Plant mitochondrial retrograde signaling: post-translational modifications enter the stage

Markus Hartl and Iris Finkemeier*
Department Biology I, Ludwig Maximilians University Munich, Planegg-Martinsried, Germany

*Correspondence: i.finkemeier@lmu.de
82152 Planegg-Martinsried, Germany.

INTRODUCTION

Plant mitochondria are central hubs in the conversion of energy and redox homeostasis and are connected to metabolic pathways from different subcellular compartments. Hence, mitochondria are ideally placed to act as sensors of the energetic and metabolic status of the plant cell (Sweetlove et al., 2007; Millar et al., 2011). Perturbations of the cellular energy status can lead to a reconfiguration of mitochondrial activities which in turn have profound effects on other cellular compartments, including major changes in nuclear gene expression (NGE) and photosynthetic activity (Rhoads, 2011; Schwarzländer et al., 2012). Changes in NGE or activate a cascade of signaling events that eventually alter NGE.

In general two types of retrograde signals can be distinguished (Figure 1):

1. Primary or direct retrograde signals are generated in the organelle and either passively diffuse or are actively transported to the nucleus, where they modulate NGE. Primary retrograde signals are therefore most likely metabolic intermediates generated from metabolic pathways in the respective organelles.
2. Secondary or indirect signals are activated by primary signals inside or outside the organelle, and travel to the nucleus or activate a cascade of signaling events that eventually alter NGE.

Post-translational modifications (PTMs) are ideally suited for signal integration and thus present a likely mechanism to transmit indirect retrograde signals. PTMs such as phosphorylation, lysine acetylation, and glutathionylation and assess their potential to regulate not only organelar processes by modifying metabolic enzymes but also to influence nuclear gene expression.

Keywords: plants, mitochondria, retrograde signaling, post-translational modifications, metabolites

Besides their central function in respiration plant mitochondria play important roles in diverse processes such as redox homeostasis, provision of precursor molecules for essential biosynthetic pathways, and programmed cell death. These different functions require the organelle to communicate with the rest of the cell by perceiving, transducing, and emitting signals. As the vast majority of mitochondrial proteins are encoded in the nuclear genome, changes in mitochondrial status must be fed back to the nucleus to coordinate gene expression accordingly, a process termed retrograde signaling. However, the nature of these signaling pathways in plants and their underlying signaling molecules – or indirect metabolite or redox signals – are not completely resolved. We explore the potential of different post-translational modifications (PTMs) to contribute to mitochondrial retrograde signaling. Remarkably, the substrates used for modifying proteins in many major PTMs are redox-active compounds, as for example ATP, acetyl-CoA, NAD+, and glutathione. This suggests that the metabolic status of organelles and of the cell in general could be indirectly gaged by the enzymes catalyzing the various PTMs. We examine the evidence supporting this hypothesis with regard to three major PTMs, namely phosphorylation, lysine acetylation, and glutathionylation and assess their potential to regulate not only organelar processes by modifying metabolic enzymes but also to influence nuclear gene expression.

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Post-translational modifications (PTMs) are ideally suited for signal integration and thus present a likely mechanism to transduce indirect retrograde signals. PTMs such as phosphorylation have key roles in signal transduction and amplification of cytosolic signaling cascades. It is therefore conceivable that primary mitochondrial signals could generate secondary signals (Møller and Sweetlove, 2010) or activate signal transduction cascades that traverse the cytosol. Here, we discuss evidence that PTMs connected to mitochondrial energy and redox metabolism occurring both outside and inside mitochondria are potential key players in transducing indirect MRR signals. We propose that recent technological advances in high resolution mass-spectrometry and sample preparation will allow wide and largely unbiased screens for mitochondrial PTMs and their dynamics (Witze et al., 2007;
PHOSPHORYLATION

Although a few phosphorylation-regulated mitochondrial enzymes are well established, such as the pyruvate dehydrogenase (Grimel and Randall, 1992), only recently the regulatory role of phosphorylation in mitochondrial signal processing and metabolic regulation has begun to emerge (Pagliarini and Dixon, 2006; Ito et al., 2007; Juszczuk et al., 2012). Foster et al. (2009). There are indications that all major kinase signaling pathways in mammals can target the mitochondrion and influence mitochondrial function (Horvath and Chu, 2005; Pagliarini and Dixon, 2006). Recent publications describe 77 phosphoproteins in mitochondria from human muscle cells and 181 phosphoproteins from murine cardiac mitochondria (Deng et al., 2011; Zhao et al., 2011). However, despite remarkable efforts merely 22 phosphoproteins are reported for Arabidopsis (Ito et al., 2009) and 14, mostly different, phosphoproteins for potato (Bykova et al., 2003). It is very likely that mitochondrial status and signaling varies with tissue and environmental conditions, which could explain why putative phosphoproteins remained undetected in studies concentrating on cell cultures or particular tissues. Similar to the fragmentary mitochondrial phosphoproteomes, the available data describing mitochondrial protein kinases and phosphatases in plants is scarce (Headleywood et al., 2004; Juszczuk et al., 2007). Several kinases and phosphatases attached to the outer mitochondrial membrane have recently been identified, but their possible role in mitochondrial signaling remains to be explored (Duncan et al., 2011; Sun et al., 2012). A large-scale yeast two-hybrid screen for interactors of mitogen-activated protein kinases (MAPKs) in rice indicates that these kinases could phosphorylate mitochondrial proteins (Singh et al., 2012). Lundquist et al. (2012) suggested that the so far largely neglected ABC1K protein kinase family could further fill this gap of mitochondrial kinases but clearly more experimental work will be necessary.

The points mentioned above indicate that phosphorylation might influence mitochondrial function but whether it could also influence MRR remains an open question. First evidence that plant MRR is indeed partially regulated via phosphorylation comes from the observation that the citrate-dependent induction of the mitochondrial alternative oxidase can be inhibited by the protein kinase inhibitor staurosporine (Djianegura et al., 2002). Furthermore, Takahashi et al. (2003) demonstrated that spermine-induced functional changes in tobacco mitochondria trigger a MAPK-cascade and activate specific hypersensitive response genes. However, both pathways were not further explored yet.

Mitochondrial signals could activate phosphorylation-dependent signaling cascades inside or outside the organelle, which transduce MRR. Strong support for the existence of such a mechanism was found in yeast, where the “RTG-dependent pathway” represents one of the best-studied MRR. It has been shown that perturbations of mitochondrial functions in yeast result in lowered mitochondrial membrane potentials, eliciting a kinase-based response that regulates the phosphorylation status and translocation of specific TFs to the nucleus (Liu and Butow, 2006; Juszczuk, 2012). Candidates for phosphorylation-dependent signaling involved in MRR in plants are SNF1-related kinases (SnRK1), with the cytosolic SnRK1 in particular, and the target of rapamycin (TOR) protein kinases. SnRK1 and TOR
Acetylation of the ε-amino group of lysine residues on proteins has recently emerged as a major PTM of proteins that has the potential to rival the regulatory role of phosphorylation (Choudhary et al., 2009, Norvell and McMahon, 2010). Although some important modulators of SnRK1- and TOR-activity have been described the main metabolic signals that activate these kinases remain unknown (Baena-Gonzalez and Sheen, 2008, Ghillebert et al., 2011, Xiong and Sheen, 2012). Although important modulators of SnRK1- and TOR-activity have been described the main metabolic signals that activate these kinases remain unknown (Baena-Gonzalez and Sheen, 2008, Ghillebert et al., 2011, Xiong and Sheen, 2012). Although some important modulators of SnRK1- and TOR-activity have been described the main metabolic signals that activate these kinases remain unknown (Baena-Gonzalez and Sheen, 2008, Ghillebert et al., 2011, Xiong and Sheen, 2012).

Interestingly, there is an overlap in regulated transcripts between SnRK1-mediated responses and specific conditions of mitochondrial dysfunction (Schwarzlander et al., 2012) and it will be interesting to ascertain whether SnRK1 integrates metabolic signals from mitochondria, thus contributing to MRR. In yeast and mammals TOR signaling is vital for the maintenance of mitochondrial respiration and it is involved in the MRR (Schieke and Finkel, 2006).

For example mammalian TOR (mTOR) interacts with PGC1α (Cunningham et al., 2007), a transcriptional activator regulating mitochondrial biogenesis and activity. Recent results in Arabidopsis suggest that TOR could have a similar function in plants but the exact mechanisms remain to be discovered (Leiber et al., 2010, Xiong and Sheen, 2012).

LYSINE ACETYLATION

Acetylation of the ε-amino group of lysine residues on proteins belong to different evolutionary conserved families of protein kinases, which likely function as master regulators and sensors of energy and nutrient metabolism during growth and development as well as under energy-depleting stress conditions (Polge and Thomas, 2007; Baena-Gonzalez and Sheen, 2008; Dobrenel et al., 2011; Ghillebert et al., 2011; Ben et al., 2011; Xiong and Sheen, 2012). Although important modulators of SnRK1- and TOR-activity have been described the main metabolic signals that activate these kinases remain unknown (Baena-Gonzalez and Sheen, 2008; Ghillebert et al., 2011; Xiong and Sheen, 2012).

lysine acetylation of non-histone proteins was confirmed to be a widespread PTM in prokaryotes and eukaryotes that has profound regulatory effects on various metabolic and developmental processes (Close et al., 2010; Xing and Poirier, 2012). From a number of studies it became evident that lysine acetylation is involved in energy-homoeostasis and regulation of carbon-flux, by directly altering NGE or the activities of key metabolic enzymes, such as glyceraldehyde 3-phosphate dehydrogenase and isocitrate dehydrogenase in Salmonella enterica (Wang et al., 2010), or mammalian mitochondrial acetyl-CoA synthetase 2 (Hallows et al., 2006; Schwer et al., 2006). Furthermore, Kim et al. (2006) demonstrated that lysine acetylation patterns varied depending on nutritional status. Anderson and Hirschey (2012) estimated 35% of all mammalian mitochondrial proteins to have at least one acetylation site, and found pathways involved in the generation of energy, fatty acid metabolism, sugar metabolism, and amino acid metabolism to be significantly enriched in acetylated proteins. Important progress has also been made in identifying lysine-acetylated non-histone proteins in Arabidopsis (Pinkmeier et al., 2011; Wu et al., 2011). These two studies describe a total number of 125 proteins to be lysine-acetylated in Arabidopsis, with cytoschrome c representing the only mitochondrial protein. Only six common proteins were identified in both studies (Xing and Poirier, 2012), which suggests that the overall coverage was fairly low and that more extensive screens are likely to identify a much larger number of lysine-acetylated proteins in plants.

The huge potential of lysine acetylation acting as a metabolic sensor and regulator lies in the chemistry of the enzymes that catalyze this PTM. Lysine acetyltransferases (KATs) transfer the acetyl moiety from acetyl-CoA to the target proteins. This suggests that the availability of the central metabolic intermediate acetyl-CoA or the acetyl-CoA/CoA ratio could be directly gaged by KATs (Xing and Poirier, 2012). As acetyl-CoA occurs in the cytosol and in organelles but cannot freely diffuse through membranes it has to be synthesized and metabolized independently in each compartment, which makes it a good indicator of local carbon status (Oliver et al., 2009). In Arabidopsis at least 12 KATs were identified by sequence homology and a number of them has been described to influence various developmental processes via acetylation of histones (Pandey et al., 2002, Earley et al., 2007, Servet et al., 2010).

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Apart from sirtuins, Arabidopsis enzymes have been identified in several studies and are awaiting been studied in detail, but phosphorylation sites of antioxidant PTMs on plant mitochondrial antioxidant enzymes have not yet of peroxides and thus is a prime target to affect redox signaling. Antioxidant defense system has a key role in the detoxification equivalent to sustain the antioxidant system. The mitochondrial energy metabolism, and is defined by the balance of ROS produced in mitochondria to mitochondrial redox state is intimately linked to mitochondrial membrane potential (Møller, 2001; Murphy, 2009). Hence, the mitochondrial antioxidant defense system has a key role in the detoxification of peroxides and thus is a prime target to affect redox signaling. PTMs on plant mitochondrial antioxidant enzymes have not yet been studied in detail, but phosphorylation sites of antioxidant enzymes have been identified in several studies and are awaiting further functional characterization (Nakahagi et al., 2010).

Oxidative PTMs of proteins that arise from increased ROS production in mitochondria can either be irreversible or reversible. The chemistry of oxidative modifications on proteins is quite complex and their full potential is not explored yet. The best-characterized irreversible protein oxidation in mitochondria is carbonylation, which is regarded as an indicator of oxidative damage to the cell (Moller et al., 2011). The iron-sulfur cluster of the TCA-cycle enzyme aconitase for example is particularly prone to oxidative inactivation, which might activate MRR in plants by increasing mitochondrial citrate levels (Gray et al., 2004; Rhodes and Subbaiah, 2007). Reversible oxidative modifications only occur at cysteine and methionine residues of proteins, which can be reversed by sulfiredoxins (in case of cysteine sulfenic acids), thiosreodoxins (TRXs; in case of disulfides), glutaredoxins (GRXs; in case of disulfides and glutathione mixed disulfides) and methionine sulfoxide reductases (in case of methionine sulfones). Disulfides formed during cysteine oxidation play important roles in regulating enzyme activities and protein functions in diverse metabolic processes as well as in transcriptional regulation and signaling in plants and animals (Foyer and Noctor, 2009; Koenig et al., 2012; Murphy, 2012). In the matrix of plant mitochondria 50 TRX-linked proteins and 18 GRX-linked proteins have been identified from various metabolic processes (Balmer et al., 2004; Rohsler et al., 2005). However, the in vivo confirmation of the functional regulation of plant mitochondrial metabolism by TRXs and GRXs is still lacking. The plant mitochondrial disulfide proteome was further assessed in a study using diagonal gel electrophoresis (Winger et al., 2007), identifying 21 proteins from major metabolic pathways which form either inter- or intramolecular disulfides under oxidizing conditions. Catalytic cysteines are important for the activities of many enzymes involved in metabolism (e.g., cysteine proteases, ubiquitin ligases, and peroxidasas) and signaling (e.g., tyrosine phosphatases). S-Glutathionylation is a reversible PTM of cysteine, which is regarded as mechanism to protect redox-active cysteines from irreversible inactivation beside its role in redox signaling (Gallegos and Muyal, 2007). Both glycine decarboxylase, a key enzyme in the photosynthetic pathway, as well as galactonolactone dehydrogenase, a major enzyme in ascorbate synthesis, were inactivated by glutathionylation in plant mitochondria (Leferink et al., 2009; Palmieri et al., 2010). Hence, glutathionylation could play a role in the temporary protection of these metabolic enzymes under conditions of oxidative stress. Metabolic changes resulting from inhibitions of these enzymes could then play a role in MRR. Irreversibly inactivated proteins can be degraded in all mitochondrial subcompartments (Fischer et al., 2012). Recent work in C. elegans demonstrated that the mitochondrial peptide exporter HAF-1 is required for MRR (Haynes et al., 2010). Moller and Svedlow (2010) suggested that oxidatively modified peptides in particular could convey specific information to regulate oxidative stress-induced MRR in plants. Novel proteomic approaches using bifunctional thiol-specific alkylation reagents coupled to an epitope tag, or to a fluorescent or isotope-label will provide useful tools to further explore the functional significance of the mitochondrial redox proteome and its putative role in regulating MRR in plants (Held and Gibson, 2012).

**FUTURE DIRECTIONS**

A recent in-depth bioinformatics analysis estimated the plant mitochondrial proteome to contain about 2500 proteins (Cai et al., 2011). Many of these proteins will contain multiple PTMs of different types, which will consequently alter protein functions or even localization of proteins within the mitochondria. When thinking of the role of PTMs in signaling, primarily the classical phosphorylation-based MAPK-cascades come to mind, which are often initiated by receptor kinases. However, it is also conceivable that different types of PTMs could be series-connected or could interact in a codified crosstalk. A recent in silico study demonstrated that lysine acetylation sites have a great potential to affect nearby phosphorylation, methylation, and ubiquitination sites (Lu et al., 2011). Such a crosstalk was indeed observed in an in vivo study using the genome-reduced bacterium Mycoplasma pneumoniae (van Noort et al., 2012). Deletion of the only two protein kinases and a unique protein phosphatase modulated lysine acetylation patterns, while in return deletion of the only two KAts had an impact on protein phosphorylation. Hence, many scenarios are conceivable that include phosphorylation-based signaling cascades regulated by various types of PTMs. Just
as conceivable is the inverse scenario, having phosphorylation or lysine acetylation regulating the activity of metabolic enzymes which would affect metabolic signaling. Such a complex PTM-based crosstalk is for example demonstrated in the regulation of the activity of the mitochondrial manganese superoxide dismutase (MnSOD). MnSOD is responsible for the decomposition of superoxide to hydrogen peroxide in the mitochondrial matrix. The activity of MnSOD can be modified by several PTMs including phosphorylation, lysine acetylation, and tyrosine nitration through phosphorylation, lysine acetylation, and tyrosine nitration. 

The activity of MnSOD would affect metabolic signaling. Such a complex PTM-based crosstalk is for example demonstrated in the regulation of metabolic enzymes which would affect metabolic signaling. Several examples of PTM-based regulation of central mitochondrial proteins in animals demonstrate the need for further dissection of the functions of PTMs in plant mitochondrial signaling. Furthermore, autotrophic plant tissues differ fundamentally from animal heterotrophic tissues in terms of energy production, consumption, and homeostasis, and it is most likely that novel plant-specific regulatory mechanisms will be identified.

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