

ATP-sulfurylase, sulfur-compounds, and plant stress tolerance

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Sulfur (S) stands fourth in the list of major plant nutrients after N, P, and K. Sulfate (SO_4^{2-}), a form of soil-S taken up by plant roots is metabolically inert. As the first committed step of S-assimilation, ATP-sulfurylase (ATP-S) catalyzes SO_4^{2-} -activation and yields activated high-energy compound adenosine-5'-phosphosulfate that is reduced to sulfide (S^{2-}) and incorporated into cysteine (Cys). In turn, Cys acts as a precursor or donor of reduced S for a range of S-compounds such as methionine (Met), glutathione (GSH), homo-GSH (h-GSH), and phytochelatins (PCs). Among S-compounds, GSH, h-GSH, and PCs are known for their involvement in plant tolerance to varied abiotic stresses, Cys is a major component of GSH, h-GSH, and PCs; whereas, several key stress-metabolites such as ethylene, are controlled by Met through its first metabolite S-adenosylmethionine. With the major aim of briefly highlighting S-compound-mediated role of ATP-S in plant stress tolerance, this paper: (a) overviews ATP-S structure/chemistry and occurrence, (b) appraises recent literature available on ATP-S roles and regulations, and underlying mechanisms in plant abiotic and biotic stress tolerance, (c) summarizes ATP-S-intrinsic regulation by major S-compounds, and (d) highlights major open-questions in the present context. Future research in the current direction can be devised based on the discussion outcomes.

Keywords: ATP-sulfurylase, sulfur assimilation, organic S-compounds, stress tolerance

Introduction

Abiotic and biotic stresses (in isolation and/or combination) are known to cause severe decline in crop productivity globally as a result of their impact on plant growth, development, and metabolism (Suzuki et al., 2014). Maintenance of plant-mineral nutrients status has been extensively evidenced to significantly improve the crop-productivity and -resistance to various stresses (Anjum and Lopez-Lauri, 2011; Gill and Tuteja, 2011). Sulfur (S) stands fourth in the list of major plant-nutrients after N, P, and K, and its importance is being increasingly emphasized in agriculture (Yi et al., 2010) and plant stress tolerance (Gill and Tuteja, 2011; Nazar et al., 2011). Nevertheless, S-deficiency in agricultural-soils is becoming widespread globally (Anjum et al., 2012a). Thus far, adopted approaches such as increased S-fertilization, -remobilization, and -uptake/accumulation may not be sufficient for S-deficiency-alleviation. Nevertheless, plant harbored-S is metabolically inert and is of no significance if it is not efficiently assimilated into physiologically/biochemically exploitable organic forms that is performed by the process of S-assimilation.

As the first committed step of primary S-assimilation in plants, ATP-sulfurylase (ATP-S; Adenylsulfurylase/ATP:sulfate adenyltransferase; E.C. 2.7.7.4) catalyzes the activation of sulfate (SO_4^{2-}) and yields adenosine-5'-phosphosulfate (APS) that is reduced to sulfide (S^{2-}) and incorporated into cysteine (Cys). Having thiol (S^{2-})-residue and due to its strong nucleophilic-characteristics, Cys performs important metabolic-functions and actively mediates redox-reactions (Hell and Wirtz, 2011). Notably, as a major component of predominant thiol-peptide found in plants and as a direct/indirect precursor, Cys is involved in the synthesis of S-containing compounds including glutathione (GSH, γ -glutamyl-cysteinyl-glycine) and its analog homo-GSH (h-GSH, γ -glutamyl-cysteinyl- β -Ala), reported in several genera within Fabaceae; phytochelatins (PCs; γ -glutamyl-cysteinyl)^{nx}; $n = 2-11$; x represents (Gly, Ser, β -Ala, Glu, Gln, or no residue), and metallothioneins (MTs), Cys-rich gene-encoded low-molecular-weight peptides. Previous S-compounds are known for their involvement in plant-tolerance to varied abiotic-biotic stresses, and metal/metalloid-homeostasis as well (Rausch and Wachter, 2005; Verbruggen et al., 2009; Anjum et al., 2010, 2012b, 2014a,b; Na and Salt, 2011; Seth et al., 2012; Gill et al., 2013). Additionally, in secondary SO_4^{2-} -assimilation, where instead of entering the reductive S-assimilation pathway after ATP-S-mediated activation, APS is phosphorylated in a APS kinase-catalyzed reaction to produce 3'-phosphoadenosine 5'-phosphosulfate (PAPS). PAPS is involved in the production of other S-containing methionine-derived (aliphatic) or tryptophan-derived (indolic) secondary metabolites such as glucosinolates (GSs). GSs (particularly indolic type) are reported to protect plants mainly against several biotic stress-factors such as herbivory and pathogenesis, and are required for plant-immunity (Frerigmann and Gigolashvili, 2014). Therefore, S-assimilation pathway-enzymes including ATP-S are the major target of current plant-nutrition research to achieve maximum benefits including improved productivity of crops and their resistance to multiple stresses with less S-input (Herrmann et al., 2014).

Thus, to briefly highlight S-compound-mediated role of ATP-S in plant stress tolerance, ATP-S structure/chemistry and occurrence are overviewed, recent literature available on ATP-S roles, regulations and underlying major mechanisms in plant abiotic and biotic stress tolerance is appraised, ATP-S intrinsic regulation by major S-compounds is summarized, and important open-questions in the topic considered are highlighted herein.

ATP-S: Structure/Chemistry and Occurrence

Described as monomers or homo-oligomeric complexes (which do not require GTPase for activation), plant-ATP-S has been reported to be a homotetramer of 52–54 kDa polypeptides, or a mono-functional, non-allosteric homodimer (100 kDa, formed by two ~48 kDa monomers; Phartiyal et al., 2006; Ravilious et al., 2013; Bohrer et al., 2014; Koprivova and Kopriva, 2014; Prioretti et al., 2014). Photosynthetic organisms can exhibit a variable number of ATP-S isoforms (Koprivova and Kopriva,

2014; Prioretti et al., 2014). X-ray crystal structure of *Glycine max* ATP-S isoform 1 in complex with APS revealed the exhibition of several highly conserved substrate-binding motifs in the active site and a distinct dimerization interface compared with other ATP-S (Herrmann et al., 2014). Enzymes involved in S-assimilation are not equally expressed in all plant cell-types/ organelles. In particular, ATP-S, APS kinase, serine acetyltransferase, and O-acetylserine-(thiol)-lyase are present in both plastids and cytosol but APS reductase and sulfite reductase are localized only in plastids for catalyzing the reduction steps (Lopez-Martin et al., 2008; Bohrer et al., 2014; Koprivova and Kopriva, 2014). Occurrence of SO_4^{2-} -activation in cytosol and plastids also supports the presence of ATP-S in these locations (Koprivova and Kopriva, 2014). Seed-plants possess multiple ATP-S-isoforms. Four ATP-S genes (*ATPS1*, -2, -3, and -4) reported in *Arabidopsis thaliana* have N'-terminal extensions typical of plastid-transit-peptides, and are located on different chromosomes; however, one of them can also be cytosolic (Rotte and Leustek, 2000; Prioretti et al., 2014). Genetic-identity of cytosolic-ATP-S has been verified recently (Bohrer et al., 2015). *A. thaliana* *ATPS2* was evidenced to be dually encode plastidic and cytosolic forms, where translational-initiation at AUG^{Met1} and AUG^{Met52} or AUG^{Met58} produced *ATPS2* in plastid and cytosol, respectively (Bohrer et al., 2015). *Oryza sativa* has two ATP-S genes (*ATPS1-2*; Kopriva et al., 2007). Plastidic and/or mitochondrial localization of ATP-S genes (*Glyma10g38760*, *Glyma20g28980*, *Glyma13g06940*; *Glyma19g05020*) was reported in *G. max* (Yi et al., 2010).

ATP-S: Roles and Regulations in Plant Abiotic Stress Tolerance

ATP-sulfurylase can be involved in plant-tolerance to several abiotic stresses *via* different S-compounds. GSH, a non-protein S-containing tripeptide acts as a storage and transport form of reduced-S. Significant induction of GSH-based defense-system, its role in reactive oxygen species (ROS)-scavenging, and in the maintenance of reduced cellular-redox environment have been extensively evidenced in plants under various abiotic stresses including metal/metalloids (Anjum et al., 2010, 2012b, 2014a,b; Gill and Tuteja, 2010; Noctor et al., 2012; Talukdar, 2012; Gill et al., 2013; Talukdar and Talukdar, 2014) and salinity (Ruiz and Blumwald, 2002; Kocsy et al., 2004; Gill and Tuteja, 2010; **Table 1**). Cys-rich metal-chelating proteins – MTs and PCs maintain homeostasis of varied metals/metalloids and mitigate major detrimental effects of their elevated concentrations (Na and Salt, 2011; Anjum et al., 2014a). h-GSH is an effective antioxidant in Fabaceae plants, where it is argued to scavenge ROS, act as PCs-precursor, and found to be involved in xenobiotic defenses *via* GSH-sulfotransferases (Frendo et al., 2013). GSs provide plant-tolerance to varied abiotic stresses including drought/salinity, metals/metalloids, and nutritional-deficiencies (Martínez-Ballesta et al., 2013).

Varied abiotic stresses differentially regulate ATP-S activity/expression in plants (**Table 1**). Among metals/metalloids, literature is full on Cd-accrued enhanced ATP-S activity and

TABLE 1 | Summary of representative studies on ATP-S activity or expression modulation/regulation in abiotic and biotic stressed plants.

Plant species	Response	Reference
Abiotic stresses		
Sulfate starvation		
<i>Arabidopsis thaliana</i>	–	Liang et al. (2010)
<i>A. thaliana</i>	+	Lappartient et al. (1999)
<i>Brassica napus</i>	+	Lappartient and Touraine (1997)
<i>Nicotiana tabacum</i> cultured cells	+	Reuveny et al. (1980)
<i>Zea mays</i>	+	Hopkins et al. (2004)
<i>Z. mays</i>	+	Schiavon et al. (2007)
Cadmium		
<i>A. thaliana</i>	+	Harada et al. (2002), Weber et al. (2006)
<i>A. thaliana</i>	+	Bashir et al. (2013)
<i>B. juncea</i>	+	Lee and Leustek (1999)
<i>B. juncea</i>	+	Masood et al. (2012)
<i>B. juncea</i>	+	Asgher et al. (2014)
<i>B. juncea</i>	+	Heiss et al. (1999)
<i>B. juncea</i>	+	Khan et al. (2009a)
<i>Lepidium sativum</i>	+	Gill et al. (2012)
<i>Sedum alfredii</i> Hance	+	Guo et al. (2009)
<i>Thlaspi caerulescens</i>	+	van de Mortel et al. (2008)
<i>Triticum aestivum</i>	+	Khan et al. (2007)
Salinity		
<i>B. juncea</i>	+	Nazar et al. (2011)
<i>B. juncea</i>	–	Khan et al. (2009b)
<i>B. napus</i>	+	Ruiz and Blumwald (2002)
Light (irradiation)		
<i>A. thaliana</i>	–	Huseby et al. (2013)
<i>Avena sativa</i> , <i>Hordeum vulgare</i> and <i>Z. Mays</i>	+	Passera et al. (1989)
H ₂ O ₂		
<i>B. napus</i>	–	Lappartient and Touraine (1997)
Glutathione		
<i>B. napus</i>	–	Lappartient and Touraine (1996)
<i>Lemna gibba</i> and <i>Salvinia minima</i>	+	Leao et al. (2014)
Chilling/Cold stress		
<i>Glycine max</i>	+	Phartiyal et al. (2006)
<i>Z. mays</i>	+	Nussbaum et al. (1988), Brunner et al. (1995)
Biotic Stress		
Infection by <i>Phytophthora infestans</i> and/or <i>Botrytis cinerea</i>		
<i>A. thaliana</i> and <i>B. juncea</i>	+	Matthewman (2010)

+, – signs indicate increase or decrease, respectively.

increased pools of Cys and GSH (Guo et al., 2009; Khan et al., 2009a; Masood et al., 2012; Bashir et al., 2013; Asgher et al., 2014). Up-regulation of ATP-S transcripts was reported in Cd-exposed *Brassica juncea* (Heiss et al., 1999) and *A. thaliana*

(Harada et al., 2002). Enhanced ATP-S activity was evidenced in several Cd/Zn-hyperaccumulators including *Sedum alfredii* (Guo et al., 2009), *A. halleri* (Weber et al., 2006), and *Thlaspi caerulescens* (van de Mortel et al., 2008). Lower ATP-S activity-exhibiting *Brassica juncea* cv. (SS2) was reported to be salt-sensitive (Khan et al., 2009b). Chilling-stress can also mediate modulation of levels and also intercellular-distribution of ATP-S mRNAs (Kopriva et al., 2001). Reports also indicate the ATP-S activity/expression-regulation by light-regimes. Forty four hours of dark was reported to down-regulate *ATPS1–ATPS3*; whereas, *ATPS4* was not affected (Huseby et al., 2013). However, after 3-h of re-illumination, *ATPS1*, *ATPS3*, and *ATPS4* were induced by light but only *ATPS2* reached the levels in control plants (Huseby et al., 2013).

Unknown for its essential-function in higher plants, Se, taken-up as selenate (SeO₂^{–4})/or selenite (SeO₂^{–3}) was reported to enhance plant growth and antioxidant activity (Pilon-Smits and Quinn, 2010). ATP-S is also involved in Se-reductive-assimilation pathway and activates SeO₂^{–4} to organic-metabolite, seleno-Cys (El Kassis et al., 2007; Pilon-Smits and Quinn, 2010). Recently, ability to hyperaccumulate and hypertolerate Se in *Stanleya pinnata* (Se-hyperaccumulator) was considered due to its potential to exhibit higher transcript levels of *APS1*, *APS2*, and *APS4* (vs. *Brassica juncea*, a non-Se-hyperaccumulator; Schiavon et al., 2015). Additionally, under Se-exposure and S-deficiency, *S. pinnata* hyperaccumulates and tolerates Se due to its ability to convert SeO₂^{–4} to non-toxic organic-seleno-compounds by down-regulating *APS1*, *APS2*, and *APS4*. However, under S-sufficient and Se-exposure, adoption of different types of regulatory mechanisms and subcellular-localization were revealed in *S. pinnata* and *Brassica juncea*, where Se up-regulated *APS1* and *APS4* but was not able to affect *APS2* in *S. pinnata* (Schiavon et al., 2015). Earlier, compared to *Camellia sinensis* grown on Se un-enriched soil, young (or mature) leaves and roots were reported to exhibit a lower and higher *APS1* and *APS2* expression levels in Se-enriched soil-grown *C. sinensis* (Tao et al., 2012).

Extensive reports are available on S-depletion-mediated regulation of ATP-S activity/expression. ATP-S isoforms can be differentially expressed by S-depletion. *AtAPS3* increased in S-depleted *A. thaliana* (Liang et al., 2010; Kawashima et al., 2011). However, response of *AtAPS2* (a putative cytosolic-isoform) to S-depletion is inconsistent between different studies (Logan et al., 1996; Takahashi et al., 1997; Kawashima et al., 2011). Plant-ontogeny/developmental-stages can also modulate ATP-S-activity/expression under S-depleted conditions (Rotte and Leustek, 2000; Honsel et al., 2012). Confirmed by ATP-S protein-immunoblotting, ATP-S-activity exhibited a linear, threefold decline between 14 and 61 days after germination in S-depleted *A. thaliana* (Rotte and Leustek, 2000). Compared to young leaves, higher transcript-levels of *PtaATPS3/4* were reported in *Populus tremula* × *Populus alba* after 21 days of S-depletion (Honsel et al., 2012). Contrarily, S-depletion did not lead any change in *PtaATPS1/2*-expression in young leaves; whereas, this ATP-S isoform increasingly expressed after 9 days in mature leaves (Honsel et al., 2012). In *A. thaliana*, both S-deficiency (–S/–Cd) and Cd (+S/+Cd) regulated ATP-S activity (Bashir et al., 2013).

ATP-S gene-regulation has been discussed in different SO_4^{2-} -starved plants. *APS1*, *APS3*, and *APS4* genes can be targeted to regulate root-shoot- SO_4^{2-} -accumulation by miR395 (small conserved non-coding RNAs with 20–24 nucleotides, specific sizes, and dedicated functions; Liang and Yu, 2010; Liang et al., 2010). In *APS4-RNAi* transgenic *A. thaliana*, loss-of-function of *APS1* or/and *APS4*-genes can lead to 5-times higher SO_4^{2-} -accumulation in shoot (vs. wild-type plants). Additionally, enhanced miR395-expression in the absence of *APS4* was considered as an indicator of a negative-feedback-loop between miR395 and *APS4* (Liang et al., 2010). Moreover, unlike *APS1* and *APS4*-mRNA, both miR395 and *APS3* can exhibit a similar response to SO_4^{2-} starvation; however, *APS1* and *APS3*-expression can be regulated *via* miR395 (Liang and Yu, 2010). MiR395 can also cleave mRNAs encoding *ATPS1* and *ATPS4*-isoforms (Jones-Rhoades and Bartel, 2004; Kawashima et al., 2009). Nevertheless, *ATPS1* and *ATPS4* were evidenced as the major targets of miRNA (miR395), in both leaves and roots (Kawashima et al., 2009). In a similar report, SO_4^{2-} -limitation decreased *ATPS4*-transcript-levels; whereas, *ATPS1* levels were unaffected (Kawashima et al., 2011). It was argued in previous and other studies that for the SO_4^{2-} -limitation-mediated decreased *ATPS4*-transcripts that *ATPS4* can undergo a canonical regulation by miR395 because its mRNA levels can decrease following miR395-induction (Kawashima et al., 2009, 2011; Liang et al., 2010). SO_4^{2-} -deficiency cannot affect (Kawashima et al., 2011) or can bring a slight decrease in the levels of *ATPS1* mRNA (Liang et al., 2010). ATP-S activity/expression can also be controlled/modulated by S-Limitation 1 (SLIM1), a TF identical to Ethylene-Insensitive3-Like (EIL3) TF in *Arabidopsis* and the regulator of many S-deficiency responsive genes (Wawrzynska and Sirko, 2014). ATP-S-relation with ethylene is supported by the role of EIN3 and EIL1, two members of EI3/EIL TF family as central regulators of ethylene signaling (Maruyama-Nakashita et al., 2006). Relation among ATP-S-activity, GSH-content, ethylene-level, and decreased Cd-impacts was reported in Se-supplemented Cd-exposed *Triticum aestivum* (Khan et al., 2015). Nevertheless, a joint action of miR395 and SLIM 1 TF can maintain optimal-levels of ATP-S-transcripts in S-starved plants (Kawashima et al., 2011).

ATP-S: Roles and Regulations in Plant Biotic Stress Tolerance

Through different S-compounds such as Cys, GSH, and GSs, ATP-S is also involved in plant-tolerance to several biotic stresses. Free-Cys and cytosolic Cys-homeostasis can orchestrate plant-pathogen responses (Gullner and Kömives, 2001; Álvarez et al., 2012). Pathogen-infection can trigger accumulation of GSH and also the modulation of transient changes in its redox-state (Noctor et al., 2012). Elevated GSH and Cys were reported to suppress and delay virus-symptoms, and decrease virus-content in zucchini yellow mosaic virus (ZYMV)-infected *Cucurbita pepo* (Zechmann et al., 2005, 2007; Zechmann and Müller, 2008; Király et al., 2012). Decreased GSH-pool and its redox-state in *Lycopersicon esculentum* signify their role against *Botrytis*

cinerea infection (Kuźniak and Skłodowska, 2005). Elevated GSH metabolism can also counteract infection in plants with tobacco mosaic virus (Höller et al., 2010; Király et al., 2012), *Pseudomonas syringae* (Großkinsky et al., 2012) and *B. cinerea* (Simon et al., 2013). Zechmann (2014) recently reviewed the compartment-specific importance of GSH in biotic stressed plants.

Evidences confirm the requirement of a certain level of GSH for disease-resistance *via* synthesis of pathogen defense-related molecules such as camalexin, an indole-phytoalexin containing one S-atom per molecule with partly Cys-derived thiazole-ring (Noctor et al., 2012). A link between GSH-deficiency and plant-susceptibility to pathogens such as *Pieris brassicae* was reported in *A. thaliana phytoalexin deficient 2-1 (pad2-1)* mutant (Dubreuil-Maurizi and Poinssot, 2012). Earlier, a higher susceptibility of previous GSH-deficient-mutant to insect-herbivore *Spodoptera littoralis* was related with a lower GSs-accumulation therein (Schlaeppi et al., 2008). GSH (and also numerous GSH-sulfotransferases) is required for wound-induced resistance to *B. cinerea* (Chassot et al., 2008; Consonni et al., 2010). Expression of defense-related genes including *PATHOGENESIS-RELATED1 (PRI)* can be activated by exogenous-GSH-mediated mimicking of fungal-elicitors (reviewed by Noctor et al., 2012). Inner chloroplast-envelope-transporters export GSH across the chloroplast envelope. In *Arabidopsis*, *CLT1*, *CLT2*, and *CLT3* genes encode these transporters (Maughan et al., 2010). Decreased *PRI*-expression and also lower resistance to the oomycete *Pieris brassicae* were reported in CLTs-defective *Arabidopsis*-mutants (Maughan et al., 2010). Numerous reports support an increased S-requirement in plants infected with *Phytophthora infestans* and/or *B. cinerea* and was advocated to be met, at least in part, by increased transcription of *ATPS1*, *ATPS3*, and *ATPS4* genes (Matthewman, 2010). To this end, in *A. thaliana*, ATP-S genes namely *ATPS1* and *ATPS3* were reported to be linked with the regulation of biosynthetic networks of aliphatic and indolic GSs, respectively (Yatusevich et al., 2010). *P. infestans* and *B. cinerea*-infection in *A. thaliana* resulted in a similar increase in the transcript levels of *ATPS1*, *ATPS3* and *ATPS4* (Matthewman, 2010). Earlier, *B. cinerea*, *P. infestans*, and aphid *Myzus persicae* were reported to induce a GSs-response in *Arabidopsis* (Kim and Jander, 2007; Rowe et al., 2010).

ATP-S: Intrinsic Regulations by S-Compounds

Literature is scarce on insights into S-compounds-mediated regulation of ATP-S activity/expression in plants. Among the thiol-compounds, GSH, rather than Cys can be used as a signal for regulating ATP-S (Lappartient et al., 1999; Vaclare et al., 2002). Externally supplied GSH-mediated increase in Cys and GSH accumulation can control both ATP-S activity and SO_4^{2-} -uptake (Vaclare et al., 2002). Compared to its lower level (up to 1.0 mM), Cys can significantly decrease ATP-S-activity at its higher level (2.0 mM). However, further increase in Cys-concentration can cause an additional accumulation of GSH that in turn can cause a decrease in ATP-S-mRNA, -protein, and -activity (Lappartient et al., 1999;

Vauclare et al., 2002). ATP-S enzymatic activity might be sensitive to redox regulation in plants, where it can be a target for thioredoxins (reviewed by Prioretti et al., 2014). As a major redox regulator, GSH feeds into glutaredoxin system

and subsequently into the thiol-redox-network (Dietz, 2008). Referring to the studies of Lappartient and Touraine (1996, 1997), cellular-redox-conditions and also that of GSH were advocated to modulate ATP-S-activity (reviewed by Yi et al., 2010).

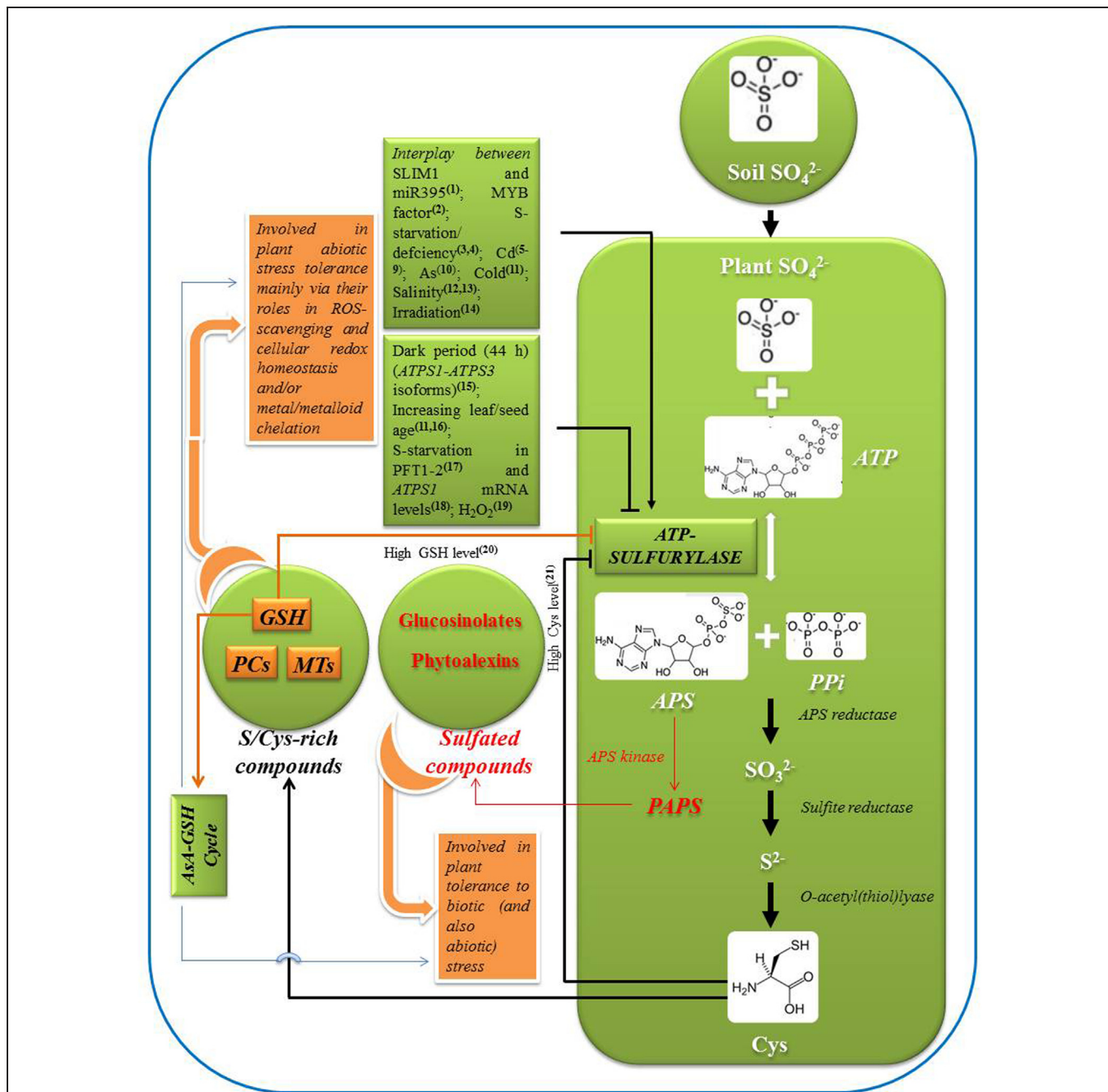


FIGURE 1 | Schematic representation of pathway of sulfate assimilation, reaction catalyzed by ATP-sulfurylase (ATP-S), and its regulation by major factors. Role of ATP-S in plant stress tolerance through sulfur/cysteine rich and sulfated compounds is outlined. Positive and negative regulation of ATP-S is indicated by arrows and blunt ends, respectively, [1Kawashima et al. (2011); 2Yatusevich et al. (2010); 3Hopkins et al. (2004); 4Schiavon et al. (2007); 5van de Mortel et al. (2008); 6Guo et al. (2009); 7Gill et al. (2012); 8Bashir et al.

(2013); 9Asgher et al. (2014); 10Leao et al. (2014); 11Phartiyal et al. (2006); 12Ruiz and Blumwald (2002); 13Nazar et al. (2011); 14Passera et al. (1989); 15Huseby et al. (2013); 16Rotte and Leustek (2000); 17Takahashi et al. (1997); 18Liang et al. (2010); 19Lappartient and Touraine (1997); 20Lappartient and Touraine (1996); 21Vauclare et al. (2002)]. (APS, adenosine 5'-phosphosulfate; Cys, cysteine; AsA, ascorbate; GSH, reduced glutathione; PCs, phytochelatin; MTs, metallothionein; ROS, reactive oxygen species).

However, the authors suggested further biochemical- and structural-analysis of ATP-S to determine how, and to what extent, ATP-S responds to redox-changes. MiR395 is related with ATP-S-genes such as *APS1*, *APS3*, and *APS4* (Liang et al., 2010). Recently, GSH-supplementation was reported to block accumulation of S-deprivation-inducible miR395 in S-deprived *A. thaliana* (Jagadeeswaran et al., 2014). Declined GSH-pools and induced miR395-levels in S-deprived *A. thaliana* were cross-talked (Kawashima et al., 2011; Matthewman et al., 2012). Nevertheless, biosynthesis of indolic-GSs in *A. thaliana* is regulated by MYB34, MYB51, and MYB122 TFs (Frerigmann and Gigolashvili, 2014). In *A. thaliana*, expression of both *ATPS1* and *ATPS3* isoforms was reported to be controlled by all six GSs-related MYB TFs namely MYB28, MYB29, and MYB76; MYB51, MYB34, and MYB122 (Yatusevich et al., 2010). *ATPS1* and *ATPS3* were expected to be strongly associated with the control of synthesis of aliphatic and indolic GSs, respectively. *A. thaliana* overexpressing or disruption in MYB51-gene showed alterations in ATP-S-transcript-levels and -activity (Matthewman, 2010; **Figure 1**).

Conclusion and Open Questions

S-containing compounds such as Met, GSH, h-GSH, PCs, and GSs, directly or indirectly modulated/regulated by ATP-S are involved in plant tolerance to both biotic and abiotic stresses. Much has been achieved on the subject considered herein; there remain numerous aspects to be enlightened and open-questions to be answered. Ample scope exists for getting more molecular-genetic insights into the energetically unfavorable-reaction that yields APS from SO_4^{2-} and ATP with ATP-S-catalytic-function. Notably, compared to APR enzyme and its encoding genes, much less amplitude and significance has been given to ATP-S in mutant-experiments. Hence, molecular-genetic dissection of so far neglected significance of ATP-S as a major control in the initial step of S-assimilation pathway is required. ATPS has

been evidenced as an integral part of GS-biosynthesis-regulatory network (Matthewman, 2010); however, unveiling insights into interrelationship of ATP-S transcripts with other secondary S-assimilation products will be rewarding. Though picture is clear regarding the relationship of *ATPS1* and *ATPS3*-expression with MYB TFs (Yatusevich et al., 2010) effort is required to unveil potential relationships of MYB TFs with *ATPS2* and *ATPS4*-expression (Prioretti et al., 2014). If done, these studies may shed light on the complexity of regulatory interactions between primary and secondary S-metabolism. Efforts are also required to dissect the molecular biology/genetics of interaction of ATP-S with ratios of oxidized and reduced GSH (GSSG/GSH) and that of oxidized (dehydroascorbate, DHA) and reduced ascorbate (AsA; DHA/AsA) in stressed plants since DHA can be recycled back to AsA at the expense of GSH (or NADPH) by the AsA-GSH cycle-enzymes (Anjum et al., 2010). Role of miR395 family of micro-RNAs in the regulation of *ATPS1-4* is known (Maruyama-Nakashita et al., 2006; Kawashima et al., 2011); however, picture is unclear in context with functions and effects of miR395 on *ATPS3* and *ATPS4*-expression. A cross-talk among GSH-pools, miR395-levels and ATP-S-transcripts/activity particularly under deprived condition of interdependent nutrients S and N can also be significant for the maintenance of the status of S-compounds, and S-N homeostasis.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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