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Glutathione as a signaling molecule
Another challenge to pathogens

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Plants harbor a variety of signaling molecules which are members of a vast array of signaling networks in maintaining their physiological balance. The well known members up till now are salicylic acid (SA), jasmonic acid (JA), ethylene (ET), abscissic acid (ABA) and reactive oxygen species (ROS) which are employed by plants for their adaptation to various environmental stresses in order to survive. GSH is gradually gaining importance and becoming a molecule of interest to a number of researchers especially in relation to plant defense to pathogens. Although the role of GSH in plant defense has long been known, a dearth of information still exists regarding the mechanism underlying this defense response. This review highlights on the progress made in the cross-communication of GSH with other established signaling molecules through which GSH acts in abating biotic stress.

Glutathione, popularly known as the "master anioxidant" or "super defender," is a nearly ubiquitous non-protein tripeptide thiol compound found in both prokaryotes and eukaryotes[1-3] except for some organisms which use different other thiol cofactors. This molecule helps to prevent or even reduce the effect of certain human diseases which are of major concern in today's world including cancer, inflammation, kwashiorkor, Alzheimer's disease, Parkinson's disease, sickle cell anaemia, liver disease, cystic fibrosis, HIV, AIDS, infection, heart attack, stroke and diabetes. GSH, in animals, participates in the detoxification of ROS and xenobiotics, plays a major role in cell proliferation and death, DNA synthesis and repair, regulation of protein synthesis, prostaglandin synthesis, amino acid transport and enzyme activation, maintains essential thiol status, regulates immune functions, plays a role in spermatogenesis and sperm maturation and so on. In prokaryotes, GSH is one of the most abundant thiols as well and is present in cyanobacteria and proteobacteria. In bacteria, in addition to its key role in maintaining the proper oxidation state of protein thiols, GSH also serves a key function in protecting the cell from the action of low pH, chlorine compounds and oxidative as well as osmotic stresses.

The well known functions performed by this molecule in plants are as a major player in redox chemistry, heavy metals and electrophilic xenobiotics elimination, serving as electron donor for biochemical reactions, long-distance transport of reduced sulfur, stress defense gene expression, posttranslational modifications through glutathionylation, role in biotic and abiotic stresses and so on.[4-13] Over the past three decades, GSH has been known to be involved in defense reactions against a variety of pathogens in addition to the induction of various defense genes. GSH when supplied at various concentrations to the cell suspension culture of bean induced several genes encoding enzymes that participate in the biosynthesis of lignin and phytoalexins.[14] Early reports also found that GSH supplementation partly mimicked induction of chalcone synthase, the expression of which occurs as a result of fungal elicitor stimulation in soybean.[15] Bean and soybean cells treated with fungal elicitor or GSH causes the rapid insolubilization of hydroxy-proline-rich structural proteins in the cell wall.[16] Previous report also revealed that significant increase in GSH levels occurred as a result of enhanced resistance of melon and tomato roots against *Fusarium oxysporum* brought about by herbicides.[17] In compatible barley-barley powdery mildew interactions the ascorbate-GSH cycle and other antioxidative enzymes (e.g., glutathione *S*-transferase) are activated and these processes might diminish the damaging effects of oxidative stress. However, in incompatible interactions these antioxidative reactions are not or are only slightly activated.[18] A considerable accumulation of GSH and, in particular, oxidized glutathione (GSSG) has been observed in tomato cells carrying *Cf-9* or *Cf-2* resistance genes after treatment with race-specific elicitors of the fungus *Cladosporium fulvum*.[19] Ball et al. reported that 32 stress-responsive genes were altered due to changed GSH metabolism in Arabidopsis *rax1-1* and *cad2-1*, mutants of γ-ECS. Previous studies also reported that Arabidopsis *pad2-1* mutant with only 22% of wild-type amounts of GSH were susceptible to *Pseudomonas syringae* as well as *Phytophthora brassicae*.[20-22] Additionally, according to a recent report, enhanced resistance of transgenic tobacco with enhanced level of GSH was observed against *P. syringae*.[23]

Recent reports have found the role of GSH in cell signaling and in signaling pathways induced by different phytohormones. This review was an effort to throw some light on understanding the role of GSH as a signaling molecule by discussing the interrelationship of this multi-faceted molecule with other established signaling molecules which have well documented signaling roles in plants against biotic and abiotic stresses.

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Crosstalk with SA

When plants face pathogen ingress, a blend of various defense reactions come into play. One of the major players that come into the scenario in this situation is SA. A substantial body of evidence indicates that SA is a critical signaling molecule in the pathway(s) leading to local and systemic disease resistance.[24] SA is synthesized by plants in response to a variety of phytopathogens thus leading to the establishment to both local and systemic acquired resistance (SAR) for its own survival. SAR is characterized by the coordinate activation of a set of PR genes which encode for proteins, many of which have antimicrobial activity.[25] SA signaling is mediated by at least two mechanisms, one requiring NPR1 and a second that is independent of NPR1.[26,27] NPR1 is an essential regulator of plant SAR which contributes to the immunity of plants. It is a central positive regulator of systemic defense and functions in multiple nodes of SA signaling network. In uninduced state, NPR1 exists as an oligomer, but after SAR induction, NPR1 is reduced to its monomeric i.e., the active form. Increase in SA triggers the reduction of disulphide bonds located on both the regulatory protein NPR1 and on certain TGA transcription factors with which NPR1 interacts.[28,29] Additionally, it has also been demonstrated that the SA-induced NPR1 oligomer-to-monomer reaction is regulated by thioredoxin through reduction or oxidation of its intermolecular disulphide bonds.[30] This reduction stimulates both the translocation of NPR1 from the cytosol to the nucleus and the physical interaction of NPR1-TGA1 that is necessary for the activation of *PR* gene transcription.[28,29] Interestingly, it has been observed that the resistance of plants to biotrophic pathogens is classically thought to be mediated through SA signaling, while that of necrotrophs is dealt with by JA or ET.[31,32] Crosstalk among the signaling pathways provides the plant facing pathogen ingress with the power to tailor its defense responses according to its needs and antagonism between SA and JA is a widely accepted fact.[32,33]

Studies over the past decades have evidenced the relationship between GSH and SA in various stress responses. Measurement of glutathione levels in response to SA treatment revealed an increase in the GSH content and a decrease in the GSSG, along with an increased GSH:GSSG ratio in pea seedlings.[34] According to a previous report, the induction of SAR by treatment with isonicotinic acid (INA), the analog of SA as well as infection with *P. syringae*, the biotrophic pathogen led to the increase in total glutathione content as well as GSH:GSSG ratio.[28] Constitutive overexpression of SA was shown to induce GSH-mediated nickel tolerance in Thlaspi hyperaccumulators.[35] The GSH biosynthesis inhibitor l-buthionine sulfoximine (BSO) strongly reduced the suppression of the JA-responsive gene *PDF1.2* by SA, which suggests that SA-mediated modulation of the cellular redox state is an important trigger for the attenuation of JA signaling.[36] According to yet another study, protection of ozone-induced leaf injury in Arabidopsis by SA occurred by increasing de novo biosynthesis of GSH.[37] A recent report has shown that GSH status regulates SA and other pathways involved in biotic stress responses at several levels in Arabidopsis, including SA-accumulation and JA-linked gene expression.[8] A recent report has shown that transgenic tobacco with enhanced level of GSH were resistant to *P. syringae* and constitutively expressed genes of the NPR1-dependent SA-mediated pathway.[23] Interestingly, studies with a number of pathogens as discussed earlier, to decipher the role of GSH in biotic stress tolerance, are biotrophic in nature. Considering these studies, it is clear that crosstalk between GSH and SA exists in plants (**Fig. 1**).

Crosstalk with JA

The role of JA in defense has been reported in previous studies in reference 38–40. JA-dependent signaling also comes into play in pathogen attack, especially necrotrophs, through increased JA synthesis and marked by consequent increases in expression of defense effector genes such as *PDF1.2*. JA signaling also results from wounding and insect feeding. The JA signal pathway involves several signal transduction events: the perception of the primary wound or stress stimulus and transduction of the signal locally and systemically, the perception of this signal and induction of JA biosynthesis, the perception of JA and induction of responses and finally, integration of JA signaling with outputs from the SA, ET and other signaling pathways.[40] JA is better known to play antagonistic actions with SA in defense signaling.

JA treatment increased mRNA levels and the capacity for GSH synthesis but did not alter the GSH content in unstressed plants.[41] In tobacco, GSH-dependent formaldehyde dehydrogenase (FALDH) levels and enzymatic activity decreased after JA treatment and increased in response to SA.[42] Recent study has shown that JA led to the increase in GSH metabolism under water stress in *Agropyron cristatum,* thus suggesting that water stress-induced JA is a signal that leads to the regulation of GSH metabolism and has important role for acquisition of water stress tolerance in *A. cristatum*.[43] The involvement of intracellular GSH has also been studied in methyl jasmonate (MeJA) signaling.[44]

Crosstalk with ET

ET is a gaseous phytohormone that is well known for its role in developmental processes in plants. In addition, it has evolved to play signaling roles in plants and participate in crosstalk with other signaling molecules. In most of the cases, the relationship between ET and JA is synergistic one like in case of defense against necrotrophic pathogens.[32,33] In contrast, synergistic interaction of ET with SA, the antagonist of JA has also been reported. ET has been shown to be essential for the onset of SA-dependent SAR that is triggered upon infection by tobacco mosaic virus.[45] Moreover, ET was shown to enhance the response of Arabidopsis to SA, resulting in a potentiated expression of the SA-responsive marker gene *PR1*. This synergistic effect of ET on SA-induced *PR1* expression was blocked in the ET-insensitive mutant *ein2*.[46,47]

ET has been reported to control GSH biosynthesis positively in ozone exposed Arabidopsis leaves.[35] In ET signaling mutants, *ein2-1*, GSH-dependent Pb(II) resistance, which was related to constitutive reduction of expression of gamma-glutamyl synthetase (γ-ECS) gene involved in GSH synthesis consequently led to

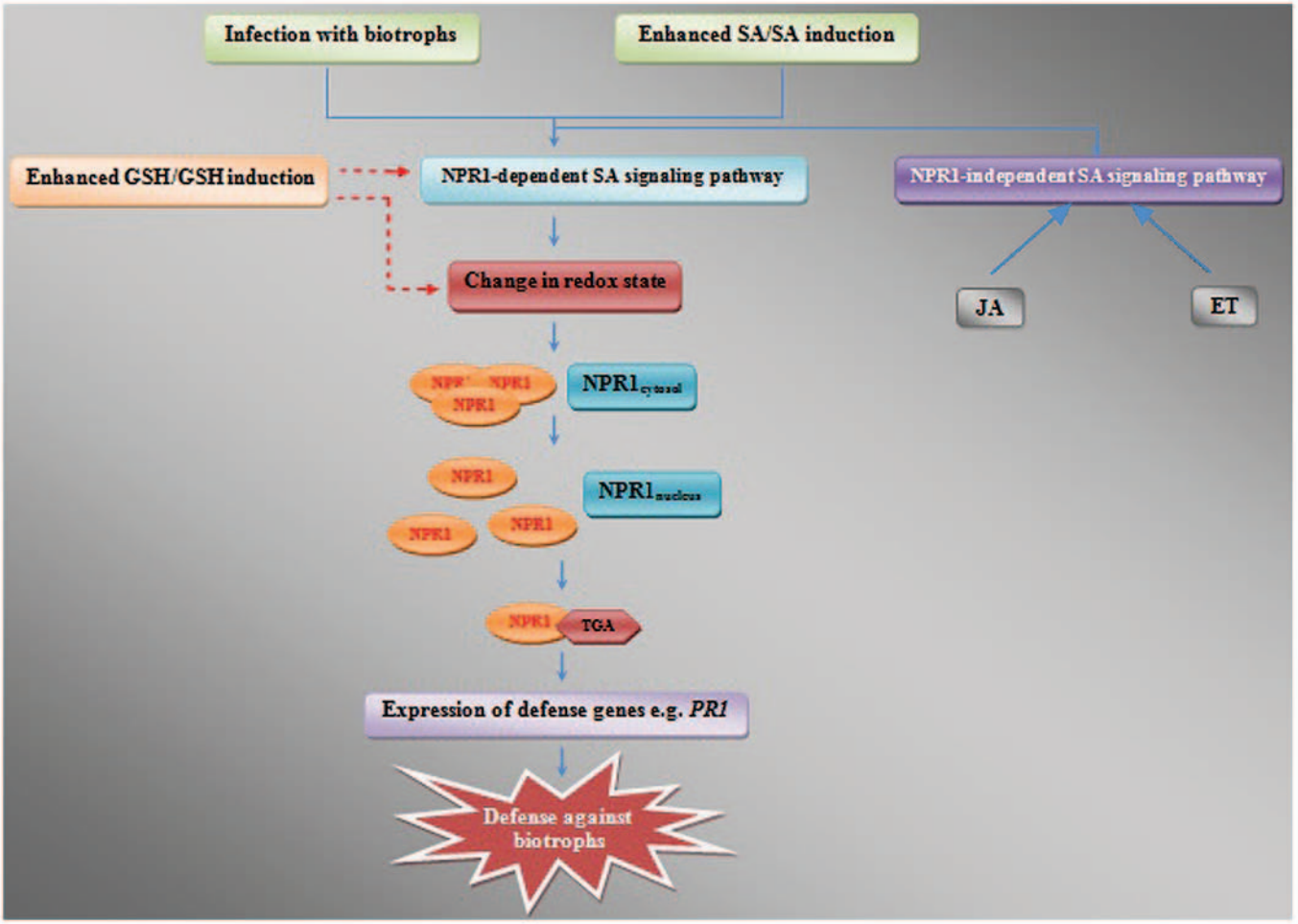

Figure 1. Position and involvement of GSH in the signaling web in plants. GSH has been known to participate in biotic stress tolerance by NPR1-dependent SA-mediated pathway. Only those signal transduction components relevant to this review has been shown. Continuous lines: established signaling pathways; broken lines: proposed signaling pathway.

reduced GSH content.[48] In transgenic tobacco with genetically enhanced level of GSH, the expression levels of *PR4*, the marker of ethylene signaling and ACC oxidase, that oxidizes ACC to ET were found to be enhanced thus demonstrating the synergism between GSH and ET.[23] However, further study is required in this field before making a statement on the interrelationship.

Crosstalk with ROS

Aerobic life forms are known for continuous formation of ROS, the damaging end-products of aerobic energy which were first and still now widely described as deleterious since they can provoke cellular damage.[49] One of the earliest observable aspects of plant's defense strategy is oxidative burst, which is a rapid and transient production of huge amounts of ROS.[50] Although ROS have been mainly associated with pathogen attack, they are also detected in other biotic interactions including beneficial symbiotic interactions with bacteria or mycorrhiza, suggesting that ROS production is a common feature of different biotic interactions.[51] They are powerful signaling components linking growth, metabolism and defense responses in cells.[52-55] ROS is now largely admitted to play a signaling role in stomatal closure,[56] various cellular mechanisms,[57] regulation of gene expression,[57,58] cellular growth[59] and plant's defense system against pathogens.[60] The role of GSH in the regulation of abiotic stress conditions have been reviewed in reference 61.

GSH being the most abundant non-protein thiol, qualifies as the "master antioxidant" among researchers, serves as a redox buffer and occurs to be at the centre of a complex antioxidant network in plants thus maintaining the intracellular environment reduced.[62,63] Redox state of cells is largely maintained by the concentration and ratio of GSH and GSSG. Activation of GSH synthesis and accumulation of GSH is a general feature of enhanced oxidation of the cytosol. Exposure to GSH is involved in both the direct and indirect control of ROS concentrations.[5,64,65] For instance, GSH takes part in the removal of H_2O_2 in a reaction in which the thiol group of cysteine in GSH is oxidized to form GSSG.[64] The reverse reaction is catalyzed by glutathione reductase (GR) using NADPH. A highly reduced GSH pool is required for active protein function. Because both the levels and

oxidation state of GSH are directly influenced by ROS, GSH is a key redox-signaling component.[6,65-68] In addition to its participation in direct detoxification of ROS, GSH may also protect cells against unfavorable stress effects through the activation of various defense mechanisms due to its involvement in redox signaling.[4,60,65,69-71] In this signaling pathway, GSH interacts with ROS, redox molecules (thioredoxins [Trxs], glutaredoxins [Grxs]) and plant hormones (SA, ABA). Additionally, regulatory functions for ROS in defense particularly the response to pathogen infection occur in conjunction with other plant signaling molecules, especially with SA and nitric oxide (NO).[69,72] Increasing evidence supports the idea that SA also plays a role in controlling the cellular redox balance at the onset of the SAR[28,73,74] thus demonstrating the crosstalk between these two signals. It is well known that production of ROS is a key event in hypersensitive response (HR) and antioxidant redox systems like that of GSH are involved in the activation of both compatible and incompatible plant responses by alterations in its level, redox state as well as in the activity of redox enzymes.[75] NO is also a major player in defense to pathogens.[76] It has been reported earlier that changes in the ascorbate and GSH metabolisms caused by the interplay between NO, ROS and plant cells can be part of the transduction signals that triggers programmed cell death.[77]

Crosstalk with ABA

Apart from SA, JA, ET and ROS which are most well documented in defense signaling, ABA also has a prominent role in biotic stress. Earlier it was known that although it acts as a negative regulator of disease resistance, ABA can also promote plant defense and is involved in a complicated network of synergistic and antagonistic interactions depending upon the nature of pathogen.[78] ABA is connected to the SA-JA-ET network, as it was shown to attenuate JA/ET-dependent gene expression[79] and to affect JA biosynthesis and resistance against JA-inducing necrotrophic pathogens.[80,81] Moreover, ABA was demonstrated to antagonize the onset of SA-dependent defenses and SAR.[82,83]

Relationship between GSH and ABA has been studied earlier. In two maize genotypes differing in their stress tolerance, ABA differentially affected the GSH content, GSH:GSSG ratio, GR activity and γ-ECS transcript level.[84] However, according to a recent report, the GSH content did not vary in potato tubers treated with ABA.[85]

Conclusions and Perspectives

In plant systems, though extensive research has been carried out to elucidate the roles of the multi-faceted molecule, GSH, the mechanism through which biotic stress tolerance against various phytopathogens occurs, is still a potential area of research. Considering the studies undergone to decipher the cross-communication of GSH with other established signaling molecules, it is clear that GSH has a distinct standpoint in the rather complicated signaling pathway crosstalk that exists in plant system. Substantial body of evidence has been gathered regarding the synergism of GSH with the much acclaimed signaling molecule SA. Accumulated evidence have indicated that GSH plays an important role in mitigating biotic stress likely through NPR1-dependent SA-mediated pathway. However, further studies and experimental evidences are essential to elucidate the relationship of GSH with JA and ET as well as the involvement of other molecular players of signaling, to gather a complete scenario about the signaling web in plants and the defense mechanisms in response to pathogen invasion.

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