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REVIEW

Protein *S*-nitrosylation in programmed cell death in plants

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Abstract

Programmed cell death (PCD) is associated with different phases of plant life and provides resistance to different kinds of biotic or abiotic stress. The redox molecule nitric oxide (NO) is usually produced during the stress response and exerts dual effects on PCD regulation. *S*-nitrosylation, which NO attaches to the cysteine thiol of proteins, is a vital posttranslational modification and is considered as an essential way for NO to regulate cellular redox signaling. In recent years, a great number of proteins have been identified as targets of *S*-nitrosylation in plants, especially during PCD. *S*-nitrosylation can directly affect plant PCD positively or negatively, mainly by regulating the activity of cell death-related enzymes or reconstructing the conformation of several functional proteins. Here, we summarized *S*-nitrosylated proteins that are involved in PCD and provide insight into how *S*-nitrosylation can regulate plant PCD. In addition, both the importance and challenges of future works on *S*-nitrosylation in plant PCD are highlighted.

Keywords Protein *S*-nitrosylation · Programmed cell death · Plants

Introduction

Programmed cell death (PCD), the process of cellular suicide, is encoded genetically and actively controlled [1]. Although it is not clear how many types of PCD exist in plants, based on a PCD classification criterion, van Doorn classified plant PCD into 'autolytic' PCD and 'non-autolytic' PCD according to the tonoplast rupture and the cytoplasm subsequent rapid destruction [2]. PCD is involved in plant growth and development such as differentiation of tracheary elements [3] and xylogenesis of pioneer roots [4, 5], development of cereal aleurone cells [6], leaf senescence [7] and floret development [8]. Actually, PCD processes in plants are associated not only with the development of regular specific cell types or tissues but also with their immune responses, which are induced by various biotic stresses, such as plant–pathogen interactions, and abiotic stresses, such as extreme temperature, excessive light and UV radiation, water deprivation, high salinity, high concentrations of heavy metals, and herbicide activity [9–11]. Reactive oxygen species (ROS) and nitrogen species (NOS) are two kinds of redox molecules that are active in plant responses to biotic or abiotic stresses. Among them, nitric oxide (NO) has been reported to have dual effects on PCD during plant stress responses. For example, a negative role of NO in resistance against Cd^{2+}-induced PCD was found in tobacco Bright Yellow-2 (BY-2) cells [12] and yellow lupine plants [13]. Conversely, a positive role of NO in delaying gibberellin-induced PCD [14] and strengthening resistance to the pathogen-induced hypersensitive response (HR) [15] has also been reported.

S-nitrosylation, an important posttranslational modification in which a NO moiety covalently and reversibly binds to a cysteine thiol forms a nitrosothiol, has been investigated in plants over the past few years. *S*-nitrosylation is thought to account for the influence of NO on cellular signaling via redox-based biochemical regulation of signaling components [16]. *S*-nitrosylation can regulate the sequences of proteins involved in all major cellular activities [17]. Recently, investigations of *S*-nitrosylation in plants have focused mainly on the identification of numerous protein candidates via proteomic analyses, and biochemical and computer structural studies have shown that the mechanisms of *S*-nitrosylation impact the structures of those proteins and thus their function [18, 19]. *S*-nitrosylation may be responsible for the PCD process in plants by regulating the activities of enzymes that mediate cell death-related signals or by reconstructing the

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functional domains of some functional proteins in plants, resulting in the PCD process [20, 21]. Reviews about the various test methods of *S*-nitrosylation in plants and the effects of *S*-nitrosylation on plant growth, development and resistance to stresses have been published. However, to date, no reviews have highlighted the roles of protein *S*-nitrosylation in PCD regulation in plants. Thus, in this review, we summarized the *S*-nitrosylated proteins that are involved in metabolism and photosynthesis, salicylic acid (SA) signaling, ROS-dependent signaling and other pathways in the PCD process, which provides insight into how *S*-nitrosylation regulates plant PCD.

ROS-related proteins

In plants, ROS and NO have been proposed to be the key factors involved in the signaling of PCD induced during the HR, senescence, self-incompatibility, and the response to metal and heat stress (HS) [22–24]. In the PCD process, NO interacts with ROS to influence redox homeostasis. For example, NO regulates ROS levels by inhibiting NADPH oxidase via *S*-nitrosylation [20]. Similarly, NO affects ROS levels via *S*-nitrosylation of antioxidant enzymes such as ascorbate peroxidase (APX) and peroxiredoxins (Prxs) in PCD (Fig. 1) and protects plants from various biotic and abiotic stresses [1]. Therefore, *S*-nitrosylation of ROS-related proteins is one of the important ways by which plants regulate PCD.

Ascorbate peroxidase (APX)

APX is one of the key factors in the ascorbate–glutathione (GSH) cycle and regulates the level of cellular hydrogen peroxide (H_2O_2), which is distributed throughout all cell compartments in higher plants [25]. APX catalyzes the electron transfer from ascorbate to H_2O_2, which produces dehydroascorbate and water, to scavenge H_2O_2 [26, 27]. Exogenous NO could inhibit the activities of APX in tobacco suspension cells, although the activity significantly recovered when NO was removed, suggesting that NO might participate in defense responses by affecting APX activity under pathogen attack [28]. Lin et al. also proved that NO and protein *S*-nitrosylation were integral to H_2O_2-induced leaf cell death in rice (*Oryza sativa*) NO excess1 (*noe1*) plants [29]. In HS- and H_2O_2-induced PCD of tobacco BY-2 cells, cytosolic ascorbate peroxidase (cAPX) was found to be *S*-nitrosylated [21]. In vivo and in vitro experiments showed that cAPX *S*-nitrosylation could be responsible for the rapid decrease in cAPX activity, and *S*-nitrosylated cAPX1 caused the ubiquitination of cAPX1, resulting in degradation [21]

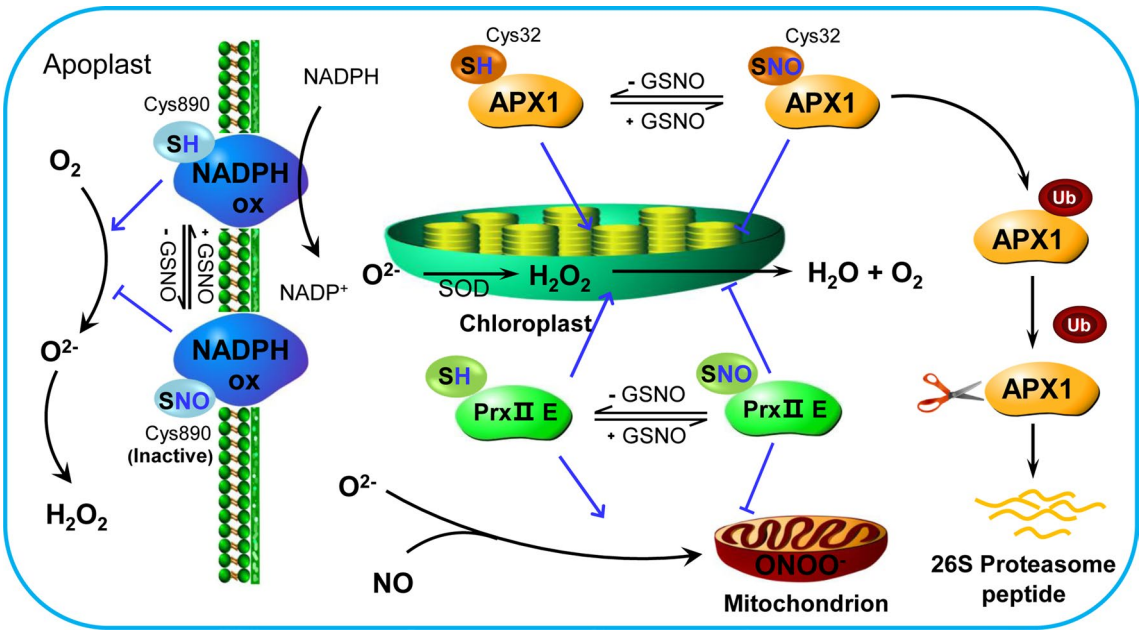

Fig. 1 *S*-nitrosylation of ROS-related proteins involved in PCD regulation. NADPH oxidase can synthesize ROS, while *S*-nitrosylation at Cys-890 inactivates NADPH ability, inhibiting ROS production. *S*-nitrosylation of two antioxidant enzymes, APX1 and PrxII E, also affect ROS accumulation. *S*-nitrosylation of APX1 at Cys-32 regulates APX1 activity, leading to APX1 ubiquitination and therefore leading to degradation. *S*-nitrosylation of PrxII E not only inhibited its activity of H_2O_2-reducing peroxidase but also reduced its ability to detoxify $ONOO^-$, leading to the accumulation of toxic O^{2-} and consequently causing PCD after *Pst* infection. *NADPH ox* respiratory burst oxidase homolog, O^2 oxygen, O^{2-} superoxide anion, H_2O_2 hydrogen peroxide, *APX1* ascorbate peroxidase 1, *SOD* superoxide dismutase, *PrxII E* peroxiredoxin II E, *Ub* ubiquitination

(Fig. 1). Thus, APX *S*-nitrosylation may be a potential way by which plants regulate PCD.

APX is a potential target of endogenous *S*-nitrosylation in *Arabidopsis* [30] (Table 1). The same result in Arabidopsis roots was reported by Correa-Aragunde et al., which was further verified in vitro via an APX recombinant [30]. *S*-nitrosylated recombinant APX1 caused an increase in its own activity, which contrasts with the results of De Pinto et al., who reported that APX S-nitrosylation inhibited the enzyme's activity in the PCD process [21]. Despite this contradiction, these two experiments revealed that APX *S*-nitrosylation could indeed regulate the activity of APX. Furthermore, multiple alignments of the amino acid sequences and the model structure prediction of *Arabidopsis* APX1 showed that, among the five cysteine residues present in *Arabidopsis* APX1, Cys-32 and Cys-168, two residues mostly conserved in plants, were candidate sites of *S*-nitrosylation [31]. Yang et al. reported that *Arabidopsis* APX1 was *S*-nitrosylated efficiently in vitro under normal growth conditions [32]. The results of liquid chromatography (LC)–tandem mass spectrometry (MS/MS) analyses and 2,3-diaminonaphthalene (DAN) assays suggested that Cys-32 and Cys-49 were the *S*-nitrosylated residues in APX1, which was further verified in $APX1^{C32S}$ and $APX1^{C49S}$ mutants. Structure modeling analysis also revealed that both the locations and the surrounding environment of Cys-32 and Cys-49 were largely in line with the consensus motif of *S*-nitrosylation. However, the authors further confirmed that the enzymatic activity of the Cys-49 recombinant was similar to that of the wild-type; this result differed from that of Cys-32, which increased APX1 activity in the presence of with *S*-nitrosoglutathione (GSNO), indicating that Cys-49 might not play a role in regulating APX1 activity [32]. Thus, *S*-nitrosylation of APX1 at Cys-32 can positively regulate APX1 activity, thereby regulating the immune response in plants. With respect to recombinant pea cAPX, APX1 was *S*-nitrosylated at Cys-32, and APX *S*-nitrosylation increased under saline conditions [33], suggesting that APX *S*-nitrosylation could contribute to alleviating oxidative damage induced by salinity stress.

The present study, therefore, provides new insight into the mechanism of the regulation of APX activity via *S*-nitrosylation mediated by NO-derived molecules. Interestingly, the effects of NO on APX activity are controversial. There are two reasons for this controversy. First, the *S*-nitrosylation of APX is reversible, whereas the tyrosine nitration of APX is irreversible, both of which lead to an inhibition of APX activity [33]. Second, other APX proteins (with the exception of APX1, which accounts for nearly 70% of APX activity) may either be regulated by NO or not, but this regulation is hard to detect since the altered activity is below the detection limit under assay conditions [32]. Overall, investigations on APX *S*-nitrosylation in plant immunity are still scarce, and the detailed molecular mechanisms of APX *S*-nitrosylation need to be further elucidated.

Table 1 List of *S*-nitrosylated proteins involved in programmed cell death in plants

Protein name		Plant species	Tissue types	Effect of *S*-nitrosylation	References
Ascorbate peroxidase 1	APX1	*N. tabacum*	BY-2 cells	Inhibition of activity and ubiquitination	[15]
		A. thaliana	Seedlings	Activation of activity	[25, 26]
NADPH oxidases	RBOHD	*A. thaliana*	Leaves	Inhibition of activity	[14]
Peroxiredoxins	PrxII E	*A. thaliana*	Seedlings	Inhibition of activity	[35]
	PrxII F	*P. sativum* L.	Seedlings	Inhibition of activity and conformational changes	[36, 37]
Salicylic acid-binding protein 3	AtSABP3	*A. thaliana*	Seedlings	Inhibition of activity and SA binding	[43]
Nonexpresser of Pathogenesis-Related Genes 1	NPR1	*A. thaliana*	Seedlings	Conformational changes	[46]
TGACG motif binding factor1	TGA1	*A. thaliana*	Leaves	Conformational and DNA/NPR1-binding behavior changes	[50]
Glyceraldehyde 3-phosphate dehydrogenase	GAPDH	*A. thaliana*	Suspension cells	Inhibition of activity	[59, 61]
		N. tabacum	BY-2 cells	Inhibition of activity	[56]
Ribulose-1,5-bisphosphate carboxylase/oxygenase	Rubisco	*B. juncea*	Seedlings	Inhibition of activity	[63]
		K. pinnata	Seedlings	Inhibition of activity	[53]
S-nitrosoglutathione reductase	GSNOR	*A. thaliana*	Seedlings	Selective autophagy	[73]
Metacaspase-9	AtMC9	*A. thaliana*	Seedlings	Inhibition of autoprocessing and activity	[80]

N.tabacum, Nicotiana tabacum; *A.thaliana, Arabidopsis thaliana; P. sativum L., pisum sativum L.; B.juncea, Brassica juncea; K.pinnata, Kalanchoe pinnata*

NADPH oxidases (RBOHs)

In plants, extracellular reactive oxygen intermediates (ROIs) can drive PCD and this phenomenon is correlated with stress responses—HR. ROIs derived from the oxidative bust in the HR are produced usually by plasma membrane NADPH oxidases [34]. NADPH oxidases are also considered as RBOHs. As the major producers of ROS, NADPH oxidases transfer electrons from cytoplasmic NADPH or NADH to oxygen (O_2) to form superoxide anions (O^{2-}), and O^{2-} is then converted into H_2O_2 by superoxide dismutase [35] (Fig. 1). ROIs generated by NADPH oxidases can suppress the spread of cell death in *Arabidopsis* [36]. This suppression might be due to the antagonistic effect of ROIs on SA-dependent death-promoting signals, thereby suppressing cell death in cells surrounding sites of NADPH oxidase activation. *S*-nitrosylation is another way to regulate RBOHD activity during effector-triggered immunity [37]. High *S*-nitrosothiol (SNO) concentrations could limit the HR via *S*-nitrosylation of NADPH oxidase in *Arabidopsis* [37]. When leaves were exposed to GSNO and *S*-nitroso-L-cysteine (Cys-NO), the activity of NADPH oxidase was reduced, although this effect was absent in the presence of reduced GSH and dithiothreitol (DTT). NADPH oxidase activity was also significantly reduced in *atgsnor1-3* and *nox1* plants (*atgsnor1-3* and *nox1* had high SNO concentrations) that were challenged with the bacterial pathogen *Pseudomonas syringae* pv. *tomato* (*Pst*) DC3000 (*avr*B). AtRBOHD is *S*-nitrosylated in a GSNO or Cys-NO concentration-dependent manner. BST and computer model structure analysis revealed that Cys-890 in the C-terminal portion of AtRBOHD was the site of S-nitrosylation [20] (Fig. 1). AtRBOHD *S*-nitrosylation at Cys-890 impeded flavin adenine dinucleotide (FAD) binding, thereby inhibiting the activity of AtRBOHD. The biological consequence of AtRBOHD *S*-nitrosylation was the prevention of ROI synthesis, ultimately inhibiting PCD in response to pathogen induction [20].

As mentioned above, *S*-nitrosylation of NADPH oxidase might play an important role in stress responses in *Arabidopsis*. However, to date, the mechanism of NADPH oxidase *S*-nitrosylation has been reported only in the model plant *Arabidopsis*. More detailed mechanisms of NADPH oxidase *S*-nitrosylation in other kinds of plants need studied.

Peroxiredoxins (Prxs)

Prxs are peroxidases in all organisms and exhibit thiol-based catalytic activity. Prxs can be classified into six subfamilies according to their different structures. Among them, the Prx1, Prx5, Prx6, and PrxQ isoforms are present in various organelles in plants [38]. Prxs are distributed in specific subcellular compartments with different specific functions in controlling plant growth and development, cellular metabolism and defense signaling [39]. Prx5, the most diverse and widely distributed Prx subfamily in plants, includes PrxII E and PrxII F, which are located in chloroplasts and mitochondria, respectively [40]. PrxII E and PrxII F can be *S*-nitrosylated by GSNO under biotic and abiotic stress [41, 42] (Table 1). Romero-Puertas et al. demonstrated that *S*-nitrosylation of PrxII E could not only inhibit the activity of H_2O_2-reducing peroxidase but also reduce the enzyme's ability to detoxify peroxynitrite ($ONOO^-$), leading to the accumulation of toxic O^{2-} and consequently causing PCD after *Pst* infection [41] (Fig. 1). In pea plants, the activity of PrxII F was similarly reduced because of its *S*-nitrosylation under salt stress [42, 43]. *S*-nitrosylation of PrxII F can alter the enzyme's conformation, which favors the interaction between citrate synthase (CS) and PrxII F and prevents the thermal aggregation of CS, thereby preventing plants from oxidative and nitrosative stress [43] (Table 1). Overall, *S*-nitrosylation of PrxII E and PrxII F plays an important role in inducing plant PCD and impacting plants' responses to various stresses.

Both NO and ROS are recognized as mediators or modulators of a wide range of cellular signaling transduction involved in plant PCD. The evidence presented above indicates that *S*-nitrosylation is a novel way for NO and ROS to regulate PCD. The effect of NO on the crucial components of the antioxidant defense system occurred mainly via the *S*-nitrosylation of some key ROS-related proteins (Fig. 1). Protein *S*-nitrosylation could inhibit or accelerate PCD by impacting the activities or interactions the interactions with other proteins (Table 1), thereby affecting plants' tolerance or resistance to stress.

SA signaling-related proteins

Once challenged by pathogens, plant host cells recognize pathogen effectors, leading to the HR [44]. Localized PCD can induce the accumulation of SA, inducing systemic acquired resistance (SAR) to defend against disease [45]. SA also participates in the signaling in response to abiotic stresses. SNO levels can modulate the accumulation of SA [46]. Salicylic acid-binding protein 3 (SABP3), Nonexpresser of Pathogenesis-Related Genes 1 (NPR1) and TGACG motif binding factor 1 (TGA1) are three important proteins in the SA signaling pathway, and their *S*-nitrosylation modification also affects the SA signaling pathway during the PCD process (Table 1).

Salicylic acid-binding protein 3 (SABP3)

SA is a kind of plant hormone that acts as a key immune activator in defense response systems. SA in plants might bind a wide variety of proteins that are integral to immunity and subsequently modulate their activities [47, 48]. For example, salicylic acid-binding protein 3 (SABP3), a soluble protein molecule with CAT activity, plays a major role in plant immunity. SABP3 exhibited high affinity for SA and presented carbonic anhydrase (CA) activity in the tobacco chloroplast [47]. *S*-nitrosylation of SABP3 was related to the resistance of pathogen infection in *Arabidopsis* plants (Table 1). Wang et al. (2009) challenged *Arabidopsis* plants with *Pst*, which could be recognized by the R protein RPM1, and reported that AtSABP3 was *S*-nitrosylated in vivo. The same result was obtained in vitro in AtSABP3 recombinants that were incubated with various concentrations of GSNO [49]. Thus, AtSABP3 was *S*-nitrosylated in *Arabidopsis* both in vitro and in vivo. AtSABP3 model structure analysis and LC–MS/MS analysis of AtSABP3 *S*-biotinylated peptides showed that Cys-280 was the only site of *S*-nitrosylation of AtSABP3 (Fig. 2). *S*-nitrosylation of AtSABP3 decreased CA activity during the defense response. Furthermore, [^{14}C]SA binding suggested that SNO-AtSABP3 also significantly reduced SA binding (Table 1). Thus, *S*-nitrosylation of AtSABP3 at Cys-280 could inhibit the SA-binding ability and CA activity of AtSABP3, thereby negatively modulating plant resistance to stress.

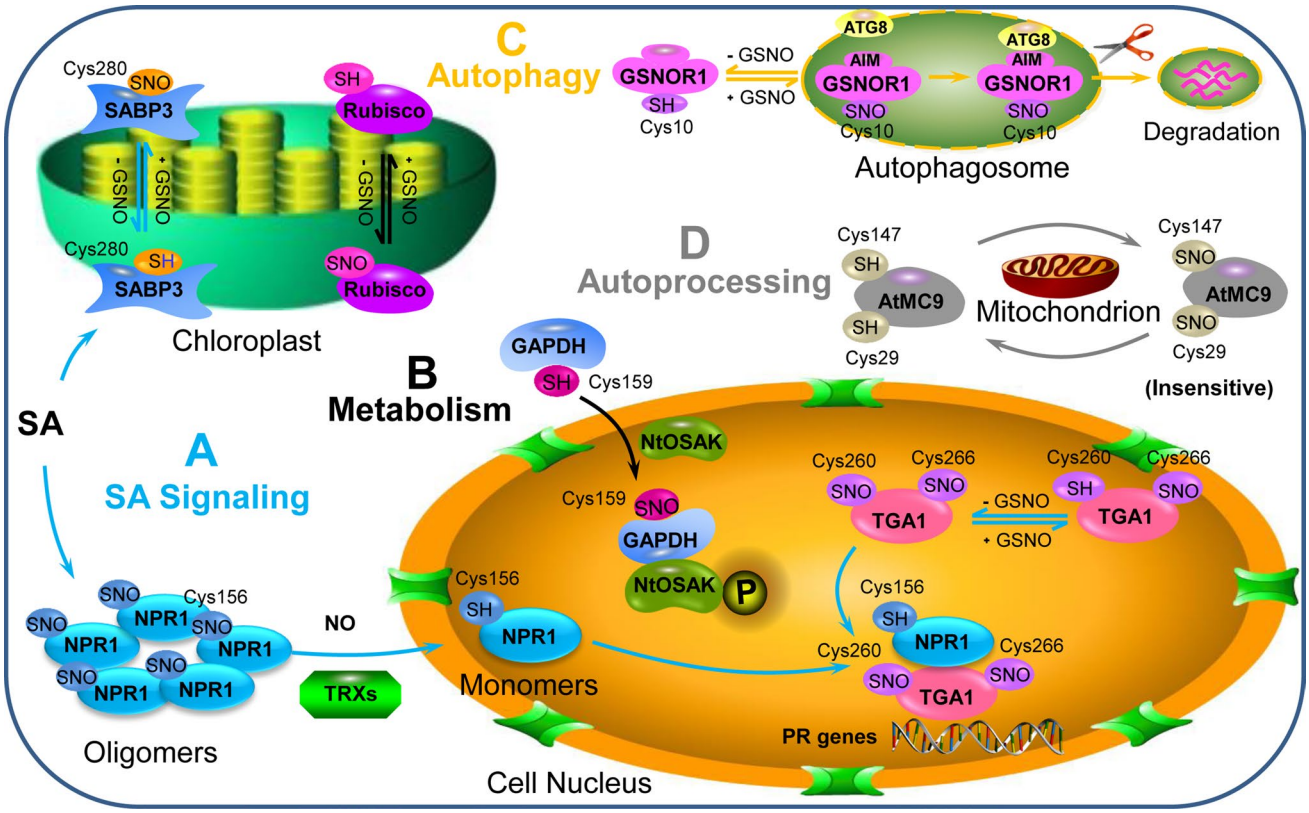

Fig. 2 *S*-nitrosylation of SA signaling-related and the metabolism- and photosynthesis -related proteins GSNOR and MC9 involved in PCD regulation. **a** *S*-nitrosylation regulates SA signaling (lines in blue): SABP3 can be *S*-nitrosylated at its Cys-280 during the SA-related defense response. Under normal conditions, *S*-nitrosylation is beneficial for NPR1 in an oligomeric state in the cytosol. The oligomer can be reduced to monomers by TRXs in a NO-dependent manner and then translocated to the nucleus; *S*-nitrosylation of TGA1 at two Cys sites results in the formation of the NPR1/TGA system, regulating the expression of downstream *PR* genes. **b** *S*-nitrosylation of two metabolism-related proteins (lines in black): Rubisco and GAPDH can be *S*-nitrosylated, and *S*-nitrosylated GAPDH can interact with NtOSAK to respond to stress. **c** GSNOR *S*-nitrosylation leads to GSNOR degradation via selective autophagy (lines in orange); **d** *S*-nitrosylation of MC9 (lines in gray). *SA* salicylic acid, *SABP3* salicylic acid-binding protein 3, *GSNO* *S*-nitrosoglutathione, *NPR1* nonexpresser of pathogenesis-related Genes 1, *NO* nitric oxide, *TRXs* thioredoxins, *TGA1* TGACG motif binding factor1, Rubisco ribulose-1,5-bisphosphate carboxylase/oxygenase, *GAPDH* glyceraldehyde 3-phosphate dehydrogenase, *NtOSAK Nicotiana tabacum* osmotic stress-activated protein kinase, *GSNOR1* *S*-nitrosoglutathione reductase 1, *ATG8* AUTOPHAGY-RELATED8, *AIM* ATG8-interacting motif, *AtMC9 A. thaliana* metacaspase 9

Nonexpresser of Pathogenesis-Related Genes 1 (NPR1)

Nonexpresser of Pathogenesis-Related Genes 1 (NPR1) is another SA-related protein that directly binds SA and activates SA-dependent genes during various immune responses [50]. In unchallenged plants, NPR1 is inactivated and localized to the cytosol as an oligomer formed through intermolecular disulfide bonds (Fig. 2). Once cells were induced by pathogens, the cellular redox state changed, and SA accumulation increased, reducing the oligomeric form of NPR1 to a monomeric form. The monomers then translocated to the nucleus, where they could regulate a group of expressed disease resistance genes [51]. The dynamic equilibrium of NPR1 between oligomers and monomers clearly plays a key role in modulating target gene transcription. *S*-nitrosylation has been reported to regulate the homeostasis of NPR1 [52] (Table 1). When extracted proteins were pretreated with GSNO, accompanied by an increase in the oligomer, the levels of the monomer decreased, while the total NPR1 levels remained unaffected. This phenomenon indicated that GSNO might impact the conformation of NPR1. BST analysis revealed that GSNO treatment caused NPR1 *S*-nitrosylation, indicating that it might be *S*-nitrosylation which affects the NPR1 conformation. In addition, the expression of SA-dependent defense genes was suppressed in *atgsnor1-3*, suggesting that GSNO could also impact the activity of NPR1 in innate immunity. *S*-nitrosylation and SA-induced oligomerization were abolished when Cys-156 was mutated [52]. These results were consistent with the results of computational analysis, suggesting that NPR1 is *S*-nitrosylated at Cys-156. Thus, the *S*-nitrosylation of NPR1 could facilitate its oligomerization. Moreover, Tada et al. demonstrated that thioredoxins (TRXs) could catalyze the SA-induced NPR1 transformation from an oligomeric to a monomeric form [52] (Fig. 2). Taken together, the above results provide a molecular mechanism of cellular redox changes in NPR1 after pathogen challenge: *S*-nitrosylation facilitates oligomer formation, while TRXs catalyze monomer release.

TGACG motif binding factor1 (TGA1)

As mentioned above, monomeric NPR1 is translocated from the cytosol to the nucleus and interacts with the reduced form of TGACG motif binding factor1 (TGA1), which increases DNA-binding activity and promotes the expression of *PR* genes and defense [53, 54] (Fig. 2). Lindermayr et al. used electrophoretic mobility shift assays (EMSAs) to show that GSNO could enhance the DNA-binding activity of TGA1 [55]. A similar result was obtained in the presence of NPR1. In addition, NPR1 and TGA1 were detected to be *S*-nitrosylated in *Arabidopsis*. Among them, TGA1 was *S*-nitrosylated at Cys-260 and Cys-266 in vitro. Thus, *S*-nitrosylation of TGA and NPR1 might influence DNA binding (Table 1). Interestingly, Lindermayr et al. also reported that the translocation of NPR1 into the nucleus was NO dependent (Fig. 2), which indicated that NO might promote NPR1 translocation [55]. Consequently, it can be speculated that the promotion of GSNO/NO to DNA binding might be due to, on the one hand, GSNO treatment changing the conformation of TGA and/or NPR1, leading to a more effective TGA-NPR1 interaction for DNA binding of TGA; on the other hand, *S*-nitrosylation of TGA1 might protect TGA1 from the state of disulfide bonds, from which low activity of DNA binding would result [56]. Overall, NO might play an important role in regulating the defense responses of the NPR1/TGA system in plants. However, the contradiction of GSNO/NO with respect to regulating PR gene expression is up-regulated by the NPR1/TGA system but down-regulated when NPR1 oligomers are favored. Neither mechanism has been defined in the physiological context, and the detailed time points of this defense process action have not been pointed out. In this scenario, these conflicting views require further analysis. Wendehenne et al. proposed that NO-induced events might have a temporal hierarchy: NO might not cause NPR1 to be in oligomeric form to inhibit *PR* genes expressed during the SAR process but rather might regulate the NPR1/TGA cascade at special time points [57]. Under these conditions, *S*-nitrosylation could be considered a negative feedback loop in controlling SAR.

SABP3, NPR1 and TGA1 are key proteins related to SA, which could accept and translate SA signaling to activate the expression of defense genes. *S*-nitrosylation of SABP3, NPR1 and TGA1 could change the original ability of these proteins to withstand adversity stress. Among them, *S*-nitrosylation of SABP3 and NPR1 inhibited the enzymes' activity and ability, while *S*-nitrosylation of TGA1 promoted its ability to bind DNA (Table 1). Thus, it is clear that *S*-nitrosylation is an important way for NO to be involved in hormone signaling in plants.

Metabolism- and photosynthesis-related proteins

The metabolism- and photosynthesis-related enzymes in plants play an important role in responding to biotic and abiotic stresses. Pathogen treatment induced the production of NO and cell death in *Arabidopsis* and 11 mitochondrial

proteins were identified as targets for *S*-nitrosylation during that process [58]. *S*-nitrosylation of metabolic and/or photosynthetic proteins in *Kalanchoe pinnata* [59], *Brassica juncea* [60], *Pisum sativum* L. [61] and *Nicotiana tabacum* [62] have been reported. Until now, proteins Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and Ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco) have been well studied to be *S*-nitrosylated.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)

GAPDH is one of the five known glycolysis enzymes related to the Calvin–Benson cycle and is sensitive to *S*-nitrosylation [63]. GAPDH contains a Cys residue in its reactive center that can be inhibited by NO. In *Arabidopsis* and tobacco, *S*-nitrosylation of the Cys residues of GAPDH could inhibit the activity of GAPDH [62, 64]. Holtgrefe et al. reported that GAPDH, which has multiple functions as a glycolytic enzyme, could also repair DNA and work as a DNA-binding protein in *Arabidopsis* [65]. In addition, *S*-nitrosylation of GAPDH at Cys-159 inactivated GAPDH activity under oxidizing conditions (Table 1), suggesting that the modification of essential Cys residues was a way to transiently protect enzymes involved in metabolism from oxidative damage [65]. In rats, *S*-nitrosylation of GAPDH could initiate the enzyme's interaction with the E3 ligase Siah1 and mediate nuclear translocation, thereby resulting in ubiquitin-mediated degradation of nuclear proteins [66]. A similar function of GAPDH has also been reported in plants. In salt-treated cells of tobacco, GAPDH and the osmotic stress-activated protein kinase (NtOSAK) form an immunocomplex, which is related to GAPDH's ability to translocate to the nucleus and bind DNA (Fig. 2) [62]. GAPDH showed increased and transient *S*-nitrosylation in response to salt stress, and NtOSAK was activated simultaneously, suggesting that *S*-nitrosylation of GAPDH might respond to salt-induced osmotic stress and impact NtOSAK [62]. Additionally, the inactivation of GAPDH caused by *S*-nitrosylation was also discovered in *Arabidopsis* under H_2O_2 treatment [67]. This approach represents another way for GAPDH to exercise its function in plants.

Ribulose-1,5-bisphosphate carboxylase/oxygenase (Rubisco)

The Cys residue of Rubisco, which plays a central role in photosynthesis, can bind NO, thereby regulating the activity and degradation of the molecule [68] (Fig. 2). This was explained later via both the large and small subunits of Rubisco being identified as *S*-nitrosylated in *Arabidopsis* and in *Kalanchoe pinnata* [59, 69] (Table 1). *S*-nitrosylation of Rubisco inhibited the enzyme's activity in a NO-dependent manner [60]. In addition, the action of Rubisco *S*-nitrosylation upon pathogen infection suggested that there might be an association between Rubisco *S*-nitrosylation and Rubisco activity during the defense response [70].

S-nitrosoglutathione reductase (GSNOR)

The enzyme GSNOR, which belongs to the class III alcohol dehydrogenase family, is highly conserved and prevalent in *Arabidopsis* [71], tomato [72], pepper [73], and poplar [74]. GSNOR works as a mobile reservoir of NO to affect GSNO homeostasis between *S*-nitrosylated proteins and GSNO [75, 76]. During pepper fruit ripening, GSNOR activity diminished, while the content of *S*-nitrosylated proteins simultaneously increased, suggesting that GSNOR activity was directly correlated with total SNO levels [77]. In addition, GSNOR1 regulated the *S*-nitrosylation extent of NPR1 and SABP3 in *Arabidopsis*, thus regulating the disease resistance that depends SA signaling [43, 46]. Therefore, GSNOR plays a critical role in regulating the defense response in biotic stress and abiotic stress by regulating intercellular SNO and NO levels.

GSNOR1 itself could also be *S*-nitrosylated in a NO-dependent way in plants [78]. *S*-nitrosylation of GSNOR1 at Cys-10 induced by GSNO could lead to the destabilization of GSNOR1 [72]. GSNOR1, which contains a highly conserved AIM-like motif and has a long half-life, is degraded via autophagy [79]. A key step of phagophore formation is the conjugation of ATG8 with ATG8-interacting proteins [80]. Additionally, specific intermolecular β-sheets, which usually contain an AIM motif, mediate selectivity autophagy [81]. *S*-nitrosylation of GSNOR1 at Cys-10 increased the exposure of AIM to the surface and allowed the AIM motif to interact with ATG8, thereby facilitating the degradation of GSNOR1 by selective autophagy (Fig. 2). Physiologically, the ability of NO to increase tolerance of *Arabidopsis* to low-O_2 stress during seed germination might be due to the *S*-nitrosylation of GSNOR1-induced autophagic degradation under hypoxic conditions [79]. Hence, *S*-nitrosylation of GSNOR1 at Cys-10 plays an important role in facilitating GSNOR1's selective autophagy (Table 1), thereby increasing the tolerance to low-O_2 stress.

Metacaspase 9 (MC9)

Metacaspase, a member of the cysteine protease family, has been demonstrated to be the ancestor of metazoan caspases and plays an important role in plant PCD [82]. Metacaspase, which has specific proteolytic activity, can balance

differentiation and cell death during the embryogenesis process in Norway spruce [83]. In animals, caspases inhibit their autoprocessing activity via the *S*-nitrosylation of cysteine, which is located at the active site under normal conditions [84]. The structure of metacaspase in plants was predicted to be similar to that of caspases in animals, and its acid–base motif favored the *S*-nitrosylation of its cysteine [85]. These findings prompted Belenghi et al. to investigate the *S*-nitrosylation of metacaspase and its function in PCD in *Arabidopsis* (Table 1). In vitro and in vivo experiments showed that *A.thaliana* metacaspase 9 (AtMC9) was *S*-nitrosylated at Cys-147, which delayed the autoprocessing of AtMC9 and suppressed proteolytic activity [86] (Fig. 2). However, during the maturation process of *Arabidopsis*, single-nucleotide polymorphism (SNP) and GSNO treatments caused a twofold decrease in VRPRase activity. Recovery of VRPRase activity after DTT addition indicated that there were other specific cysteine residues within AtMC9. AtMC9 has another highly conserved cysteine residue, Cys-29. This Cys was located inside the catalytic groove and close to Cys-147 but was insensitive to *S*-nitrosylation (Fig. 2). Single and double Cys mutants of AtMC9 showed that at least one Cys was needed for AtMC9 activity. When treated with SNP, the activity of AtMC929A was highly inhibited [86]. Hence, Cys-29 could act as an alternative nucleophile for catalyzing the proteolytic reaction. Metacaspases in plants remained inactive via *S*-nitrosylation; moreover, they were insensitive to *S*-nitrosylation when the genuine catalytic center was replaced with a second Cys during maturation. Collectively, *S*-nitrosylation plays a crucial role in modifying the structure and function of metacaspases, although some Cys residues are more susceptible to this kind of modification.

Conclusions and future perspectives

PCD is a key event in plant growth and development as well as in stress responses. The PCD process triggered by a series of stimuli is always accompanied by a burst of nitrosation, resulting in a change in *S*-nitrosylated proteins to respond to stress signaling. Once a plant is subjected to biotic or abiotic stress, the number of *S*-nitrosylated proteins increases, impacting the PCD process positively or negatively.

In ROS-related proteins, the effects of *S*-nitrosylation on two antioxidant enzymes, APX1 and Prx, are different. *S*-nitrosylation of APX1 increases the enzyme's antioxidative activity, while that of Prx is the opposite, thereby inhibiting or facilitating PCD, respectively. Facilitation of the HR by NO occurs because *S*-nitrosylation abolishes the ability of NADPH to synthesize ROIs. During SA signaling, *S*-nitrosylation of SABP3 reduces the activity of CA and the ability of SA binding, negatively regulating resistance to stress. *S*-nitrosylation of NPR1 sustains the protein in an oligomeric state, which is unfavorable for SA signaling. Conversely, the expression of PR genes, which are mediated by SA signaling, is promoted by *S*-nitrosylation of TGA1. In addition, *S*-nitrosylation of some proteins that are involved in metabolism has been reported. Among them, GAPDH *S*-nitrosylation occurs in response to osmotic stress, while the function of *S*-nitrosylation of Rubisco and the *S*-nitrosylation site is still unknown, warranting further attention. Interestingly, metacaspase has important roles in regulating PCD in plants. AtMC9 has two different cysteine residues whose sensitivities to NO differ. *S*-nitrosylation of Cys-147, which is sensitive to NO, delays the autoprocessing of AtMC9 and suppresses proteolytic activity, while *S*-nitrosylation at Cys-29 is not sensitive to NO. All *S*-nitrosylated proteins can be regulated by GSNOR, and GSNOR is the only protein that reportedly can balance the level of SNOs in plants. In fact, *S*-nitrosylation of GSNOR1 promotes the enzyme's degradation and increases its ability to defend abiotic stress.

It is clear that *S*-nitrosylation has important roles in regulating PCD in plants. However, little is known about the potential roles of *S*-nitrosylation in regulating plant growth and development, aging and death, and resistance to stress. Thus, many studies need to be carried out to explore the *S*-nitrosylation molecular regulatory mechanism of PCD as well as stress resistance.

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