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Molecular components of stress-responsive plastid retrograde signaling networks and their involvement in ammonium stress

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Plastid retrograde signaling (chloroplast to nucleus) has been proposed to play an important role in the acclimation of plant function to environmental stress. Although several pathways and molecular components, as well as some signals, have been identified in recent years, our understanding of the communication between plastid and nucleus under stress remains fragmentary. This mini-review summarizes the properties of currently proposed candidate signals, chief molecular components, and their roles in the plastid retrograde signaling network in a variety of stress responses. We provide special emphasis on the recently characterized AMOS1/EGY1-dependent plastid retrograde signaling pathways engaged during ammonium stress.

Introduction

Chloroplasts are essential not only as sites of photosynthetic function but are also critically involved in the synthesis of hormones and metabolites, such as those derived from inorganic nitrogen. Nevertheless, of the approximately 3,000 plastid proteins, in excess of 95% are encoded by nuclear genes.[1] Over the last several decades, plastid-derived retrograde (plastid-to-nucleus) signals have been found to be essential for the expression of photosynthesis and stress-associated nuclear genes during chloroplast development and in response to environmental stresses. In particular, the regulation of plastid retrograde signaling in the expression of photosynthesis-associated nuclear genes and those related to chloroplast development has been extensively studied.[2-16] More recently, several plastid retrograde signaling pathways have been identified to regulate the expression of stress-related nuclear genes during several stresses such as high light, drought, wounding, heat, and excess ammonium.[17-31] Based on the new stress-responsive plastid retrograde signaling pathways just reported in 2012 alone, this review will focus on properties of currently proposed molecular components in the plastid retrograde signaling network under stress. We also specifically discuss possible plastid retrograde signals involved in plant response to ammonium stress.

Several major signals, including singlet oxygen ($^1O_2$),[17-20] 3'-phosphoadenosine 5'-phosphate (PAP),[26] hydrogen peroxide (H_2O_2),[27] and methylerythritol cyclodiphosphate (MEcPP),[29] are known to be produced as metabolic intermediates in chloroplasts in response to a variety of stresses. However, the involvement of these signals remains to be established for heat and ammonium stress.[30,31] It is typically assumed that the plasma membrane serves as the first site of perception of environmental changes in a cell,[32,33] and chloroplasts, as the metabolic center of photosynthetic activity, may act as a secondary, but vital, downstream modulator in the sensing of environmental signals originally perceived by the plasma membrane. As a result of effective signal transduction, modulation of nuclear gene expression ensues, impacting chloroplast function and, more generally, cell growth.

Molecular Components in Plastid Retrograde Signaling To Regulate Stress-Related Genes

Mutant screens and gene function analysis have played a significant role in the endeavor to dissect the molecular components and identify plastid retrograde signals (**Table 1**). For example, several regulatory molecular components involved in $^1O_2$-mediated plastid-to-nucleus signaling have been identified through extensive genetic mutation screens in the background of the conditional *flu* mutant, such as EX1, EX2, SOLDAT10, PRL1, CAA33, CAA39 in Arabidopsis.[20-25] Two new plastid retrograde signals (PAP and MEcPP) during drought, high light and wounding stress responses have been revealed by two research teams, involving the analysis of the Arabidopsis mutants *sal1* and *ceh1*, which encode the plastid nucleotidase/phosphatase SAL1 and hydroxyl-2-methyl-2-(E)-butenyl4-diphosphate synthase (HDS), respectively.[26,29] Analysis of the *rps1* mutant demonstrated that the chloroplast ribosomal protein S1 (RPS1) mediates retrograde signaling to modulate the expression of the heat-responsive nuclear transcription factor HsfA2 and its target genes during heat stress, although the specific plastid retrograde signal is unknown.[30] Recently, gene cloning and transcriptional analysis of the Arabidopsis *ammonium-overly-sensitive 1* (*amos1*)

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Table 1. Molecular components in plastid retrograde signaling under several stresses

Gene name	Gene ID	Molecular function	Plastid signal	Stress	Reference
EX1	AT4G33630	unknown	$^1O_2$	$^1O_2$-stress	20
EX2	AT1G27510	unknown	$^1O_2$	$^1O_2$-stress	21
SOLDAT10	AT2G03050	mTERF	$^1O_2$	$^1O_2$-stress	22
PRL1	AT4G15900	Nuclear WD40 protein	$^1O_2$	$^1O_2$-stress	23
CAA33	AT5G51020	Unknown	$^1O_2$	$^1O_2$-stress	24
CAA39	At5g02820	Topoisomerase VI	$^1O_2$	$^1O_2$-stress	25
SAL1	AT5G63980	Phosphatase/nucleotidase	PAP	Drought/high light	26
tAPX	AT1G77490	ascorbate peroxidase	H_2O_2	Several stresses	27
HDS	AT5G60600	HMBPP synthase	MEcPP	High light/wounding	29
RPS1	AT5G30510	ribosomal protein	unknown	Heat stress	30
AMOS1/EGY1	AT5G35220	metalloprotease	unknown	High ammonium	31

mutant revealed that plastid metalloprotease EGY1 is required for plastid retrograde signaling in response to ammonium stress.[31] Further, the role chloroplastic H_2O_2 plays in triggering retrograde signaling to regulate the expression of nuclear genes induced by abiotic and biotic stresses was established by the construction of silencing lines of thylakoid membrane-bound ascorbate peroxidase (tAPX), using RNAi.[27,28]

The regulatory role of these molecular components in stress-responsive plastid retrograde signaling can be preliminarily divided into five functional types, based on their targets: regulation of the signal compound level, signal transfer, gene transcription in the nucleus, chloroplast homeostasis, and interaction with other signaling pathways. An example of the first type can be seen in chloroplastic SAL1, a phosphatase that regulates the level of its substrate 3'-phosphoadenosine-5'-phosphate (PAP); high levels of PAP were demonstrated to accumulate in *sal1* mutants.[26] Similarly, the stress-inducible nuclear HDS gene encodes a plastidial enzyme that participates in isoprenoid synthesis, converting methylerythritol cyclodiphosphate (MEcPP) to hydroxymethylbutenyl diphosphate (HMBPP) in the methylerythritol phosphate (MEP) pathway in plastids; large amounts of MEcPP were shown to accumulate in *ceh1* mutants.[29] Likewise, tAPX regulates the production of H_2O_2 in chloroplasts.[27] As examples of the second type, plastid EX1 and EX2 proteins are required for the transfer of $^1O_2$-mediated plastid-to-nucleus signaling, although their detailed molecular function is unknown.[20,21] As an example of the third type, transcript profile analysis of *flu* and *flu caa39* mutants revealed that topoisomerase VI (Topo VI) acts as a nuclear component of $^1O_2$-mediated plastid-to-nucleus signaling to directly regulate the expression of the AAA-ATPase and other $^1O_2$-responsive genes.[25] As an example of the fourth type, mutation of plastid SOLDAT10 disrupts chloroplast homeostasis by attenuating the decrease in plastid-specifc rRNA levels and protein synthesis, and affects the communication of $^1O_2$-mediated signaling between chloroplasts and the nucleus.[22] Similarly, mutation of plastid CAA33 disturbs chloroplast homeostasis by impeding plastid division, interfering with $^1O_2$-mediated plastid-to-nucleus signaling.[24] A further example can be seen in chloroplastic RPS1, involved in plastid protein translation and displaying a role in the synthesis of thylakoid membrane proteins that are needed for maintaining the stability of the thylakoid membrane system under normal growth conditions.[30] As an example of the fifth type, PLEIOTROPIC RESPONSE LOCUS 1 (PRL1) protein, located in the nucleus, appears to play a major role in modulating plant responses to environmental changes by interconnecting $^1O_2$-mediated retrograde signaling with energy signaling pathways.[23] The most recently characterized molecular component, EGY1, the first metalloprotease site-2 protease (S2P) homolog discovered in plants and located in plastids, is required for normal chloroplast development such as thylakoid grana stacking, the development of the lamellae system, and the accumulation of chlorophyll and chlorophyll a/b binding proteins.[34] The metalloprotease S2P and homologs act in the manner of regulated intramembrane proteolysis (RIP) that regulates signal transduction across the membrane by recruiting membrane-bound proteases to cleave membrane-spanning regulatory proteins, and, as such, are involved in controlling several fundamental processes such as cholesterol and fatty acid synthesis, stress responses, cell division, and polar organelle biogenesis in a number of organisms.[35,36] A mutant of EGY1 was found to reduce H_2O_2 accumulation in guard cell chloroplasts, and interact with ABA signaling to regulate the expression of nuclear genes in response to excess ammonium.[31] Thus, the function of EGY1 in retrograde signaling at least incorporates, but may not be limited to, the fifth type. Therefore, the diversity of molecular components and signal compounds suggests a fundamental regulatory function of plastid retrograde signaling in plant acclimation to a variety of environmental stresses.

Interaction of Plastid Retrograde Signaling and ABA Signaling Revealed by *amos1* and Other Mutants

Despite the greatly increased understanding of retrograde signaling in stress responses acquired over the past several years, details of the signaling network(s) remain unknown. Many experiments support the contention that abscisic acid (ABA) is a key second messenger to orchestrate stress signal transduction and defensive responses in plants.[37,38] However, ABA is not regarded as a direct candidate for the plastid signal,[39] because ABA biosynthesis occurs in the cytosol,[40] ABA can repress the expression of

Lhcb (encoding a light-harvesting chlorophyll a/b-binding protein) in wild type and the GENOMES UNCOUPLED (*gun*) mutant, and the ABA-deficient *aba1* mutant does not accumulate *Lhcb* mRNA as is seen in *gun* mutants in response to lincomycin, an inhibitor of plastid protein synthesis.[39] Interesting, ABA-insensitive *abi4* displays a *gun* phenotype, and ABI4 is identified to act downstream of GUN1 in plastid retrograde signaling.[39]

Recently, ABA signaling has been shown to be a critical downstream component of AMOS1/EGY1-dependent ammonium-induced plastid retrograde signaling, using a combination of approaches.[31] First, 'ACGTG', the core motif of ABA-responsive genes,[41,42] was observed in the promoter region of more than 60% of AMOS1/EGY1-dependent ammonium-activated genes. Second, application of low concentrations of ABA treatment led to recovery of the ammonium-induced chlorosis phenotype in the *amos1* mutant. Third, the expression of AMOS1/EGY1-dependent ammonium-activated genes reverted to the wild-type level in *amos1* upon ABA treatment. Fourthly, the ABA content in *amos1* mutant was significantly lower than in wild type during ammonium stress. Lastly, *abi4* mutants defective in ABA-dependent and retrograde signaling, but not ABA-deficient mutants, exhibited leaf chlorosis during ammonium stress. These results also suggest ABA signaling is not the sole downstream component in AMOS1/EGY1-dependent plastid retrograde signaling during ammonium stress. Similarly, ABA signaling has also been found to be involved in the H_2O_2-dependent plastid signal that activates high-light responsive gene expression in leaves[43] and to be recruited by an $^1O_2$-dependent plastid signal during late embryogenesis where it affects plastid differentiation by reactivating relevant nuclear-encoded genes.[44] Therefore, interactions between plastid retrograde signaling and ABA signaling may be a common occurrence during stress responses. In an earlier review, a hypothesis was advanced to describe the interaction between plastid retrograde signaling and ABA signaling in the context of high light stress. According to this hypothesis, high light triggers increased H_2O_2 production in chloroplasts of bundle sheath cells, then initiates retrograde signaling, which, in turn, feeds into the ABA regulatory network, speeding it up.[13]

Possible Plastid Retrograde Signaling Pathways in Ammonium Stress

In a recent study, we have shown the operation of an ABA-dependent and an ABA-independent pathway as downstream components of AMOS1/EGY1-dependent ammonium-induced plastid retrograde signaling.[31] The largely non-chloroplastic location of AMOS1/EGY1-dependent ammonium-stress-responsive proteins and the results of an ABA rescue experiment (in response to ammonium) provided strong evidence that AMOS1/EGY1-dependent ammonium-induced plastid retrograde signaling plays a primary role in alleviating ammonium toxicity, rather than simply promoting chloroplast development.[31] However, the specific AMOS1/EGY1-dependent ammonium-induced plastid signal has not as yet been identified. Drawing upon information on plastid retrograde signals identified in other published works, we propose possible plastid retrograde signals for the AMOS1/EGY1-dependent ammonium stress response (**Fig. 1**).

First, reactive oxygen species (ROS), released in chloroplasts, may be a candidate retrograde signal during ammonium stress. A major source of chloroplastic H_2O_2 has been proposed to result from the reduction of molecular oxygen in the Mehler reaction, which is increased during ammonium stress.[45] The H_2O_2 response is defective in guard-cell chloroplasts of the *amos1* mutant, independent of external ammonium treatment and the absence or presence of ABA.[31] The expression of H_2O_2-responsive genes, such as small heat shock proteins (HSPs),[27,46] is induced greatly in wild-type Arabidopsis, but not in the *amos1* mutant, upon exposure to excess ammonium.[31] These data indicate that a chloroplastic ROS signal is a highly plausible candidate for the AMOS1/EGY1-dependent ammonium-induced plastid retrograde signal. According to this hypothesis, chloroplastically generated ROS promote the expression of ammonium-stress-responsive genes (most containing the ACGTG motif in their promoter region) to alleviate ammonium toxicity. Further, the AMOS1/EGY1-dependent plastid retrograde signal recruits ABA signaling to amplify its effect.[31] A similar role of ABA signaling in a plastid ROS retrograde regulatory pathway has been documented under high-light stress.[43]

Second, other candidates for the AMOS1/EGY1-dependent ammonium-induced plastid retrograde signal are plausible, if the H_2O_2 defective response in guard cell chloroplasts is merely a secondary outcome of impaired chloroplast functionality in the *amos1* mutant. Very recently, the plastid metabolite methylerythritol cyclodiphosphate (MEcPP), a precursor in isoprenoid synthesis in the methylerythritol phosphate (MEP) pathway, has been identified as a novel retrograde signal involved in the regulation of the expression of nuclear stress-responsive genes under high-light and wounding stresses.[29] Isoprenoids derived from the MEP pathway also regulate the biosynthesis of chlorophyll and several phytohormones, including brassinosteroids, cytokinins, gibberellins, and abscisic acid (ABA). These, in turn, modulate plant growth and acclimation to environmental change.[47] In addition to chlorophyll and ABA, an alteration of jasmonic acid content was observed in the *amos1* mutant response to ammonium stress, as indicated by the significantly depressed biological process "response to jasmonic acid stimulus".[31] These data suggest that key metabolites of the MEP pathway are reduced in the *amos1* mutant response to ammonium. Recently, it has been found that enzymes of the MEP pathway require posttranslational modification, such as can be seen in the stromal ClpPR proteolytic complex.[48] Therefore, it is possible that the AMOS1/EGY1 metalloprotease activates MEP pathway enzymes in such a manner, modulating MEcPP levels, to regulate the expression of ammonium-stress-responsive genes in the nucleus.

Concluding Remarks

Plastid retrograde signaling (Mg-protophorphrin IX and heme as the candidates for the signal) was first found to regulate the expression of photosynthesis-associated nuclear genes and chloroplast development.[49,50] However, retrograde signals induced

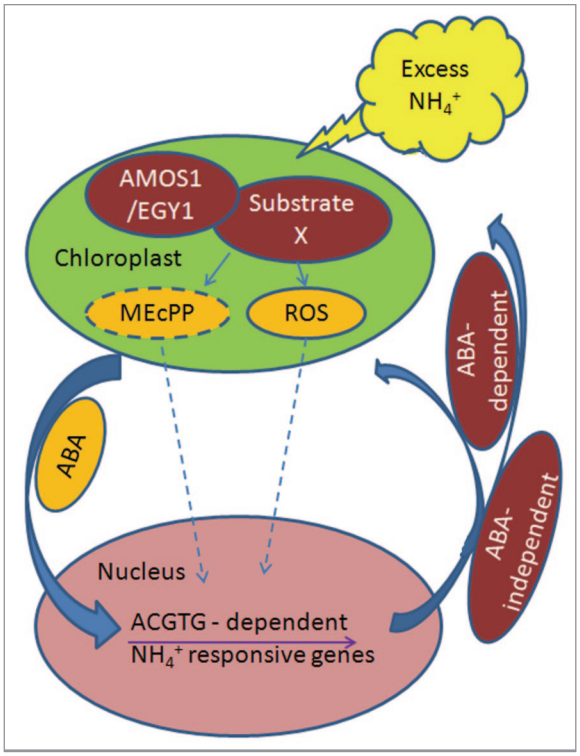

Figure 1. Model for AMOS1/EGY1-dependent plastid retrograde signaling during ammonium stress. X, the unknown substrate of AMOS1/EGY1. All dashed lines indicate areas that require further research. During ammonium stress, AMOS1/EGY1 activates X to regulate the level of ROS or MEcPP, triggering plastid retrograde signaling, which is required for the expression of ammonium-stress-responsive nuclear genes including those encoding ABA-dependent proteins and others, such as small heat shock proteins. Most of these genes contain the 'ACGTG' regulatory element in their promoter region. Further, AMOS1/EGY1-dependent plastid retrograde signaling can recruit ABA signaling to enhance the expression of ammonium-stress-responsive ABA-dependent nuclear genes. These proteins cooperate to enhance the resistance of leaves to high ammonium and help maintain chloroplast functionality.

by environmental stress, such as $^1O_2$, H_2O_2, PAP, and MEcPP, seem to occur much more widely. Recent studies confirm the important role of plastid retrograde signaling in plant acclimation to a variety of environmental stresses, as proposed in earlier reviews.[10,13] One recent example is the detailed analysis of the role of the metalloprotease AMOS1/EGY1 in plastid retrograde signaling under high-ammonium stress. It remains an open question whether the AMOS1/EGY1-dependent ammonium-induced plastid retrograde signal belongs to the two proposed candidates (ROS and MEcPP) or whether other chloroplastic metabolites are involved. A dissection of the ROS response in chloroplasts, coupled to high-throughput metabolomics, in the *amos1* mutant in response to ammonium stress may enable the identification of the retrograde signal. Additionally, aside from external supply, ammonium is produced in substantial amounts plant-internally in protein metabolism and in photorespiration, a large fraction of which is re-assimilated in chloroplasts.[51,52] The properties of ammonium stress are clearly distinct from other abiotic stresses such as excess light and drought. Therefore, elucidation of chloroplast development under ammonium stress may provide significant new insight into the variable nature of plastid retrograde signaling pathways during plant acclimation to the environment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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