The signaling role of a mitochondrial superoxide burst during stress

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Plant mitochondria are proposed to act as signaling organelles in the orchestration of defense responses to biotic stress and acclimation responses to abiotic stress. However, the primary signal(s) being generated by mitochondria and then interpreted by the cell are largely unknown. Recently, we showed that mitochondria generate a sustained burst of superoxide (O$_2^-$) during particular plant-pathogen interactions. This O$_2^-$ burst appears to be controlled by mitochondrial components that influence rates of O$_2^-$ generation and scavenging within the organelle. The O$_2^-$ burst appears to influence downstream processes such as the hypersensitive response, indicating that it could represent an important mitochondrial signal in support of plant stress responses. The findings generate many interesting questions regarding the upstream factors required to generate the O$_2^-$ burst, the mitochondrial events that occur in support of and in parallel with this burst and the downstream events that respond to this burst.

ROS and RNS Generation by Plant Mitochondria

Mitochondria are a source of ROS. This is due to "single electron leak" from electron transport chain (ETC) components to O$_2^-$ producing superoxide (O$_2^-$). In both plants and animals, complexes I and III are proposed to be major sites of such electron leak$^{17,18}$ (Fig. 1). Once produced, matrix O$_2^-$ can be further converted to H$_2$O$_2$ by a matrix-localized manganese superoxide dismutase (MnSOD)$^{19}$.

The rate of ROS generation by mitochondria depends upon the reduction state of ETC components. In animals, this reduction state is generally dependent upon the rate of electron transport and the membrane potential, which in turn are primarily dependent upon the rate of dissipation of membrane potential, particularly by oxidative phosphorylation. Hence, when ADP is readily available and being actively phosphorylated to ATP, dissipation of the proton gradient lowers

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Figure 1. The plant mitochondrial ETC includes two terminal oxidases able to catalyze the 4-electron reduction of O$_2$ to H$_2$O, the usual cyt oxidase (complex IV) and AOX. Electron transport from the ubiquinone pool (Q) to complex IV is coupled to the generation of a membrane potential that is subsequently dissipated by ATP synthase (complex V) to produce ATP. However, electron flow from Q to AOX is non-energy conserving. When the ability of an ETC component to transport electrons is reduced and/or membrane potential is high, electron transport can slow, leading to an over-reduction of the ETC. Under these conditions, single electron leak to O$_2$ or nitrite increases, producing O$_2^-$ and NO, respectively. In plants, the specific sites and mechanisms of O$_2^-$ and NO generation are not yet well understood. See text for further details. I, II, III, IV, V: complexes I to V.

Plant Mitochondria as Signaling Organelles During Biotic Stress

We hypothesized that plants may use mitochondrial-derived ROS and RNS as signaling molecules, and further that AOX could provide a means to modulate their generation, particularly during stress. Below we describe recent evidence supporting this hypothesis.

It is well known that plant infection by a pathogen can lead to the rapid activation of a plasma membrane-localized NADPH oxidase. This activation results in an apoplastic “oxidative burst” that is closely associated with subsequent intracellular signaling events that culminate in defense responses such as the hypersensitive response (HR), a programmed cell death (PCD) at the site of infection. Beside this well-characterized apoplastic source of ROS, it is possible that intracellular sources of ROS (and RNS) are also important in orchestrating defense responses to pathogens. The mitochondrial is one such potential source that has been implicated.

Recently, we examined the interaction of Nicotiana tabacum with the bacterial pathogen Pseudomonas syringae. We showed that the incompatible P. syringae pv maculicola induced defense responses that included the HR, which was preceded by an early and persistent increase of O$_2^-$ in the mitochondrial matrix (Fig. 2). This “O$_2^-$ burst” was specific to the interaction with the HR-inducing pv, not being seen in response to a compatible (i.e., disease-causing) pv or in response to the incompatible pv phaseolicola that induced well-known defense responses but not including the HR. The disparate effect of the two incompatible pv’s appears to be due to a coordinated response of AOX (as a means to modulate the rate of O$_2^-$ generation) and MnSOD (the sole enzymatic means to scavenge matrix O$_2^-$). While pv phaseolicola infection resulted in a strong induction of AOX and a maintenance
of high MnSOD activity, pv maculicola infection failed to induce AOX and was accompanied by a loss of MnSOD activity.\(^{30}\) (Fig. 2). We further established that, in transgenic AOX knockdown plants unable to induce AOX in response to pv phaseolicola, a \(O_2^-\) burst was now generated in response to infection.\(^{23}\) Further, AOX knockdown plants infected with pv maculicola displayed a delayed \(O_2^-\) burst that manifested itself in a delayed HR. These results place AOX as a potential key regulator of a mitochondrial \(O_2^-\)-based signaling pathway that subsequently impacts plant responses to biotic stress.\(^{23,30}\)

It is worth emphasizing that the \(O_2^-\) burst we have reported is clearly distinct from “mitochondrial \(O_2^-\) flashes” that have been detected, mostly in animals but also in plants.\(^{31,32}\) Those apparent flashes in \(O_2^-\) are short-term (seconds) in duration and have been detected using circularly permuted yellow fluorescent protein as the \(O_2^-\) sensor. Recently, it has been strongly argued that these \(O_2^-\) flashes are in fact an artifact of the detection system.\(^{33}\) On the other hand, the \(O_2^-\) bursts we have reported are long-lived (hours) and have been measured using a mitochondrion-localizing version of hydroethidine (MitoSOX; Molecular Probes), a well-established small-molecule fluorescent \(O_2^-\) probe.\(^{23,30}\) As controls, we showed that the fluorescence signal observed with this probe could be strongly attenuated by the \(O_2^-\) scavenger SOD-PEG (a membrane-permeable SOD) or strongly amplified by AA.

### Characterization and Significance of the Mitochondrial \(O_2^-\) Burst

Our results\(^{23,30}\) generate many interesting questions about mitochondrial signaling in general and the \(O_2^-\) burst, in particular. Some of these questions are summarized in Figure 3 and further discussed below.

First, work to date has been done exclusively with \(P.\ syringae\). Hence, it will be interesting to establish whether the HR induced by viruses and fungi is also preceded by a \(O_2^-\) burst. Changes in mitochondrial ROS have been implicated as important during such pathogen interactions.\(^{3,4,34,35}\) Further, AOX overexpression did result in smaller TMV-induced HR lesions.\(^{36}\) However, definitive experiments to test for the appearance of a \(O_2^-\) burst in response to such pathogens are now needed.

If the mitochondrion has a signaling role during biotic stress, it would be interesting to establish whether this role extends to abiotic stresses as well. A common theme among several disparate mitochondrial mutants is their increased or decreased stress tolerance.\(^{2,4,37,38}\) Are specific mitochondrial ROS and/or RNS signatures responsible for this altered tolerance state? Disparate mitochondrial mutants also exhibit changes in stomatal aperture, particularly under stress conditions.\(^{39-41}\) An intriguing possibility is that changes in mitochondrial-derived ROS and/or RNS are impacting the signal path(s) that control stomatal movement.

Previous work shows that AOX can provide a level of protection against PCD.\(^{24}\) Since the HR is a natural example of PCD that is likely of benefit to the plant, it is perhaps not surprising that AOX would be kept suppressed after \(pv\) maculicola infection. An interesting question is how this suppression is achieved since infection results in the rapid elevation of several molecules previously described as inducers of AOX synthesis such as salicylic acid (SA), NO and \(H_2O_2\). We provided evidence that SA levels above a threshold amount might be responsible suppressing

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**Figure 2.** The impact of two incompatible pv’s of \(P.\ syringae\) on the mitochondria of tobacco leaf mesophyll cells. (A) Infection with the HR-inducing pv maculicola results in an early and persistent burst of \(O_2^-\) in the mitochondrial matrix that may have a signaling role in support of the HR. (B) Infection with pv phaseolicola, that causes induction of plant defenses but not including the HR, lacks a matrix \(O_2^-\) burst. The differential effect of the two pv’s is supported by a coordinated response of the major ETC mechanism to avoid \(O_2^-\) generation (AOX) and the sole enzymatic means to scavenge matrix \(O_2^-\) (MnSOD). In response to pv phaseolicola, AOX is strongly induced and MnSOD activity remains high, while in response to pv maculicola MnSOD activity declines and AOX remains low. As a result, the two bacterial pv’s each generate distinct mitochondrial ROS signatures that may impact defense responses and cell fate.
AOX induction, but this is clearly an area that requires further study. Whether AOX activity is also being suppressed by some post-translational mechanism is also relevant. In this regard, it is intriguing that AOX has been identified as a target of tyrosine nitration, albeit the study was not in relation to biotic stress and how the modification impacted AOX activity is not known. Suppression of AOX activity could also occur by oxidation of regulatory cysteine thiols but again, whether this occurs in response to pathogen is not yet known.

As discussed earlier, membrane potential is typically a key factor determining the rate of O$_2^-$, and perhaps NO, generation by the ETC. A persistent O$_2^-$ burst implies that membrane potential remains high and perhaps even increases after infection with the HR-inducing pv maculicola. A few studies have reported increases in membrane potential as an early event preceding various sorts of plant PCD, but more often it has been reported that loss of membrane potential is an early event. Loss of membrane potential is sometimes attributed to the opening of a permeability transition pore (PTP), which in turn is often implicated to result in the release of cyt c to the cytosol. Unfortunately, the cause-effect relationship of these mitochondrial events, how they relate to O$_2^-$ generation and how they impact cell fate is still largely unknown and is an important area for continued study. One possible means to promote a high membrane potential, beside keeping AOX activity low, would be disabling of the adenine nucleotide translocator, which could restrict oxidative phosphorylation and hence dissipation of membrane potential.

While AOX knockdown plants have constitutive higher amounts of O$_2^-$ than wild-type, this amount is nonetheless further strongly enhanced by the interaction with incompatible P. syringae indicating that, in addition to keeping AOX low, additional factor(s) associated with infection are required for the O$_2^-$ burst to fully manifest itself. These factors are unknown but a prime candidate may be SA. Studies with plant suspension cells and isolated mitochondria strongly suggest that SA can target mitochondrial function. However, its mechanism and site of action are not well understood, and the reported effects of SA on energy metabolism need further confirmation in intact leaf. Interestingly, our results hint that complex III might be the mitochondrial target of biotic stress, and studies with isolated mitochondria have implicated SA to impact the function of this complex. This provides a potential mechanism by which the different incompatible pv’s, which did elicit different SA amounts, could have impacted mitochondria in disparate ways. Besides SA acting on the mitochondrion, another possibility is that increased NO inhibits cyt oxidase, which could then promote further generation of NO and O$_2^-$ due to over-reduction of the ETC. NO is a potent inhibitor of cyt oxidase, but AOX is NO-resistant, which further illustrates how AOX amount could strongly impact mitochondrial function during biotic stress.

Beside suppressing AOX induction, pv maculicola infection was associated with a loss of MnSOD activity, which likely

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**Figure 3.** Simple cartoon of a plant cell and mitochondrion. This figure is meant to highlight some key questions regarding the upstream factors required to generate a mitochondrial O$_2^-$ burst, the mitochondrial events that occur in support of or in parallel with this burst, and the downstream events that may be responsive to this burst. See text for further discussion of these aspects. PM, plasma membrane; OMM, outer mitochondrial membrane; IMS, intermembrane space; IMM, inner mitochondrial membrane.
supported the O$_2^-$ burst by lessening the conversion of O$_2^-$ to H$_2$O$_2$ in the matrix. The mechanism by which MnSOD activity is lost is not known. Interestingly, animal MnSOD is a major target of tyrosine nitration, resulting in a loss of activity.\(^6\)

Tyrosine nitration requires peroxynitrite (ONOO$^-$), the product of the reaction of O$_2^-$ and NO (Fig. 1). As MnSOD activity is lost, it promotes still higher O$_2^-$ responsive to a mitochondrial O$_2$ vide a list of candidate genes that may be blocked by bongkrekic acid, an inhibitor to mitochondrial dysfunction could be a signal molecule. For example, while ETC, particularly in relation to it acting in turn promotes further ONOO$^-$ for - nitration, resulting in a loss of activity.\(^49\) 

When we elicited a mitochondrial O$_2^-$ burst and the oxidative burst lead to activation of NADPH oxidase. In animals, there are several model systems in which activation of NADPH oxidase depends upon intracellular ROS.\(^50\) Interestingly, it is reported in tobacco that SA potentiates the oxidative burst\(^61\) and that intracellular ROS rises prior to the oxidative burst.\(^29\)

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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