Retrograde Signals: Integrators of Interorganellar Communication and Orchestrators of Plant Development

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Abstract

Interorganellar cooperation maintained via exquisitely controlled retrograde-signaling pathways is an evolutionary necessity for maintenance of cellular homeostasis. This signaling feature has therefore attracted much research attention aimed at improving understanding of the nature of these communication signals, how the signals are sensed, and ultimately the mechanism by which they integrate targeted processes that collectively culminate in organellar cooperativity. The answers to these questions will provide insight into how retrograde-signal-mediated regulatory mechanisms are recruited and which biological processes are targeted, and will advance our understanding of how organisms balance metabolic investments in growth against adaptation to environmental stress. This review summarizes the present understanding of the nature and the functional complexity of retrograde signals as integrators of interorganellar communication and orchestrators of plant development, and offers a perspective on the future of this critical and dynamic area of research.

Contents

Anterograde signaling: signaling events that initiate the transcription of nuclear genes encoding proteins with functional consequences in the organelles

Retrograde signaling: communication signals that relay cellular status from organelles to the nucleus in response to developmental and environmental cues

Interorganellar communication: signaling communication between organelles with or without nuclear mediation

Reactive oxygen species (ROS): reactive molecules containing oxygen, such as H_2O_2, $^1O_2$, O_2^-, and $HO^{\cdot}$

INTRODUCTION

Organisms perceive and respond to developmental and environmental cues through tightly regulated inter- and intracellular communication networks. The integrity of this communication circuitry enables cellular homeostasis sustained through interorganellar interactions that are controlled by processes known as anterograde (nucleus-to-organelle) and retrograde (organelle-to-nucleus) signaling. Recent reports have expanded the known repertoire of intercellular signaling modules and extended knowledge of the original bilateral communication module between the nucleus and organelles to include potential multilateral interactions among organelles.

This review provides a perspective on the present knowledge of retrograde signals in interorganellar communication and speculates on the future development of the field. Specifically, we describe both the proven and the probable connections among the known general and specific retrograde signals, outline their potential roles in multilateral interorganellar communication, and describe retrograde-signal-mediated regulation of plant growth and developmental processes (123–125). Finally, we present models depicting the integration of signaling cascades that orchestrate interorganellar cooperation and coordinate the physiological and metabolic processes required to strike a metabolic balance between growth and adaptation through a series of processes, including the biogenesis and degradation of organelles, morphological transitions, and juxtaposition of organelles that alters their proximity to enable an optimal response to developmental and environmental cues.

MASTER INITIATORS OF INTERORGANELLAR COMMUNICATION

Environmental fluctuations potentiate the accumulation of evolutionarily conserved cellular signals such as reactive oxygen species (ROS) (10, 14) and the modulation of intracellular Ca^{2+} signatures, the two best-known triggers of an array of molecular and biochemical responses in living organisms (**Figure 1**). These cellular signals are therefore considered the master switches that

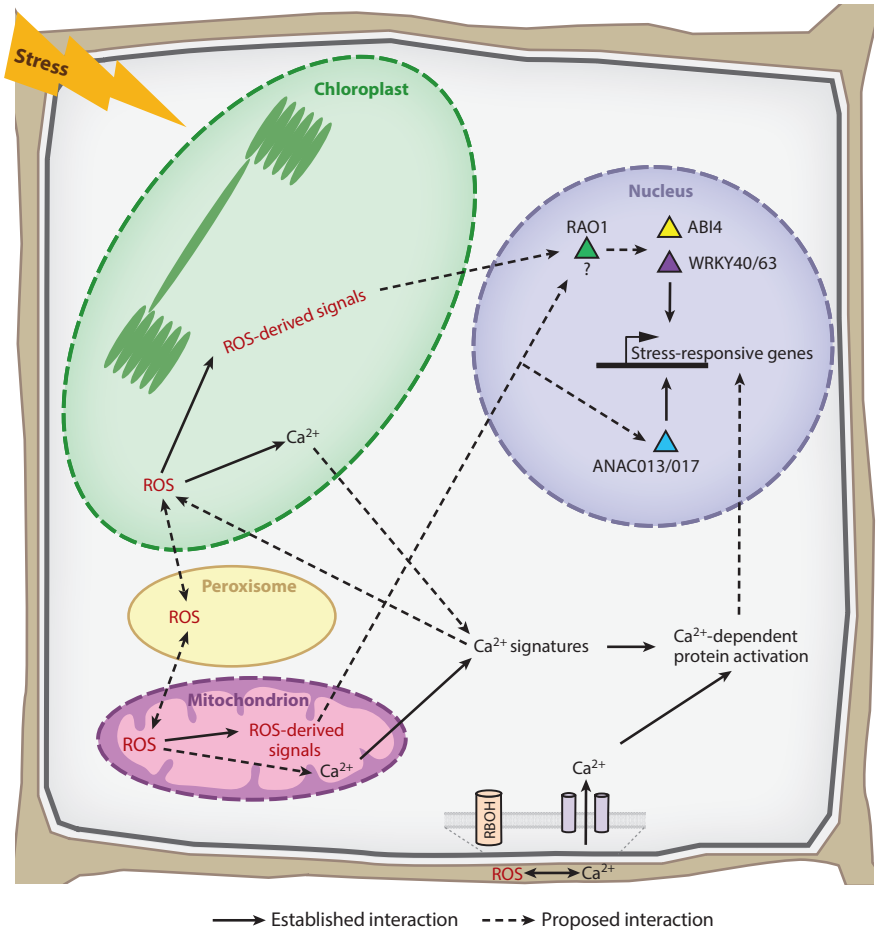


Figure 1

Ca^{2+} and ROS as the master initiators of interorganellar communications. Shown here are both confirmed and proposed connections between Ca^{2+} and ROS signals and the transducing regulatory components of stress-responsive genes. Selected proteins involved in signal transduction are shown, including RBOH, RAO1, ANAC013 and ANAC017, ABI4, and the transcription factors WRKY40 and WRKY63. Abbreviations: ABI4, ABSCISIC ACID INSENSITIVE 4; ANAC013/017, NO APICAL MERISTEM/ ARABIDOPSIS TRANSCRIPTION ACTIVATION FACTOR/CUP-SHAPED COTYLEDON 013/017; RAO1, REGULATOR OF ALTERNATIVE OXIDASE 1; RBOH, respiratory burst oxidase homolog; ROS, reactive oxygen species.

initiate molecular and biochemical processes involved in inter- and intracellular communication in response to environmental cues.

In eukaryotes, ROS is a by-product of aerobic metabolism generated in various forms—most commonly hydrogen peroxide (H_2O_2), superoxide, the hydroxyl radical, and singlet oxygen ($^1O_2$)—in multiple cellular compartments. In plants, ROS is produced in the chloroplast, mitochondria, cytoplasm, peroxisome, and plasma membrane (16) (**Figure 1**). The rapidly stress-induced ROS in plants is generated primarily by the action of NADPH oxidases of the respiratory burst oxidase homolog (RBOH) family (51), imbalances in membrane electron transport (16, 18, 77), and photodynamic molecules (13, 112). Increased accumulation of ROS may lead to the

degradation of various cellular components that, if not contained, will further amplify ROS production (18, 77), resulting in irreversible damage and ultimately cell death (18, 41). To safeguard cellular functionality, therefore, cells have evolved redox systems to rapidly scavenge ROS (14). The ROS instability, combined with the high turnover rates of ROS realized by cellular antioxidants, features these molecules as the most likely candidates for master signal elicitors. Interestingly, however, these same features argue against the direct function of ROS as interorganellar signals; rather, the signals are the molecules generated from ROS action.

Different species of ROS have dissimilar reactivities and are generated in distinct compartments, and as such, they are implicated as triggers of partially overlapping as well as stimulus-specific responses in plants (27). Hence, it has been proposed that unknown secondary signals derived from ROS-oxidized molecules (such as peptide products of oxidatively damaged proteins) or elicited by ROS in different compartments confer the cellular specificity required to differentiate among diverse stresses (69) (**Figure 1**). Specifically, it is argued that the different protein modifications resulting from different ROS species are determinants of the response specificity, and therefore that recognition of and differentiation among the various ROS signals are among the initial enabling steps to tailor cellular responses to the nature of the stimuli perceived (**Figures 1** and **2**).

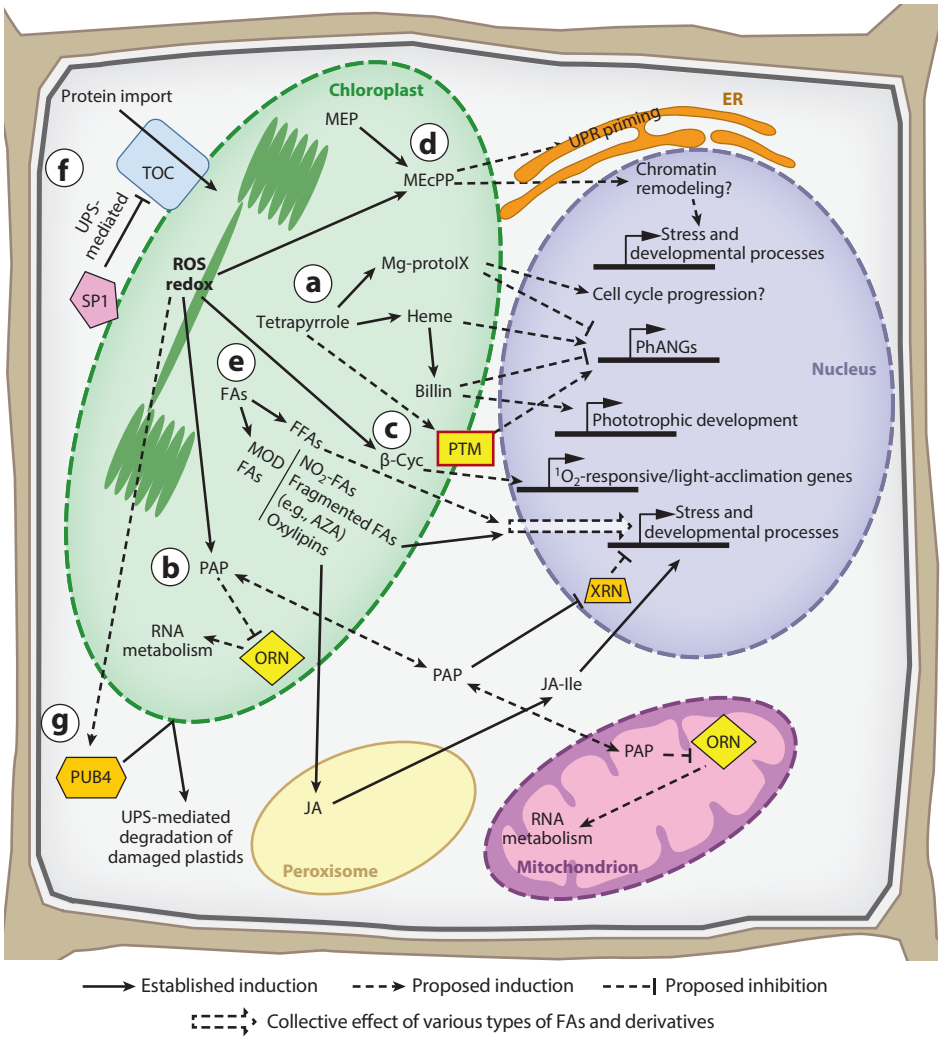
In addition to ROS, spatial and temporal modulations of Ca^{2+} concentration, known as Ca^{2+} signatures, are established triggers of cellular signaling cascades (86, 115). Moreover, rapid, transient, and ubiquitous distribution of Ca^{2+} signatures is suggestive of their function as direct and/or indirect interorganellar communication signals (**Figure 1**).

Figure 2

Confirmed and proposed actions of signaling metabolites in interorganellar communication. (*a*) Tetrapyrrole derivatives have been implicated in retrograde-signaling cascades and transcriptional alteration of PhANGs facilitated by the membrane-bound transcription factor PTM, as well as in the direct modulation of protein degradation that affects cell cycle control, as reported in primitive red algae. (*b*) PAP, a by-product of sulfur assimilation involved in abiotic-stress responses and multilateral organellar communication, acts in part by inhibiting XRNs and ORNs. (*c*) Degradation of β-carotene by $^1O_2$ generates β-cyc, a volatile compound involved in the activation of $^1O_2$-responsive/light-acclimation genes. (*d*) Accumulation of MEcPP, an intermediate of isoprenoid biosynthesis in the MEP pathway, is triggered by a range of stresses, leading to its function as a retrograde signal that potentially alters chromatin architecture. These alterations induce the expression of selected nuclear genes that regulate stress and developmental processes. MEcPP also potentiates induction of the UPR in the ER. (*e*) FAs can be present as FFAs available for further modifications, including alteration by NO_2, fragmentation leading to production of derivatives (e.g., AZA), or oxygenation and formation of oxylipins. Production of the best-known oxylipin, JA, is initiated in the chloroplast and terminated in the peroxisomes, followed by its subsequent conjugation in the cytosol to the active form of JA-isoleucine, JA-Ile. These chemical entities function as stress signals that alter responses to environmental and developmental cues. (*f*) Stress activation of the RING-type ubiquitin E3 ligase SP1 ubiquitinates the plastidial protein import machinery TOC for 26S proteasome degradation. (*g*) PUB4 targets ROS-damaged plastids for proteasome degradation. Abbreviations: AZA, azelaic acid; β-cyc, β-cyclocitral; ER, endoplasmic reticulum; FA, fatty acid; FFA, free fatty acid; JA, jasmonic acid; JA-Ile, jasmonoyl-L-isoleucine; MEcPP, 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate; MEP, methylerythritol phosphate; Mg-protoIX, Mg–protoporphyrin IX; MOD FA, modified fatty acid; $^1O_2$, singlet oxygen; ORN, oligoribonuclease; PAP, 3′-phosphoadenosine 5′-phosphate; PhANG, photosynthesis-associated nuclear gene; PTM, PLANT HOMEODOMAIN–TYPE TRANSCRIPTION FACTOR WITH TRANSMEMBRANE DOMAINS; PUB4, U-BOX DOMAIN–CONTAINING PROTEIN 4; ROS, reactive oxygen species; SP1, SUPPRESSOR OF PPI1 LOCUS 1; TOC, translocon at the outer envelope membrane of chloroplasts; UPR, unfolded protein response; UPS, ubiquitin-proteasome system; XRN, 5′-3′ exoribonuclease.

Cells have evolved mechanisms to differentially accumulate Ca^{2+} in distinct compartments, such as in the apoplast, vacuole, chloroplast, and mitochondria (**Figure 1**). It is worth noting that, in plants, the endoplasmic reticulum (ER) is not the major source of Ca^{2+} during cytosolic calcium fluctuations elicited by external stimuli, representing a fundamental difference between plants and animals in the ER's role during cytosolic Ca^{2+} dynamics (5). Distinct Ca^{2+} signature profiles (e.g., number of phases, magnitude, and duration) are produced in response to a range of stimuli, including ozone (107), elicitors of defense (56), nodulation factors (66), and circadian and diurnal rhythms (60). The stimulus-specific information encoded by Ca^{2+} signatures is subsequently sensed by several Ca^{2+}-binding proteins, such as calmodulin (CaM), calmodulin-like proteins (CMLs), calcium-dependent protein kinases (CDPKs), and calcium- and calmodulin-dependent protein kinases (CCaMKs) (2) (**Figure 1**). Ultimately, this information is decoded and transmitted to downstream responses.

An increasing body of evidence has highlighted the reciprocal interplay between ROS and Ca^{2+}. For example, plastid ion transporters are activated by ROS (88), and Ca^{2+} signatures can



induce ROS production at the plasma membrane and possibly in other organelles via RBOH activity (51, 110). Recently, it has been proposed that ROS and Ca^{2+} can cooperate to relay rapid systemic signals in a self-amplifying ROS-Ca^{2+} wave in plants (31). These complexities in the interplay between ROS and Ca^{2+} and the integration of their corresponding signals guide stimulus-dependent cellular responses. As such, ROS and Ca^{2+} signals are representative of master initiators of intra- and intercellular signaling cascades that sequentially or concurrently trigger general stress-response cascades (3) (**Figure 1**) and further facilitate the tailoring of responses to environmental cues.

ORGANELLE-SPECIFIC RETROGRADE SIGNALS

The significance of a highly orchestrated and interlinked metabolic balance between growth and adaptation to environmental cues positions the cellular metabolic hubs involved in metabolism and energy production—the chloroplasts and the mitochondria—as the operational control centers of retrograde signaling.

Chloroplasts

The chloroplast, as the cell's metabolic hub, is the site of photosynthesis; de novo biosynthesis of fatty acids; production of fatty-acid-derived metabolites, such as oxylipins, amino acids, and starches; and hormone metabolisms. To safeguard these central processes against frequent and prevailing challenges, the chloroplast thus functions not only as a central metabolic hub but also as an environmental sensor that perceives stress and produces retrograde signals to coordinate nuclear-encoded adaptive responses.

***gun* mutants.** The notion of retrograde signaling, relaying information from plastid to nucleus, first emerged from studies of two barley mutants that displayed a notable reduction in the expression of nuclear-encoded, plastid-localized proteins as the result of defects in plastidial functions (6). This concept was solidified upon characterization of the *genomes uncoupled* (*gun*) mutants based on their sustained expression of photosynthesis-related genes, including *LIGHT-HARVESTING COMPLEX B* (*LHCB*, coding for chlorophyll *a*/*b*–binding protein), under photobleaching stress (109). Six *gun* mutants have been identified. The screening for the first five mutants (*gun1–5*) was based on identification of negative regulators of photosynthesis-related genes, whereas for the last mutant (*gun6*), a gain-of-function screening method was employed (128).

The *GUN1* gene encodes a plastid-localized protein containing a pentatricopeptide repeat domain. The promoters of genes misexpressed in *gun1* are enriched for abscisic acid response elements, and indeed, overexpression of the transcription factor ABSCISIC ACID INSENSITIVE 4 (ABI4) rescues the *gun1* phenotype by competitively binding to the G-box motif, thereby preventing binding of the G-box transcription factor to the *LHCB* promoter (54). Interestingly, recent evidence has helped unravel an elegant and central interplay among various transcription factors in retrograde signaling. Specifically, Sun et al. (108) reported that one or more chloroplast retrograde signals activate proteolytic cleavage and nuclear localization of a chloroplast envelope–bound transcription factor designated PLANT HOMEODOMAIN–TYPE TRANSCRIPTION FACTOR WITH TRANSMEMBRANE DOMAINS (PTM) (**Figure 2*a***) and that the accumulation of PTM in the nucleus activates *ABI4* transcription.

The remaining five *gun* mutants (*gun2–6*) are affected in tetrapyrrole metabolism. *GUN4* and *GUN5* are involved in Mg–protoporphyrin IX (Mg-protoIX) biosynthesis (55, 67), *GUN2* and *GUN3* in phytochromobilin biosynthesis (67), and *GUN6* in heme biosynthesis (128). The direct role of Mg-protoIX in altering gene expression (**Figure 2*a***) has remained ambiguous in part

because of discordance between metabolite levels and gene expression (68, 74, 103). However, the production and degradation rates of Mg-protoIX could certainly function as a signal directly or indirectly, either through alteration of the redox status of chloroplasts or through the proposed function of Mg-protoIX in altering tetrapyrrole flux into production of heme (103, 128). In fact, heme has been proposed as a retrograde signal because of the upregulation of photosynthetic genes (**Figure 2*a***) in *gun6*, which has a gain-of-function mutation in plastidial ferrochelatase I, a protein that causes an increase of heme synthesis (13, 128). Similarly, in algae, heme acts as a retrograde signal (119), and billin, a metabolite originating from tetrapyrrole synthesis, is also an essential plastidial signal involved in light-dependent greening and phototrophic growth in *Chlamydomonas* (23) (**Figure 2*a***).

Retrograde signaling based on plastidial metabolites is not involved exclusively in modifying nuclear gene expression; it can also control processes such as DNA replication. For example, Kobayashi et al. (52, 53) elegantly demonstrated that in a primitive red algae, Mg-protoIX is necessary to synchronize plastidial and nuclear DNA replication events (**Figure 2*a***), enabling the maintenance of the plastid through rounds of cell division. The underlying molecular mechanism consists of the interaction of Mg-protoIX, an endosymbiont metabolite, with the host's F-box protein 3 (FBX3), which prevents the ubiquitination and consequent degradation of CYCLIN 1, a protein responsible for cell cycle progression (111). This mechanism alludes to a central role for tetrapyrrole derivatives such as Mg-protoIX in interorganellar communication that cannot be dismissed in plants.

Other plastidial metabolites implicated in retrograde communications include 3′-phosphoadenosine 5′-phosphate (PAP), β-cyclocitral (β-cyc), 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP), ROS, fatty acids (FAs), and their corresponding derivatives (**Figure 2*b–f***).

2-*C*-Methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP): a chemical entity that functions as a MEP pathway intermediate and a plastidial stress-specific retrograde signal

3′-Phosphoadenosine 5′-phosphate. PAP is a by-product of sulfur assimilation reactions present in every organism in all domains of life. Various stresses, such as drought and excessive light, lead to accumulation of PAP and consequent activation of nuclear abiotic-stress-responsive genes (24) (**Figure 2*b***). As such, mutant plants with high levels of PAP display enhanced expression of abiotic-stress-response genes and physiologically manifest heightened tolerance to drought stress. The mode of PAP action is proposed to be through inhibition of the RNA-degrading activity of 5′-3′ exoribonucleases (**Figure 2*b***) that alters RNA processing, a functional property suggested to be responsible for the observed altered gene expression profile (21, 113). Although the role of PAP as a signal molecule that mediates stress responses is indisputable, its function as a canonical chloroplast-to-nucleus retrograde signal has remained debatable (132).

β-Cyclocitral. β-Cyc is a volatile that is derived from $^1O_2$-induced cleavage of β-carotene and is capable of inducing nuclear $^1O_2$-responsive genes (93, 94) (**Figure 2*c***), as well as upregulation of genes involved in acclimation to excess light (61). Importantly, exogenous application of β-cyc impedes production of ROS in chloroplasts and enhances the ISOCHORISMATE SYNTHASE 1 (ICS1)–mediated synthesis of salicylic acid, which increases the nuclear localization of the salicylic acid signaling coactivator NONEXPRESSOR OF PATHOGENESIS-RELATED GENE 1 (NPR1) and ultimately transcriptionally reprograms genes implicated in ROS detoxification (61). Based on the proposed model, β-cyc, a chloroplast-produced signaling intermediate, links the cytoplasm and nucleus during acclimation or increasing tolerance to photooxidative stress in *Arabidopsis* (61).

Methylerythritol phosphate (MEP) pathway: the essential and plastid-localized nonmevalonate pathway responsible for isoprenoid production

2-*C*-Methyl-D-erythritol 2,4-cyclodiphosphate. The plastidial stress–induced signaling metabolite MEcPP functions both as an intermediate of the isoprenoid biosynthetic pathway and as a retrograde signal. Several lines of evidence have confirmed that MEcPP is a retrograde signal capable of altering expression of selected nuclear stress-responsive genes (**Figure 2*d***), such as *hydroperoxide lyase* (*HPL*) and *ICS1*, resulting in increased salicylic acid levels and thus enhanced resistance to infection by the biotrophic pathogen *Pseudomonas syringae* (131). Under natural conditions, this retrograde-signaling metabolite accumulates in response to a range of stimuli, including wounding, high light, and oxidative stress. Intriguingly, stress-mediated induction of MEcPP levels is not limited to plants; it also occurs in bacterial cultures exposed to oxidative stress (84, 85). This similarity in modulations of the MEcPP levels in response to abiotic stresses suggests at least some conservation of the function of this metabolite as a stress sensor in regulating selected stress-responsive processes in eubacteria and plants. Although studies have established that modulation of MEcPP levels in response to stress signals induces transcription of selected stress-responsive genes (121, 131, 132), the exact nature of the signaling mechanisms that couple MEcPP levels to changes in gene expression remains unknown. However, the finding that MEcPP can directly disrupt histone H1–like (Hc1) protein interaction with DNA in chlamydial cultures indicates that the remolding of chromatin could be a mode of function of this metabolite (33, 34) (**Figure 2*d***).

Collectively, the established functions of MEcPP identify it not only as a biochemical intermediate of the methylerythritol phosphate (MEP) pathway, but also as a global and evolutionarily conserved stress-induced metabolite that may function by altering the functional organization of the chromatin structure, leading to dynamic changes in the expression of selected stress-responsive genes (131, 132).

Reactive oxygen species: a common enabler in plastidial metabolite signaling. The common denominators affecting the levels of the above-mentioned metabolites are imbalanced ROS and redox potential (**Figure 2**). That is, synthesis of 3′-phosphoadenosine 5′-phosphosulfate, the precursor of PAP, is dependent on ATP levels, which in turn are directly affected by redox potential and increased levels of ROS that affect the synthesis and availability of ATP (24). Similarly, the presence of an iron-sulfur cluster in the catalytic site of 4-hydroxy-3-methylbut-2-enyl diphosphate synthase, the enzyme responsible for reduction of MEcPP to hydroxymethylbutenyl diphosphate, causes extreme sensitivity of this enzyme to the oxidative state of the chloroplast (105), resulting in reduced enzyme activity and, consequently, the stress-induced accumulation of MEcPP. Furthermore, accumulation of β-cyc is caused by $^1O_2$-induced cleavage of β-carotene (93). Collectively, these data support the notion that ROS accumulation is the master switch enabling the generation of a range of secondary signals in the chloroplast, several of which function directly as retrograde signals.

Fatty acids. FAs are functionally and structurally conserved macromolecules with distinct characteristics, such as their stimulus-dependent rapid and transient changes of profile and concentration that can affect membrane permeability, and their ability to alter biochemical events (e.g., modifying the membrane composition and activities of various enzymes). These cross-kingdom conserved characteristics transcend their established roles (as constituents of cellular structure and in intrinsic metabolic functions) and enable them to act as signaling molecules evoked by stimuli (116, 120). In fact, the signaling role of free FAs released by particular lipases in response to developmental and environmental stimuli, in various cellular processes (e.g., transcriptional activation), has gained much recognition (**Figure 2*e***). A prime example is the rapid activation (peak at 90 min) of a stress-specific functional *cis*-element, known as rapid stress response element (RSRE), in plants

exogenously treated with a drop of free linolenic acid or linoleic acid (120). Activation of RSRE in plants treated with arachidonic acid, an FA absent in the membrane lipids of higher plants but abundant in some plant pathogens, such as *Phytophthora* (97), furthered the notion that free FAs act as intraplant signaling molecules and potentially as interorganismal signaling metabolites (101).

The significant signaling role associated with modifications of components of the plastidial FA synthase complex that catalyzes de novo FA synthesis in response to developmental and environmental stimuli is well recognized. One example is the role of the enoyl-acyl carrier protein reductase, an active plastidial subunit of the FA synthase complex, in the regulation of both development and programmed cell death, as displayed in the corresponding *Arabidopsis* mutant plant, *mosaic death 1* (*mod1*) (73). Interestingly, the suppressor screen for the *mod1* mutant—generated through T-DNA insertion mutagenesis—revealed the key function of mitochondrial complex I in MOD1-regulated programmed cell death (129), thereby extending the regulatory role of plastidial FA machinery to mitochondrial control of programmed cell death and signifying the function of FA in interorganellar communication.

Significant insight into the retrograde-signaling role of specific FAs has come from characterization of mutant plants impaired in their production, as exemplified by the induction of nuclear-encoded resistance (R) genes in the *suppressor of salicylic acid insensitivity 2* (*ssi2*) mutant (47). These plants are compromised in their ability to accumulate oleic acid as the result of a mutation in the plastidial stearoyl-acyl carrier protein desaturase SSI2. The search for a second site mutation of *ssi2* also identified several lipid biosynthetic pathway genes that, when mutated, not only restore oleic acid levels but also normalize R gene expression patterns, providing additional evidence for the retrograde-signaling function of FAs (46, 48, 130). Additionally, the reduction of oleic acid enhances the levels of nitric oxide (NO), a regulator of disease physiology and a conserved cellular metabolite present in diverse organisms (63). Importantly, application of NO or alteration of oleic acid induces expression of similar nuclear genes, implying that oleic acid is a regulator of NO synthesis and hence of NO-mediated signaling. Notably, the reaction between NO and unsaturated FAs leads to production of modified FAs. A recent study highlighted the signaling role of modified FAs in response to environmental challenges by establishing the involvement of NO_2–linolenic acid in plant responses to abiotic stress, mainly through induction of heat shock proteins (64). A comparable signaling role of these metabolites in animals (104) is exemplified in a murine system in which NO_2–oleic acid reduces myocardial ischemia and reperfusion damage by inhibiting nuclear factor κB, which is implicated in inflammatory processes (98).

Another class of modified FAs with an evolutionarily conserved signaling function is the oxylipins, which are oxidized FAs derived mainly from oxidation of linoleic acid and linolenic acid in plants and from arachidonic acid in animals (**Figure 2*e***). Both plants and animals use oxylipins as signals in responses to biotic and abiotic stresses. Reports have suggested that plants and animals are more similar than expected in terms of the role of oxylipins in coordinated responses to the environment. The role of oxylipins as signaling molecules that enable between-kingdom interactions is also evident in a broad range of pathogenic fungi, protozoa, and helminths that produce eicosanoids and other oxylipins by novel synthesis pathways, and in the finding that these microbial oxylipins play a significant role in host-pathogen crosstalk that contributes to chronic infection (80).

The most studied plant oxylipins are jasmonates and aldehydes, which are derived from the competing HPL and allene oxide synthase (AOS) pathways, respectively (11). These compounds are intimately involved in inter- and intracellular communication and play pivotal roles in optimizing plant defense responses (62).

The HPL branch of the oxylipin pathway, among other metabolites, produces C6 volatile aldehydes that function as inter- and intraplant stress signals and are instrumental in defense

responses against biotic stresses (26, 62). The role of green leafy volatiles in triggering tritrophic responses (which affect a plant, an herbivore, and the herbivore's natural enemies) signifies their interorganismal signaling role (11).

The AOS pathway is responsible for producing the stress-inducible plastidial product 12-oxophytodienoic acid (12-OPDA) and the biosynthetic precursor for the peroxisomal products of the pathway, the jasmonates, namely jasmonic acid (JA) and methyl jasmonate (25, 102). This organization of oxylipin metabolism necessitates a tightly regulated coordination and cooperation between plastids and peroxisomes as well as a balanced export of a portion of 12-OPDA from plastids to peroxisomes for JA production by one or more mechanisms that are not yet understood. The JA-isoleucine conjugate, jasmonoyl-L-isoleucine (JA-Ile) (**Figure 2*e***), is the active form of the hormone that facilitates the degradation of JASMONATE ZIM-DOMAIN (JAZ) transcriptional repressors by promoting binding of JAZ to the F-box protein CORONATINE INSENSITIVE 1 (COI1) and subsequent degradation of the JAZ proteins by the 26S proteasome pathway (106). Removal of JAZ proteins relieves their repression of gene expression and, by extension, transcription of defense-related genes (7). Proteinase inhibitors are among the JA-induced gene products that are produced rapidly and systemically in tomato and other solanaceous plants (99), and their consumption disrupts digestive processes in the insect gut, as shown by a study of two JA-inducible proteins, arginase and threonine deaminase (12). 12-OPDA is also an established signaling molecule that mediates gene expression with or without the canonical JA signaling framework (96). A major part of these altered expression profiles is dependent on the TGACG motif–binding factors, suggesting a specific interaction of 12-OPDA with these transcription factors (75). Among the established physiological ramifications of 12-OPDA-mediated alterations in gene expression are regulation of stomatal closure in response to drought, which is functionally most effective with abscisic acid, and the links between 12-OPDA signaling and amino acid biosynthesis and between 12-OPDA signaling and cellular redox homeostasis in stress responses (87, 100).

Lipid peroxidation by ROS (predominantly $^1O_2$) generated by biotic and abiotic stresses results in fragmentation of FAs and the formation of products such as azelaic acid (AZA). This metabolite is now recognized as a long-distance mobile signal that is essential for systemic acquired resistance (9, 126, 138) (**Figure 2*e***).

The findings described above briefly illustrate the intricate regulatory capacity and multifaceted signaling roles of these remarkably conserved and chemically diverse FA-based metabolites and their huge pool of derivatives in many cellular processes.

Mitochondria

As in chloroplasts, ROS and Ca^{2+} have been implicated in mitochondrial retrograde-signaling cascades (17, 35, 45) (**Figure 1**). Specifically, elevated ROS can alter membrane potential and induce the production of signaling peptides from mitochondrial proteins (69). Mitochondrial retrograde signals have not been well studied in plants (in contrast to those in chloroplasts) but have been extensively studied in yeast and mammalian cells, where they were identified as key regulators of cellular functions. For example, mitochondrial dysfunction in retrograde signaling is associated with reprogramming of nuclear gene expression in several human pathologies, including cancer (35). Similarly, in yeast, mitochondrial retrograde signaling is triggered by alterations in membrane potentials leading to a transduction pathway that ultimately culminate in the reprogramming of targeted nuclear gene expression, a process often described as mitochondrial retrograde regulation (45, 77). In yeast, the dysfunctional mitochondrial signal is primarily a means to ensure continued nitrogen fixation via glutamate (45). Among the mitochondrial retrograde-signal-responsive genes is peroxisomal *citrate synthase 2* (*CIT2*), indicating that a signal originating in the mitochondria will activate genes acting in the peroxisomes.

In yeast, the three *RTG* genes (*RTG1–3*) mediate mitochondrial retrograde signaling (44, 57, 114, 118). Mutants defective in RTG-dependent mitochondrial retrograde signaling display higher oxygen consumption, a reduced ability to decompose H_2O_2, and therefore reduced viability when challenged with H_2O_2 (114). RTG2, a key player in the signal transduction mechanism, is a phosphatase/transcriptional activator that mediates the phosphorylation status of RTG3 and is involved in the formation of a transcriptional activator, the SAGA-like complex (91). This complex harbors the histone acetyltransferase GCN5, suggesting that chromatin remodeling is involved in the mitochondrial retrograde-signaling process.

The evidence for the involvement of metabolites in mitochondrial retrograde signaling in plants is not conclusive; however, metabolites such as PAP are potential candidates (**Figure 2*d***), and studies have suggested that the transcription factors NO APICAL MERISTEM/ARABIDOPSIS TRANSCRIPTION ACTIVATION FACTOR/CUP-SHAPED COTYLEDON 013 (ANAC013) and ANAC017 are involved in mediating mitochondrial retrograde signals (17, 79) (**Figure 1**). Moreover, Giraud et al. (32) reported that the function of ABI4 is regulated by both plastidial and mitochondrial signals (**Figure 1**). In fact, subsequent studies have identified REGULATOR OF ALTERNATIVE OXIDASE 1 (RAO1) as the nucleus-localized cyclin-dependent kinase E1 (CDKE1) protein that integrates mitochondrial retrograde signals with energy signals under stress conditions (78) (**Figure 1**). Interestingly, *rao1* mutants are compromised in their response to altered redox and energy status in both chloroplasts and mitochondria, suggesting the key role of CDKE1 in establishing metabolic homeostasis by harmonizing the activities of these two organelles (4). These results illustrate the exquisite coordination of molecular and metabolic processes that synchronize the activity of these energy-regulating organelles.

INTERORGANELLAR COMMUNICATION: A NEW PARADIGM

The major role of ROS in initiating retrograde communications in response to a multitude of stresses, such as excess light, high temperature, and drought, is well established (10, 14). The resulting organellar signals coordinate signaling pathways that are ultimately required for appropriate rechanneling of energy between growth and stress responses, thereby establishing cellular homeostasis in the context of prevailing conditions. For example, a mitochondrial retrograde signal in yeast is capable of activating a peroxisomal gene to ensure maintenance of nitrogen assimilation during stress (45). Similarly, plastidial signals regulate selected mitochondrial nuclear-encoded genes (such as the gene encoding alternative oxidase) upon redox perturbations (22, 134, 135). Alternative oxidase is a critical component for sustaining photosynthetic rates, lowering oxidative stress, and buffering excessive reducing power under stress conditions (28). Importantly, transcriptional regulators such as WRKY40 and WRKY63 commonly control the expression of genes responding to both plastidial and mitochondrial dysfunction (117) (**Figure 1**).

The collective evidence demonstrates the presence of intricate and essential communication networks among organelles that are regulated in part by retrograde signals. One example is that the mitochondrial retrograde-regulation mediators ANAC013 and ANAC017 are bound to the ER but are released and relocated to the nucleus to exert transcriptional regulation in response to stress (17, 79), providing evidence that the ER functions as a key signaling intermediate in mitochondrial retrograde regulation. Moreover, a recent report demonstrated communication between the chloroplast and the ER through the plastidial retrograde-signaling metabolite MEcPP (121) (**Figure 2*d***).

The ER is a key organelle in maintaining cellular protein homeostasis, and almost a third of all proteins in the cell are synthesized, folded, and ultimately secreted and redistributed to other organelles from the ER (37). However, the limited protein-folding capacity of the ER results in an adaptive response termed the unfolded protein response (UPR), which serves as a monitoring

Unfolded protein response (UPR): a set of regulatory processes that adjust protein-folding capacity, thereby maintaining ER homeostasis

process that decreases the load of proteins to the ER and increases the capacity for folding and degradation of unfolded proteins (72, 122). In plants, the UPR signaling pathway has two parallel arms. One involves the dual-functioning protein kinase inositol-requiring enzyme 1 (IRE1) and its target, *basic leucine zipper 60* (*bZIP60*) mRNA (38, 40). The other pathway includes two integral membrane-bound transcription factors, bZIP17 and bZIP28 (38, 40). Various stresses differentially activate ER adaptive responses (19, 36). Furthermore, the two arms of the UPR can be either coactivated, as observed by exogenous application of salicylic acid (76), or individually activated, as in the case of plant pathogen infection that induces only the *IRE1-bZIP60* branch (71, 137).

Supporting these reports, accumulation of the plastid metabolite MEcPP induces expression of a subset of UPR genes, including *IRE1* and *bZIP60* but not the *bZIP28* branch (121), demonstrating the selectivity of MEcPP in its induction of one branch of the UPR. Importantly, exogenous application of MEcPP led to increased transcript levels of *bZIP60u* and *bZIP60s* 15 and 30 min after treatment, respectively. The timing of this induction suggests the direct function of MEcPP in potentiating induction of the UPR in the ER (**Figure 2*d***). This direct communication requires importing MEcPP from plastids to the ER. One potential scenario is that MEcPP is exported through membrane contact sites, a known conduit for metabolite trafficking between the ER and other organelles (92). Indeed, the established presence of membrane contact sites between chloroplasts and the ER (1) suggests the presence of a conduit for direct communication between the two. This notion is further supported by the recent report on localization of the lipid transfer protein–like AZELAIC ACID INDUCED 1 (AZI1) and its closest paralogs, EARLY ARABIDOPSIS ALUMINUM INDUCED 1 (EARLI1) and DEFECTIVE IN INDUCED RESISTANCE 1 (DIR1), which are the candidates for proteins that transport or act in the perception of AZA, which is necessary for systemic acquired resistance and induced systemic resistance (9). These proteins are localized at the ER or plasmodesmata, the chloroplast outer envelopes, and the membrane contact sites between them, and display a structural adaptation to promote lipid-based signaling between organelles (9).

MULTILATERAL COMMUNICATION AND ORGANELLAR JUXTAPOSITION

Interorganellar communication naturally encompasses multiple organelles, including chloroplasts, mitochondria, and peroxisomes, that are functionally interconnected in central metabolic processes (**Figure 3**). Montes & Bradbeer (70) used microscopy to establish the physical interactions among these compartments more than 40 years ago, and their findings have recently been expanded through the use of femtosecond laser technology. This technology enabled analyses of adhesion between organelles and demonstrated the light-dependent adhesion between peroxisomes, chloroplasts, and mitochondria as a mechanism for ensuring efficient metabolite flow during photorespiration (83). The physical connection, together with biochemical evidence during photorespiration, demonstrates the central role of organellar homeostasis in responses to metabolic perturbation (136). Thus, there must exist a tightly regulated communication avenue to align proximity and the optimal interdependent functional status of organelles.

One common feature shared by organelles is the central signaling roles of ROS and redox states in balancing their respective functions (**Figures 1** and **3**). As such, H_2O_2, a stable species of ROS, is a communication signal candidate. Caplan et al. (8) recently demonstrated that, during activation of the innate immune system or exogenous application of defense signals such as H_2O_2, chloroplasts produce dynamic tubular extensions known as stromules that surround the nucleus. Stromule formation also correlates with accumulation of the chloroplast-localized nuclear receptor-interacting protein 1 (NRIP1) defense protein and H_2O_2 in the nucleus, supporting the

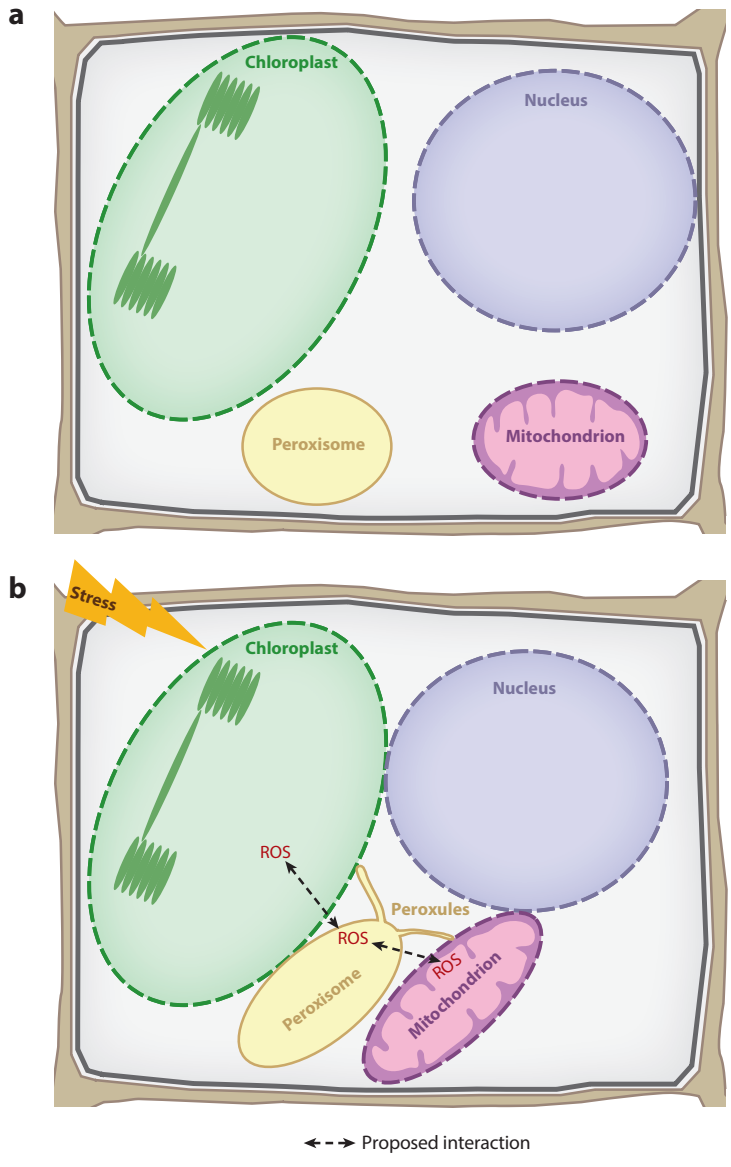


Figure 3

Stress-mediated organellar morphological transitions and juxtaposition. (*a*) Model depicting morphology and organellar juxtaposition in an undisturbed cell. (*b*) Model depicting altered morphology and organellar juxtaposition in a stressed cell. ROS-mediated peroxule formation in the peroxisome tethers this organelle to the chloroplast and mitochondrion. Abbreviation: ROS, reactive oxygen species.

function of stromules as a conduit for signal transport. The potential bridging of chloroplasts to the mitochondria and peroxisomes via stromules is presently under study (8).

The function of retrograde signaling is not limited to the interorganellar communication required for maintenance of cellular homeostasis; it extends to the integration of processes that

regulate biogenesis and degradation of cellular organelles. One prime example is the tight control of chloroplast biogenesis by fine tuning of the levels of the multiprotein complexes known as translocon at the outer envelope membrane of chloroplasts (TOC). A chloroplast outer membrane protein, the RING-type ubiquitin E3 ligase SUPPRESSOR OF PPI1 LOCUS 1 (SP1), was identified as the mediator of the ubiquitination of TOC components that are subsequently recognized by the cytosolic ubiquitin-proteasome system for degradation, thereby controlling chloroplast development, consistent with findings in mitochondria (43, 58) (**Figure 2*f***). In addition to the reorganization of the TOC machinery and regulation of plastid biogenesis, SP1 plays a central role in plant stress responses. Specifically, abiotic stresses cause the overproduction of ROS in chloroplasts and the depletion of the chloroplast protein import apparatus by SP1, which in turn limit the import of the photosynthetic apparatus and thus restrict ROS production (59). In light of the role of ROS as a general elicitor of retrograde signals, it has been proposed that elevated chloroplast ROS in response to stress relays information to the ubiquitin-proteasome system to regulate organellar proteome composition and function. Moreover, the ubiquitin-proteasome system plays a critical role in chloroplast quality control in photosynthetic cells because severely ROS-damaged chloroplasts are ubiquitinated by the ubiquitin E3 ligase U-BOX DOMAIN–CONTAINING PROTEIN 4 (PUB4) and selectively degraded by the ubiquitin-proteasome system (127) (**Figure 2*g***). The direct target of PUB4 is unknown; however, this finding provides a novel insight into the complexity of mechanisms recruited and the array of biological functions regulated by retrograde signals.

Another proposed interorganellar communication signal is PAP. Exchange among organelles during photorespiration could potentially mediate direct interorganellar communication in parallel with the reprogramming of nuclear gene expression. Mechold et al. (65) established that PAP inhibits bacterial oligoribonucleases (**Figure 2*b***); thus, by extension, PAP could potentially interfere with similar enzymes in plants, leading to disruption of RNA metabolism in mitochondria and chloroplasts (**Figure 2*b***).

Organellar juxtaposition enables proximity and potential physical interactions between organelles, enabling cellular homeostasis and thus the success of a wide array of biological processes in response to stress (**Figure 3**). One such process is programmed cell death. In animals, during specific stages of apoptotic cell death, mitochondria gain close proximity to the nucleus to enable the association of these two organelles (20). A similar phenomenon occurs to the chloroplasts of plant cells undergoing programmed death during the hypersensitive response (8). In both organisms, ROS plays a central role in cell death, and it is tempting to speculate that it might mediate direct interorganellar communication, resulting in the movement and juxtaposition of the compartment to allow physical association (**Figure 3**). Further supporting evidence for the role of ROS is provided by the observation that peroxule formation in peroxisomes is induced as a conduit for maintaining peroxisome-organelle interaction and specifically tethering this organelle to the chloroplast (30). Jaipargas et al. (42) provided further support in a study in which they proposed that ROS-distressed mitochondria may release one or more proteins that aid peroxule formation in order to enhance cellular ROS-combating capacity.

RETROGRADE SIGNALS AND ORGANELLAR MORPHOLOGICAL TRANSITIONS

Stress-mediated morphological transitions in organelles are a structural output critical for functions that direct the signaling pathways required for optimized adaptive response to stimuli. The association of spherical small mitochondria with intense ROS production clearly illustrates the link between organellar morphological transitions and function and cell death programs, in contrast to long-fused mitochondria, which are linked to greater oxidative capacity and enhanced functional

states (89). Such morphological transitions in plants include the modified shapes of peroxisomes as well as mitochondria interacting with peroxisomes and chloroplasts in response to light/dark cycles (**Figure 3**). Of note is the transition of both mitochondria and peroxisomes from a spherical shape in the dark to an elliptical shape in the light (83).

Dynamic alterations of morphology and function play a significant role in shaping cellular processes that in turn modify the signaling cascades necessary for mounting the appropriate response to a perceived stimulus. As such, a dynamic interface between morphological transitions and retrograde signaling suggests an exciting scenario in which there is a bidirectional link between the two processes.

FUNCTIONAL INTEGRATION OF RETROGRADE SIGNALS IN GROWTH AND DEVELOPMENT

Plants have evolved abundant adaptive strategies to cope with the inevitable challenges of environmental perturbation. Metabolic rechanneling is one such adaptation necessary to reallocate resources from growth and development to timely adaptive responses to environmental stresses. These stress-mediated alterations are collectively termed stress-induced morphogenic responses (90).

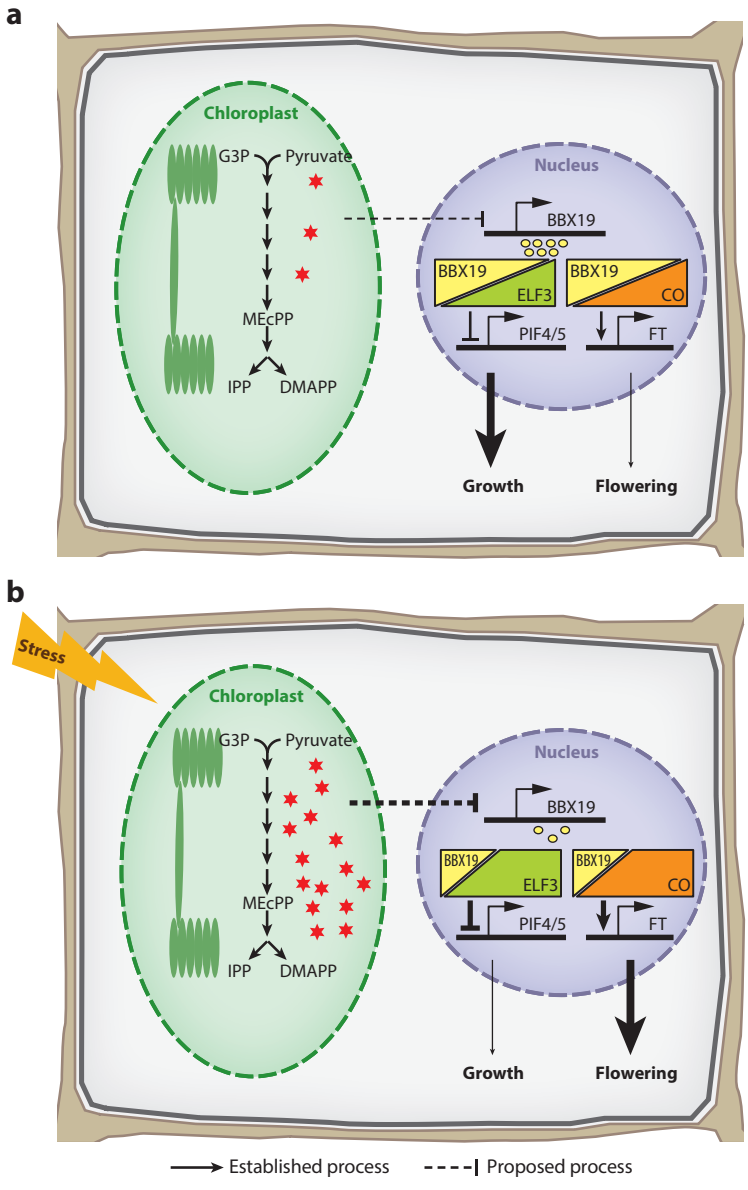
Chloroplasts, the metabolic hubs in plant cells, sense stress signals and then, in coordination with nuclear machinery, reprogram a repertoire of intricate networks crucial for coordinating the physiological and metabolic processes required for stress-induced morphogenic responses and stress adaptation. The *constitutively expressing HPL* (*ceh1*) mutant plants accumulate elevated MEcPP levels, are severely dwarfed, and flower early (123–125, 131). The compromised growth and early flowering of *ceh1* mutants result from MEcPP-mediated reduced expression of *B-BOX DOMAIN PROTEIN 19* (*BBX19*) (**Figure 4**). The BBX family of proteins comprises 32 zinc-finger transcription factors characterized by the presence of one or two B-box motifs at the N-terminal domain, either alone or in combination with a C-terminal CONSTANS, CONSTANS-like, and TOC (CCT) domain (29, 39, 49).

Growth

Hypocotyl elongation is a physiological response controlled by a myriad of internal and external cues (81, 82). Light-grown *ceh1* mutant plants, which accumulate high MEcPP levels, are severely dwarfed (131). A detailed exploration of the function of BBX19 as a regulator of photomorphogenesis in *ceh1* demonstrated that this transcriptional regulator determines the hypocotyl length of the mutant plant. The full compensation of *ceh1* reduced hypocotyl length by overexpression of *BBX19* established a direct link between the retrograde signal MEcPP and regulation of photomorphogenic growth through adjustment of *BBX19* expression levels (125). The specific mechanism of action of BBX19 is through binding to and recruitment of EARLY FLOWERING 3 (ELF3) for CONSTITUTIVE MORPHOGENESIS 1 (COP1)–mediated ubiquitination, which increases expression of the growth-promoting transcription factors PHYTOCHROME-INTERACTING FACTOR 4 (PIF4) and PIF5 (124) (**Figure 4**).

Flowering

The flowering transition is a pivotal event of the plant life cycle and is precisely controlled by a complex range of internal and environmental signals. Environmental cues can typically either induce or delay flowering. For example, salt stress triggers degradation of GIGANTA (GI), which delays the flowering transition and releases the GI-interacting protein SALT OVERLY



SENSITIVE 2 (SOS2) in order to promote salt-stress tolerance in *Arabidopsis* (50). Adaptation to drought stress, by contrast, is typically accompanied by a shortened life cycle because it promotes the flowering transition (15, 95, 133). Indeed, the time of flowering determines the adaptive fitness of plant species; for example, the *ceh1* mutant flowers early. Studies of the mechanism involved in this early transition identified BBX19 as a regulator of flowering time (123, 124) (**Figure 4**). Specifically, BBX19 is a negative regulator of flowering time that interacts with the flowering-inducer protein CONSTANS (CO). This interaction leads to depletion of the active CO pool required for the transcription of *FLOWERING LOCUS T* (*FT*) and the corresponding

Figure 4

MEcPP regulation of hypocotyl growth and flowering time via BBX19. (*a*) The functional mode of BBX19 in seedling growth is through binding to and recruitment of ELF3 for COP1-mediated ubiquitination, enabling enhanced expression of the growth-promoting transcription factor genes *PIF4* and *PIF5*. The functional mode of BBX19 in determining flowering time is through depletion of the active CO pool required for the transcription of *FT*. (*b*) Stress-mediated accumulation of MEcPP (*red stars*) represses *BBX19* expression (*yellow dots*). This results in (*i*) decreased expression levels of *PIF4* and *PIF5*, leading to reduced growth, and (*ii*) an increase in the available CO pool to activate *FT* expression and, by extension, early flowering. Arrow thickness indicates the intensity of each response. Abbreviations: BBX19, B-BOX DOMAIN PROTEIN 19; CO, CONSTANS; COP1, CONSTITUTIVE PHOTOMORPHOGENESIS 1; DMAPP, dimethylallyl pyrophosphate; ELF3, EARLY FLOWERING 3; FT, FLOWERING LOCUS T; G3P, glyceraldehyde 3-phosphate; IPP, isopentenyl pyrophosphate; MEcPP, 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate; PIF4/5, PHYTOCHROME-INTERACTING FACTOR 4/5.

downstream flowering-promoting genes *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1*, *LEAFY*, and *FRUITFUL* (123, 124).

Collectively, the findings described above identify BBX19 as a link between the stress-specific plastidial retrograde signal MEcPP and regulation of hypocotyl growth and the flowering transition (**Figure 4**).

CONCLUDING REMARKS

The recent widespread attempts to unravel the nature and function of retrograde signals have led to exciting discoveries of new roles for these signaling molecules. A sharper focus on this challenging area of research will help to elucidate the operational mode of retrograde signals, and potentially expand it from a bilateral connection between an organelle and the nucleus to a multilateral interorganellar communication system that regulates morphological transitions and functions, juxtaposition of organelles within the cell, and the biogenesis and degradation of organelles. These multifaceted outputs of retrograde signals assume their central role in cellular function in response to a wide range of environmental and developmental cues. Advances in our understanding of retrograde-signaling networks in various organisms will help to reveal the basis and complexities of this remarkable signaling system and provide a perspective on its origin and evolution.

SUMMARY POINTS

1. Reactive oxygen species and calcium are the master triggers for inter- and intracellular communication processes, including canonical retrograde- and anterograde-signaling pathways.
2. The retrograde-signaling mode of operation expands from a bilateral to a multilateral interorganellar communication mode involved in cellular adaptive responses.
3. Interorganellar signals are likely mediators of organellar morphological transitions, movement, and the respective juxtaposition, enabling proximity and potential physical interaction.
4. Interorganellar communication signals mediate reallocation of metabolic resources and energy currencies to balance growth and development against adaptive responses.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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