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Review

Review of stress specific organelles-to-nucleus metabolic signal molecules in plants

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ABSTRACT

Plants, as sessile organisms, have evolved an exquisitely tuned response network to survive environmental perturbations. Organelles-to-nucleus signaling, termed retrograde signaling, plays a key role in stress responses by communicating subcellular perturbations to the nucleus, thereby coordinating expression of stress specific nuclear genes essential for adaptive responses to hostile environment. Recently, several stress specific retrograde signals have been identified; most notable amongst them are reactive oxygen species, tetrapyrroles, 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP), unsaturated fatty acids, nitric oxide (NO), 3′-phosphoadenosine 5′-phosphate (PAP), and β-cyclocitral (β-CC). It is expected that this trend will continue to provide fundamental insight into the integrative network of sensory systems central to the adaptive responses of plants to the prevailing environment. This review focuses on the recent advancements in the field.

Contents

1. Introduction

Information flow between organelles and the nucleus is achieved through complex and highly synchronized anterograde (nucleus-to-organelle) and retrograde (organelle-to-nucleus) signaling pathways. Retrograde signaling is a communication pathway from organelles to the nucleus and is central to regulation and coordination of numerous processes in living organisms, including developmental progression, responses to biotic and abiotic challenges, protein trafficking and remodeling of chromatin structure. Plants, because of their sessile nature, have evolved a complex and intricate regulatory network to coordinate cellular activities and modify their energy production and metabolism in accordance with environmental changes to improve their chance of survival under unfavorable conditions. Mitochondria and chloroplasts, the main metabolic hubs, function as stress sensors that perceive stress and produce retrograde signals that coordinate nuclear-encoded network of adaptive responses.

Mitochondria and chloroplasts are considered semi-autonomous organelles as the vast majority of their proteins are encoded by nuclear genome [1,2]. Almost every functional aspect of mitochondria and chloroplasts are tightly controlled by nuclear gene expression. In return, mitochondria and chloroplasts also send signals back to regulate nuclear gene expression to coordinate their developmental and functional status [3–5]. Thus, interorganellar signaling cascades are necessary to coordinate subcellular proteome and balance protein stoichiometry. To date,

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however, our understanding of chloroplast retrograde signaling is further advanced than mitochondria-to-nucleus signaling. So far, the best described examples of interorganellar communication are the chloroplast-to-nucleus signaling pathways that control photosynthesis-associated nuclear genes (PhANGs) during chloroplasts biogenesis and function. Specifically, in response to stresses such as high light or disruption of the carotenoid biosynthesis, chloroplasts initiate signaling cascades that result in reduced expression of PhANGs; a process well described by studies performed on the *genome uncoupled* (*gun*) mutants [6–8]. These studies showed that during photo-oxidative stress induced by the disruption of carotenoid synthesis the expression of nuclear genes encoding PhANGs are altered through the function of intermediates of the tetrapyrrole pathway. These potential retrograde signals are mediated in part through the transcription factor ABI4 [6,7]. Additional studies using the green alga *Chlamydomonas reinhardtii* lend support to the putative roles of several tetrapyrrole pathway intermediates, such as Mg-Protoporphyrin IX (Mg-ProtoIX), heme and billins, which function as plastids-to-nucleus retrograde signals regulating expression of the *PhANGs* during chloroplast biogenesis, development and function [9,10].

In the past few years, in addition to reactive oxygen species (ROS), a number of metabolites of diverse origins were identified and/or proposed as stress-specific organelles-to-nucleus retrograde signals including (1) methylerythritol phosphate (MEP) intermediate 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP) [11,12]; (2) unsaturated fatty acids [13–15]; (3) nitric oxide (NO); and (4) 3′-phosphoadenosine 5′-phosphate (PAP) [16,17]. Here we briefly review the current state of the available information on these stress-specific retrograde signaling candidates.

2. Reactive oxygen species and redox mediated retrograde signaling

Reactive oxygen species (ROS) include hydrogen peroxide, superoxide radicals, singlet oxygen, and hydroxyl radicals [18–22]. These chemically reactive molecules were initially recognized as toxic by-products of central metabolism in plant cell, that are removed through antioxidative enzymes and antioxidants [18]. However, it is now apparent that ROS play a signaling role controlling a myriad of processes including responses to biotic and abiotic stresses [19–22]. Because of the tight link between ROS and metabolism, almost any perturbation in cellular homeostasis could lead to a change in the steady-state level of ROS in a particular compartment(s), thereby affecting the redox status of plant cells. Plants produce significant amounts of ROS during electron transport and metabolism in mitochondria and chloroplasts, and subsequently use antioxidants or scavenging systems to maintain their cellular ROS and redox homeostasis. The ROS burst, or stress-mediated elevation of ROS levels, initiates signaling pathway(s) to reprogram nuclear gene expression encoding chloroplast and mitochondrion localized proteins. Bioinformatics analyses of transcriptomics, proteomics and metabolomics data sets have revealed ROS-mediated general, as well as source and/or species-specific responses [23,24]. This information has raised an intriguing question of how the same signal, which is produced in different organelles, convey the information and lead to signaling cascades that trigger source-specific nuclear responses. It is postulated that, signal specificity is mediated through interaction of ROS with locally produced secondary messengers. In the case of mitochondria, it is proposed that oxidized peptides derived from proteolytic breakdown of oxidatively damaged proteins mediate mitochondrial ROS specific responses [25]. In the case of chloroplast ROS specific signaling, β-cyclocitral (β-CC), an oxidative product of carotenoid, is reported to mediate singlet oxygen signaling [26].

3. 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP)

The MEP pathway is an essential metabolic pathway present in plant plastids, apicomplexan protozoa and eubacteria. It is responsible for the biosynthesis of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), the building blocks of all isoprenoids [27,28]. Any deficiencies in the MEP pathway result in defects in chloroplast biogenesis and development. Null mutants in this pathway are lethal [11], due to disruption of the synthesis of essential isoprenoids such as carotenoids, prenyl chains of chlorophylls and quinones, cytokinins, gibberellins and abscisic acid (ABA).

Genetic studies have established that the MEP pathway is not solely a biochemical route essential for providing substrates for plastidial isoprenoids synthesis, but it also functions as a stress sensor that communicates environmental perturbations sensed by plastids back to the nucleus [11]. The MEP pathway also plays a role in plant development as demonstrated by studies in *Nicotiana benthamiana* [29]. The virus-induced gene silencing of *CMK*, *a* gene encoding 4-diphosphocytidyl-2-C-methyl-D-erythritol (DPC-ME) kinase, the fourth enzyme of the MEP pathway, resulted in increased cell numbers and reduced cell size in all leaf layers, a unique phenotype not observed in mutants of the other MEP pathway genes [29]. This suggests that the accumulation of the CMK substrate DPC-ME might act as a signal regulating leaf cell number and cell size. However, a direct evidence for signaling function of DPC-ME is yet to be provided.

The enzyme 4-hydroxy-3-methylbut-2-enyl diphosphate synthase (HDS) catalyzing the sixth and the bottleneck step reaction in the MEP pathway, is responsible for conversion of MEcPP to (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP). In *Arabidopsis*, *hds* mutants with compromised HDS enzymatic activities alter plant responses to biotic and abiotic stresses [11,12]. The *csb3* mutant, an allele of *HDS*, has constitutive expression of *Subtilisin*-like protease *P69C* together with enhanced basal as well as pathogen induced salicylic acid (SA) levels. Accordingly, *csb3* mutants are more resistant to the bacterial pathogen *Pseudomonas syringae pv. tomato* (*Pst*). These phenotypes in *csb3* can be reverted by the application of the fosmidomycin, an inhibitor of 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), the enzyme controlling the second step of the MEP pathway. This indicates that the phenotypes of *csb3* mutant are controlled by the accumulated intermediate metabolites produced in between steps catalyzed by DXR and HDS enzymes [12].

Studies of a second allele of HDS, *ceh1*, established that the accumulation of HDS substrate “MEcPP” in *ceh1* mutants specifically alters expression of selected stress responsive nuclear genes encoding plastidial proteins, such as hydroperoxide lyase (HPL) and isochorismate synthase 1 (ICS1). *HPL* is a stress-inducible nuclear gene encoding a plastid-localized protein in the oxylipin pathway. HPL-derived metabolites, predominantly C6-aldehydes, are implicated as intra- and inter-plant stress-responsive signaling metabolites [30]. *ICS1* is a stress-inducible nuclear gene encoding a key plastidial enzyme in the SA-biosynthetic pathway, which is required for plant defense responses to biotic pathogens [31]. Indeed the high level of SA led to notable enhanced resistance of *ceh1* to the biotrophic pathogen *Pst*. Increased expression of *HPL* and *ICS1* genes were, however, restricted to *ceh1* mutant line and not in any mutants of the other MEP pathway genes. Further genetic and metabolic analyses confirmed that the observed *ceh1* mutant phenotypes are caused by elevated levels of MEcPP. Accumulation of MEcPP was observed in plants challenged with