that enhance SNC1 mediated responses, thus isolating *muse* (mutant snc1-enhancing) genes. One of the genes identified encodes the ortholog of the *Saccharomyces cerevisiae* PAM16 (pre-sequence translocase-associated protein import motor) of the inner mitochondrial membrane (IMM) (Fig. 1, #16). Mutants in *AtPAM16* show increased *PR1* and *PR2* transcript levels, elevated ROS production under basal conditions, smaller rosette size and enhanced resistance to virulent pathogen attack (Huang et al., 2013). AtPAM16 localizes to mitochondria and is connected to the TIM23 translocase complex of the IMM. According to these results, and considering the close connection with TIM23, AtPAM16 could be involved in the import of a negative regulator of plant immunity to the mitochondrial matrix, where it would function as a modulator of ROS generation (Huang et al., 2013). This is the first evidence showing an unexpected mitochondrial role as a negative regulator of plant immunity.

### 2.3. Are mitochondria at the core of ETI?

ETI or effector-triggered immunity is recognized as an amplified version of PTI that usually leads to HR, a response aimed to retard pathogen spread (Lam et al., 2001). HR is a form of local PCD that is triggered at the site of infection and shares typical characteristics of animal cell death like cytoplasmic shrinkage, chromatin condensation, mitochondrial swelling, as well as some plant specific characteristics such as vacuolization and chloroplast disruption during the final stages (Coll et al., 2011; Hoeberichts and Woltering, 2002). Molecular consequences that lead to ETI-induced HR share some aspects with PTI and include the accumulation of SA, sphingolipids, ROS and RNS, changes in intracellular $Ca^{2+}$ levels, activation of MAPK cascades and transcriptional reprogramming (Del Pozo and Lam, 1998; Mur et al., 2008; Torres, 2010).

During HR, mitochondria can be proposed to be a death integrator, playing a central role in the perception, integration and amplification of signals coming from different pathways (Amirsadeghi et al., 2007; Jones, 2000; Mur et al., 2008). Among the signals that converge in mitochondria we can mention the influx of $Ca^{2+}$ from apoplast sources and other signals such as sphingolipids (i.e. ceramides) that increase the levels of $Ca^{2+}$ and cytosolic ROS (Fig. 1, #8). These events initiate a depolarization of the mitochondrial membrane which initiates the formation of the PTP (permeability transition pore). The PTP is a large multiprotein complex firstly characterized in mammals, formed after stimuli that induce apoptosis in the site of apposition between the inner and outer mitochondrial membranes. Plants contain several components of the PTP like cyclophilin D (CypD) and the adenine nucleotide translocator (ANT) in the IMM and the VDAC protein in the OMM (Brenner and Grimm, 2006; Coll et al., 2011; Kusano et al., 2009) (Fig. 1, #10).

ROS, SA and NO are important signaling molecules that increase after pathogen recognition and are key players in HR induction (Lamb and Dixon, 1997; Lorrain et al., 2003). Increases in NO and SA initiate a decrease in electron transfer leading to an over-reduction of respiratory components and higher production of mROS, leading to mitochondrial injury and decreased ATP generation, thus amplifying the initial signals and originating HR (Mur et al., 2008; Senthil-Kumar and Mysore, 2012; Xie and Chen, 1999).

There are several lines of evidence showing that mitochondria are involved in plant PCD as well (Lam et al., 2001; Vianello et al., 2007; Yao et al., 2004). Elicitors produced by *Erwinia amylovora* and *P. syringae* rapidly inhibit ATP synthesis and alter mitochondrial functions in cultured tobacco and *Arabidopsis* cells, respectively (Krause and Durner, 2004; Xie and Chen, 2000). Moreover, induction of PCD in *Arabidopsis* cell cultures by ceramide, PPIX (protoporphyrin IX) and an avirulence factor (*AvrRpt2*) leads to the dissipation of the MMP, morphological changes in the organelle and cytochrome *c* release (Yao et al., 2004). These authors also detected a burst of mROS preceding mitochondrial destabilization. This was clearly an early event, and was followed by a loss of MMP that could be blocked by CsA (cyclosporine A). Furthermore, the *Arabidopsis* chloroplast protein ACD2 (Accelerated Cell Death 2) increased its level and localized also to mitochondria after induction of PCD by *Pseudomonas* and PPIX treatments (Yao and Greenberg, 2006).

An important mitochondrial player during HR-like PCD is the voltage-dependent anion-selective channel (VDAC) of the OMM (Kusano et al., 2009; Takahashi and Tateda, 2013). VDAC is the most abundant protein of the OMM and the major transport pathway of metabolites and other compounds between the cytosol and mitochondria (Homble et al., 2012; Kusano et al., 2009). VDAC-encoding genes are recognized as early HR marker genes, and this is probably due to an interaction between VDAC and the PPT (Takahashi and Tateda, 2013; Tateda et al., 2009). Interestingly, VDAC from mammalian cells has been co-purified with some glycolytic enzymes, such as hexokinase, aldolase and G3PD (glyceraldehyde 3-phosphate dehydrogenase). Binding of hexokinase to the cytosolic side of the mitochondrial VDAC protein interferes with the interaction between VDAC and pro-apoptotic Bcl-2 family proteins, thus blocking apoptosis (Kusano et al., 2009) (Fig. 1, #10, #15).

Mitochondria play key roles in the intrinsic pathway of apoptosis in mammalian cells. Mitochondrial membrane permeabilization, leading to the release of cytochrome *c* and other pro-apoptotic factors into the cytosol, is regulated by the interaction between pro- and anti-apoptotic Bcl-2 family members (e.g. Bax, Bim, Bcl-XL, among others) (Narita et al., 1998). Interaction between the pro-apoptotic factor Bax and VDAC causes cytochrome *c* release, a key initial step in apoptosis (Narita et al., 1998). Even if plant homologues of the Bcl-2 protein

family were not identified, it was extensively demonstrated that heterologous expression of mammalian Bax induces HR-like plant cell death in *Arabidopsis* and tobacco (Kawai-Yamada et al., 2001, 2004; Lacomme and Santa Cruz, 1999; Tateda et al., 2009). Also, expression of the anti-apoptotic factor Bcl-XL in tobacco plants prevented cell death induced by UV-B, paraquat or the HR induced by infection with the tobacco mosaic virus (Mitsuhara et al., 1999). Phenotypes of plant PCD induced by the heterologous expression of Bax resemble the HR-phenotype induced by tobacco mosaic virus and progress with an increase of PR1 expression. Together, these observations suggest that, although there are no members of the Bcl-2 family in plants, some features of animal and plant cell death processes are conserved (Lacomme and Santa Cruz, 1999).

### *2.4. The role of the mitochondrial respiratory chain in the response of plants to pathogens*

As we highlighted above, mROS and mRNS have become targets of different studies because it is believed that they have a signaling and defensive role under pathogen attack. ROS formation is closely linked to the function of the mitochondrial respiratory chain. Under "normal" conditions, electrons flow from reduced substrates to $O_2$ through a series of respiratory complexes that use the energy of this redox process to translocate protons for the subsequent synthesis of ATP. However, under certain conditions (i.e. blocking of the respiratory chain, lack of acceptors) the respiratory complexes may become over-reduced and directly transfer electrons to $O_2$ leading to the production of ROS (Møller, 2001). Since ROS damage mitochondrial components, this generates a positive feedback loop. Different from mammals, plant mitochondria contain "electron valves" or alternative electron transport pathways, capable of redirecting electrons out from the respiratory complexes and thus decreasing the production of ROS. These valves are AOX, type II NAD(P)H dehydrogenases and the alternative proton transporter UCP (uncoupling protein). The first two mediate bypasses of respiratory pathways through Complexes III and IV and Complex I, respectively, while UCP disrupts the MMP that leads to ATP production (Møller, 2001; Rasmusson et al., 2004, 2008; Siedow and Umbach, 1995; Vanlerberghe et al., 2009). These alternative pathways have been linked to biotic and abiotic stress responses (Cvetkovska and Vanlerberghe, 2013; Cvetkovska et al., 2012; Florez-Sarasa et al., 2011; Podgorska et al., 2013; Rasmusson and Møller, 2011; Wallström et al., 2014).

In addition to their role as effectors due to their strong oxidant properties, ROS also have unspecific signaling roles. Since electron flow to AOX bypasses proton-pumping Complexes III and IV, AOX activity could potentially reduce ROS and NO generation by the respiratory chain and thus modulate signaling pathways related to ROS production (Maxwell et al., 1999; Møller and Sweetlove, 2010). There are several reports showing the importance of AOX in plant defense against bacterial, viral and fungal pathogens (Cheng et al., 2011; Cvetkovska and Vanlerberghe, 2012, 2013; Lee et al., 2011; Ordog et al., 2002; Simons et al., 1999; Vanlerberghe et al., 2002; Zhang et al., 2012).

Electron leakage from the respiratory chain generates $O_2^-$, which is then converted to $H_2O_2$ by MnSOD (manganese superoxide dismutase) (Fernández-Ocaña et al., 2011; Morgan et al., 2008). It was recently shown that AOX and MnSOD participate in defense processes and that plants with different combinations of AOX and MnSOD expression show different responses, which means that mitochondria can orchestrate a "multiple-layer" response by combining the activities of these two enzymes. It was proposed that AOX and MnSOD can determine the specificity of the response by confining the signal to the mitochondrial matrix ($O_2^-$) or spreading it to the rest of the cell ($H_2O_2$) (Cvetkovska and Vanlerberghe, 2012, 2013).

The AOX pathway is also related to the effect of SA as a hormone involved in defense signaling and response. SA-elicited respiratory dysfunction correlated with the induction of AOX, which interrupts electron flow at the ubiquinone pool thus preventing over-reduction of ETC components and suppressing ROS and RNS production (Norman et al., 2004; Yip and Vanlerberghe, 2001). Significantly, down regulation of AOX by RNA interference in tobacco leaves initiates an increase of $O_2^-$ inside mitochondria and high cellular concentrations of NO and ROS (Cvetkovska and Vanlerberghe, 2012). Also, antisense AOX lines exhibited cell death when the cytochrome pathway was inhibited. In contrast, overexpression of AOX in tobacco cells prevented HR and plant cell death after inhibition of the cytochrome pathway (Robson and Vanlerberghe, 2002; Vanlerberghe et al., 2002).

There are other respiratory components that are also involved in plant responses against biotic stress. Through a forward genetic screen, Gleason et al. (2011) identified an *Arabidopsis* mutant unable to induce *GSTF8*-promoter dependent expression in response to SA treatment and with increased susceptibility to fungal and bacterial pathogens. The mutant carried a mutation in the catalytic subunit SDH1-1 of succinate dehydrogenase (SDH), the Complex II of the respiratory chain, thus reinforcing the idea that mitochondrial ETC is involved in the propagation of plant stress and defense responses (Gleason et al., 2011; Navrot et al., 2007). A *Nicotiana* mutant deficient in respiratory Complex I was also shown to have different responses than wild-type to elicitor-induced HR and cell death (Boccara et al., 2001; Vidal et al., 2007). Finally, genes encoding COX17 and COX19, two proteins involved in the biogenesis of Complex IV, were shown to be induced after infection of plants with a bacterial pathogen, thus suggesting a role of these proteins under biotic stress conditions (Attallah et al., 2007a, b).

Finally, the controversial and not completely elucidated role of the electron transfer protein cytochrome *c* in plant PCD should be mentioned. In mammalian cells cytochrome *c* has an important role as one of the first markers of the molecular events conducing to apoptosis (Hoeberichts and Woltering, 2002). Release of cytochrome *c* from mitochondria is a key step in the caspase activated apoptosis pathway (Kluck et al., 1997; Liu et al., 1996). Several authors have described a cytochrome *c* release as an event preceding plant cell death (Balk et al., 1999; Sun et al., 1999). Release of cytochrome *c* from mitochondria into the cytosol was described following the treatment of plants with the pathogen toxin victorin, after application of the elicitor harpin (Curtis and Wolpert, 2004; Krause and Durner, 2004) and during HR induced by *P. syringae* (Kiba et al., 2006). Nevertheless, in the case of plant HR-induced PCD, cytochrome *c* release may simply reflect a final phase of mitochondrial dysfunction rather than an initial step of the process (Mur et al., 2008; Xie and Chen, 2000).

## 3. Conclusion

As we summarize in Fig. 1, the interaction of plants with pathogens is a complex process where multiple barriers are strategically arranged in order to establish a defense strategy. Current evidence suggests that mitochondria have an important role in the perception and transduction of several signals elicited by the cell upon pathogen recognition, thus amplifying the first "alarm signal" in order to trigger the defense at the cellular level. As major sites of ROS action and production, it is not surprising that mitochondrial activities, and especially respiration, are able to influence different steps of the plant immune response, which is characterized by profound redox changes. In recent years, however, it is becoming clear that mitochondria also participate in more specific aspects of the immune response, as a target of pathogen effectors and a site of action of proteins involved in effector triggered immunity (ETI). This indicates that plants and pathogens have developed mechanisms to influence the immune response acting on mitochondrial function and is a further evidence for the important role of these organelles in the defense of the plant against invading organisms. In the near future, it is expected that more mitochondrial proteins involved in the modulation of the immune response and the mechanisms and molecular signals connecting mitochondria with the rest of the cell during this response will be discovered.

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