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Invited Review Article

Expanding roles for *S*-nitrosylation in the regulation of plant immunity☆

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ABSTRACT

Following pathogen recognition, plant cells produce a nitrosative burst resulting in a striking increase in nitric oxide (NO), altering the redox state of the cell, which subsequently helps orchestrate a plethora of immune responses. NO is a potent redox cue, efficiently relayed between proteins through its co-valent attachment to highly specific, powerfully reactive protein cysteine (Cys) thiols, resulting in formation of protein *S*-nitrosothiols (SNOs). This process, known as *S*-nitrosylation, can modulate the function of target proteins, enabling responsiveness to cellular redox changes. Key targets of *S*-nitrosylation control the production of reactive oxygen species (ROS), the transcription of immune-response genes, the triggering of the hypersensitive response (HR) and the establishment of systemic acquired resistance (SAR). Here, we bring together recent advances in the control of plant immunity by *S*-nitrosylation, furthering our appreciation of how changes in cellular redox status reprogramme plant immune function.

1. Introduction

A key feature in response to pathogen recognition is the rapid and largely parallel production of reactive oxygen species (ROS) and reactive nitrogenous species (RNS); termed the oxidative and nitrosative burst, respectively [1,2]. The synthesis of these small, redox-active and largely interconvertible molecules aids the orchestration of a plethora of immune responses including: the hypersensitive response (HR) [3,4], cell wall strengthening via oxidative cross-linking [5,6], callose deposition [7], synthesis of immune-related signal molecules [8–10] and provides direct antimicrobial activity against attempted pathogen infection [11].

The oxidative and nitrosative bursts generate ROS and RNS, respectively, largely in the apoplastic space, at the site of attempted pathogen ingress, initially following host recognition of pathogen-associated molecular patterns (PAMPS) by pathogen recognition receptors (PRRs), resulting in PAMP triggered immunity (PTI) [12]. Subsequently, host recognition of pathogen effector proteins delivered inside the plant cell by resistance (R) proteins triggers another more powerful and sustained burst of ROS and RNS, contributing to the establishment of effector triggered immunity (ETI).

A direct role for NO in plant immunity was first outlined when a NO donor induced the accumulation of the anti-microbial phytoalexin, rishitin, in potato [13]. NO was subsequently demonstrated to increase following *R*-gene dependent pathogen recognition, which in turn induced the production of the immune activator, salicylic acid (SA) and immune-response genes in tobacco [8]. NO was also shown to strongly promote HR cell death in concert with H_2O_2, promoting the induction of immune-related genes in cultured soybean cells [2]. This key redox molecule is now implicated in the orchestration of immunity against a wide variety of pathogens.

1.1. NO production, homeostasis and bioactivity transfer

NO bioactivity is efficiently transferred and stored within the cell through its co-valent attachment to specific reactive cysteine (Cys) thiols of proteins, forming *S*-nitrosothiols (SNOs). This redox-based, post-translational modification, termed *S*-nitrosylation, is reversible and functions as a molecular switch that enables target proteins to be responsive to changes in cellular redox status, thereby enabling the modulation of protein function accordingly [14,15]. *S*-nitrosylation serves as the central route for the transfer of NO bioactivity within the

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cell and can significantly modify protein function, localisation, conformation and activity [16–18]. To this effect, a major role for the nitrosative burst is to engage a specific set of NO-responsive proteins that initiate SNO signalling to regulate plant immune responses such as the synthesis of SA [19], the HR [20] and perhaps even cell-specific responses such as the closing of guard cells [21]. Numerous important regulators of the plant immune response have now been identified as targets for *S*-nitrosylation. Some of these include the transcriptional co-activator Non-Expressor of Pathogenesis-Related Genes 1 (NPR1) which positively regulates SA-dependent immune responses [22], the NADPH Respiratory Burst Oxidase Homolog D (RBOHD) which synthesises ROS, associated with HR formation [23], the TGA1 transcriptional activator [24] and SA-Binding Protein 3 (SABP3) which facilitates SA-dependent responses [19] (see Table 1).

Unlike animals, where production of NO is largely controlled by NO synthases (NOS) which catalyse the production of NO and L-citrulline from L-arginine, the predominant route for NO production in plants is attributed to the reduction of nitrite and nitrate by nitrate reductases (NRs) [25]. While no structurally similar NOS has been detected in plants [26], there is some evidence that suggests NOS-like activity, from a structurally unrelated enzyme, may be present in plant cells. For instance, inhibitors of mammalian NOS reduce NO generation and similarly, limiting arginine and NADPH has been demonstrated to blunt NO synthesis [25,27,28]. The NRs NIA1 and NIA2 from *Arabidopsis thaliana* are both strongly associated with NO synthesis and have been linked with key roles relating to NO production during immunity [29–31]. In mutant lines *nia1*, *nia2* and *nia1nia2*, application of SA produced significantly less NO compared to a wild-type controls and similarly, inoculation of these mutant lines with the pathogen *Pseudomonas syringae* pv. *maculicola* triggered an impaired NO response [30,32]. While NO production is generally attributed to NR activity, other RNS are also generated from interactions with cellular O_2 and O_2^- producing NO_x and peroxynitrite ($ONOO^-$), respectively [33].

Several studies have now described an influx of extracellular Ca^{2+} as an initiating factor acting upstream of endogenous NO production in response to both pathogens and PAMPs in a variety of different plant species. Here, use of pharmacological inhibitors that target Ca^{2+} influx channels cause a significant reduction in the NO synthesis, highlighting a critical role for Ca^{2+} mobilisation upstream of the NO burst [34–36]. Additionally, a calmodulin (CaM) isoform, conserved within CaM families I and II has been demonstrated to be *S*-nitrosylated on Cys-27 following cryptogein treatment of tobacco suspension cells [37]. While it has yet to be demonstrated whether CaM activity is inhibited after receiving this NO modification, it may suggest that NO targets CaMs to regulate Ca^{2+} influx to reduce the production of NO during the nitrosative burst [38].

Overproduction or dysregulation of either ROS or RNS on can lead to significant oxidative and nitrosative stress, respectively, which is both damaging to host proteins and cell structures and can dysregulate redox related immune signalling, potentially exacerbating pathogenesis [39,40]. In particular, the presence of $ONOO^-$ is a useful indicator of high nitrosative stress as it can inflict damage to important cellular structures including the fatty acid lipids of the cell membrane, resulting in tyrosine nitration, an understudied post-translational modification (PTM) that

Table 1
Plant immunity-related targets of *S*-nitrosylation.

Protein	Consequence to Protein Function After *S*-nitrosylation	Treatment	*S*-nitrosylated Cysteine(s)	Species	Reference
Immunity-related proteins demonstrated to be *S*-nitrosylated *in planta* following immune activation					
Peroxiredoxin II E (PRXIIE)	Inhibition of $ONOO^-$ detoxification activity increasing tyrosine nitration	*avr P. syringae* pv. *tomato* inoculation	Cys-121	*A. thaliana*	[84]
Glyceraldehyde 3-Phosphate Dehydrogenase isoform C (GAPC1)	Inhibition of roles in glycolysis & calvin cycle, may operate as a HR initiator *	*avr P. syringae* pv. *tomato* inoculation	Cys-149	*A. thaliana*	[20,135]
Salicylic Acid Binding Protein 3 (SABP3)	Inhibits SA-binding and carbonic anhydrase activity	*avr P. syringae* pv. *tomato* inoculation	Cys-280	*A. thaliana*	[19]
RBOHD	Inhibits cofactor binding and ROS production	*avr P. syringae* pv. *tomato* inoculation	Cys-890	*A. thaliana*	[23]
Non-pathogenesis related 1 (NPR1)	Enhancement of NPR1 oligomer formation	Salicylic acid	Cys-156	*A. thaliana*	[22]
Ascorbate Peroxidase (APX1)	Enhancement of H_2O_2 detoxification	flg22	Cys-32	*A. thaliana*	[85]
Calmodulin Isoform, families I & II (CaM)	Unknown, may inhibit influx of exogenous Ca^{2+} *	Cryptogein	Cys-27	*N. tabacum*	[37]
S-nitrosothiol Regulated 1 (SRG1)	Inhibition of DNA binding relieving transcriptional repression	*avr P. syringae* pv. *tomato* inoculation	Cys-87	*A. thaliana*	[116]
SRG3	Inhibition of DNA binding relieving transcriptional repression	*avr P. syringae* pv. *tomato* inoculation	Cys-87	*A. thaliana*	[117]
Histone deacetylase 2B (HDT2)	May inhibit histone deacetylase activity, suppressing the HR development *	*avr P. syringae* pv. *tomato* inoculation	Unknown	*A. thaliana*	[121]
Histone deacetylase 2C (HDT3)	May inhibit histone deacetylase activity, suppressing the HR development *	*avr P. syringae* pv. *tomato* inoculation	Unknown	*A. thaliana*	[121]
SUMO conjugating Enzyme 1 (SCE1)	Inhibition of SUMO-conjugating activity facilitating SA-dependent immune responses	*avr P. syringae* pv. *tomato* inoculation	Cys-139	*A. thaliana*	[141]
AAA + ATPase cell division cycle 48 (CDC48)	Inhibition of ATPase activity, may engage in SNO signalling and HR regulation *	Cryptogein treatment, avr *P. syringae* pv. *tomato* inoculation	Cys-110, Cys-526, Cys-664	*A. thaliana*	[37,121]
Immunity-regulated proteins demonstrated to be *S*-nitrosylated either *in vitro* or during abiotic stress					
Catalase 3 (CAT3)	*Trans*-nitrosylates GSNOR to facilitate its autophagy	Abiotic hypoxia	Cys-343	*A. thaliana*	[72]
TGACG-binding factor 1 (TGA1)	May enhance DNA binding to *as-1* element *	*in vitro* GSNO treatment	Cys-260, Cys-266	*A. thaliana*	[24]
S-nitrosoglutathione Reductase (GSNOR)	Inhibition of GSNO reduction activity, *S*-nitrosylation of Cys-10 leads to autophagy of GSNOR	Cys-NO, abiotic hypoxia	Cys-10, Cys-271, Cys-370	*A. thaliana*	[50,70]
MYB30	Inhibition of DNA binding dampening cell death associated gene expression	*in vitro S*-nitroso-N-acetylpenicillamine (SNAP)	Cys-48, Cys-53	*A. thaliana*	[113]
Arginine Methyltransferase 5 (PRMT5)	Enhances abiotic stress-related pre-RNA splicing and may enhance expression of defence related genes	Abiotic salt stress	Cys-125	*A. thaliana*	[132]

For some proteins an *in vivo* change in protein function following *S*-nitrosylation has not yet been established and in such cases a potential response is proposed and described further in the text (*).

may have yet unidentified roles in immune signalling [33,41]. NO is also scavenged by phytoglobins which are likely to play an important role regulating NO accumulation and by extension, NO-induced cell death, through their NO-dioxygenase activity [42,43]. This is evidenced by the *A. thaliana* phytogloblin mutant, *atglb1*, which shows increased resistance to *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst*DC3000) and *Botrytis cinerea*. Conversely, resistance to these pathogens was impaired in a GLB1 overexpression line. Similarly, *atglb1* plants show higher NO levels, in addition to higher SA production in response to avirulent *Pst*DC3000 and higher ethylene and jasmonic acid production following challenge by *B. cinerea*. In contrast, the opposite outcomes were observed for the GLB1 overexpression line. Further, *GLB1* is down-regulated in response to both pathogens, suggesting that GLB1 may have a role in suppressing NO-related responses through its NO-oxidising activity [42].

1.2. GSNOR function is critical for NO homeostasis and plant immunity

The major route for NO stabilisation and signal transduction within the cell lies in its high affinity for glutathione (GSH) which, in the presence of oxygen, forms *S*-nitrosoglutathione (GSNO). GSNO stabilises NO, acting as a mobile reservoir of NO bioactivity. Further, GSNO can transfer an NO group to highly specific, reactive Cys residues of target proteins in a process termed *trans*-nitrosylation [44–47]. Key to SNO signalling is the enzyme *S*-nitrosoglutathione reductase (GSNOR), which controls cellular GSNO levels by irreversibly metabolising GSNO into glutathione disulphide (GSSG) and ammonia (NH_3) in an NADH dependent manner [44,48–51]. The rate of protein *trans*-nitrosylation via GSNO is determined by both the size of the GSNO pool and current redox state of the cell; both of which shift rapidly during the immune response [16,51]. Interestingly, GSH accumulation increases in response to either NO treatment of plant cells [52,53] or pathogen inoculation [54,55]. The ratio of GSH/GSNO determines the amplitude of SNO signalling, where the level of protein *trans*-nitrosylation is controlled by GSNOR mediated turnover of GSNO which subsequently increases the GSH/GSNO ratio [56,57] (Fig. 1). The potency of GSNO-dependent *trans*-nitrosylation has been exploited in studies aimed at identifying new candidate proteins regulated by NO [58]. Numerous important regulators of immunity have now been identified as targets for *S*-nitrosylation, placing GSNOR activity at the centre of cellular protein-SNO control and by extension, plant immunity regulation.

GSNOR is a highly evolutionary conserved enzyme from microbes to humans [59,60] and its ability to catalyse the reduction of GSNO has also been demonstrated in a wide variety of plant species [51,59]. GSNOR plays a general role in NO homeostasis and GSNOR activity is tied to plant development, growth and abiotic and biotic stress responses [48,61,62]. The link between GSNOR activity and immune functionality was first identified through a loss-of-function mutation in *A. thaliana*, *atgsnor1-3*, which resulted in a substantial increase in the cellular SNO level. The *gsnor1-3* line exhibits loss of multiple modes of plant immunity including non-host resistance, basal defence and *R*-gene mediated protection. This appears to largely result from loss of both SA

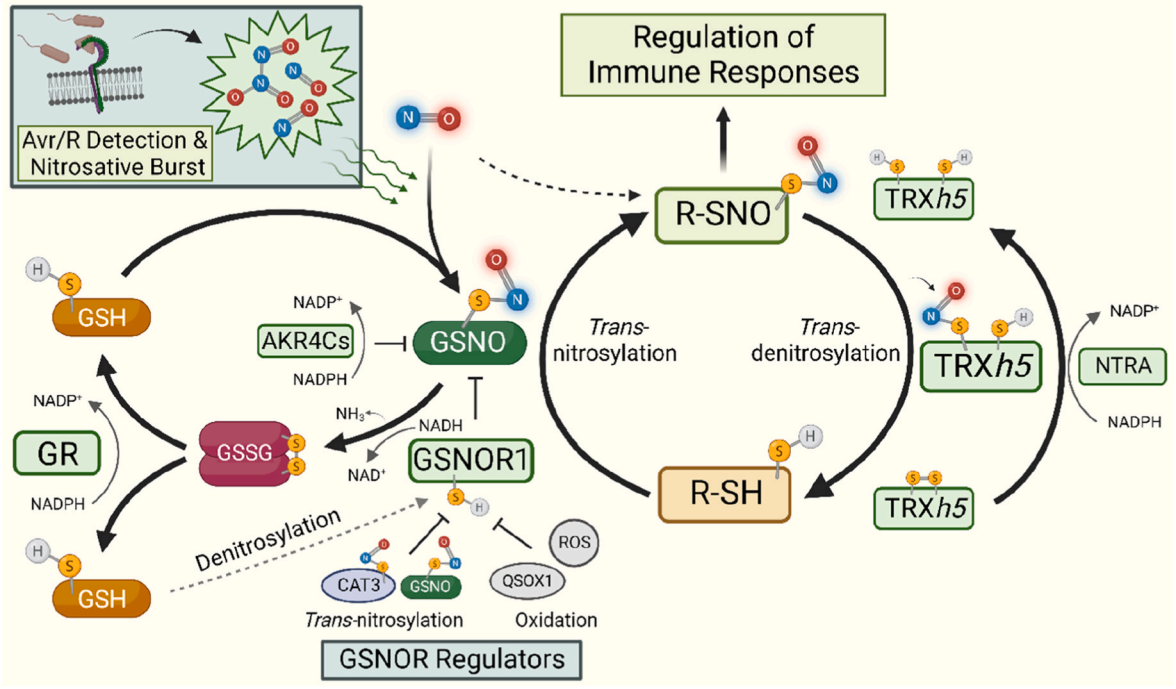

Fig. 1. Schematic Depicting *S*-nitrosylation and Denitrosylation Mechanisms Involved in Plant Immunity
S-nitrosoglutathione (GSNO) is formed in a stable reaction with glutathione (GSH) and nitric oxide (NO), serving as a mobile reservoir NO bioactivity. The ratio of cellular GSH to GSNO is controlled by *S*-nitrosoglutathione reductase (GSNOR) activity, which catalyses the NADH dependent reduction of GSNO to reduced glutathione (GSSG), which in turn can be converted back to GSH by glutathione reductase (GR). GSNO can transfer its NO group to solvent exposed, highly reactive cysteine (Cys) thiols of target proteins resulting in an *S*-nitrosothiol (SNO), in a process termed *trans*-nitrosylation that can regulate target protein function. Following pathogen recognition, plant cells rapidly engage a nitrosative burst, resulting in the accumulation of reactive nitrogen species (RNS) that accumulate at pathogen entry sites. During the early stages of the burst, GSNOR activity increases, in correspondence with the increasing GSNO, attenuating (S)NO signalling. Pathogen detection also leads to an increase in GSH synthesis, which can denitrosylate GSNOR, maintaining its activity. Turnover of GSNO may also be supported by family 4C aldo-keto reductases (AKRs) that can reduce GSNO in an NADPH dependent manner. During prolonged immune activation, GSNOR is regulated through oxidation by reactive oxygen species (ROS) such as H_2O_2 and the enzyme quiescin sulfhydryl oxidase homolog 1 (QSOX1), which enhance GSNO accumulation, facilitating continued SNO signalling. Similarly, GSNOR activity is also regulated through *trans*-nitrosylation by catalase 3 (CAT3) during hypoxia and by high concentrations of GSNO during prolonged immune activation. A subset of *S*-nitrosylated proteins (R-SNO) are *trans*-denitrosylated by thioredoxin *h5* (TRX*h5*) and this function is maintained by NADPH-dependent thioredoxin reductase A (NTRA) which regenerates TRX*h5* activity by reducing the resulting disulphide bond. Figure generated in BioRender.com.

accumulation and SA signalling [44,63]. In contrast, a gain-of-function *AtGSNOR* mutation, *atgsnor1-1*, leads to an increase of AtGSNOR1 activity, resulting in increased GSNO turnover, reduced cellular SNO levels and enhanced disease resistance [44]. Proteomic analysis has shown that at least 900 proteins are *S*-nitrosylated in the *gsnor1-3* mutant, attributed to the abundance of cellular GSNO [64] and of 170 genes found to undergo reduced expression in *gsnor1-3* compared to a wild-type line, one third were found to be associated with plant immune responses [49]. Loss of *AtGSNOR* function also enhanced resistance to the herbicide and oxidative stress inducer paraquat [65], which otherwise causes rapid cell death in wild-type plants, outlining a potentially additional role for AtGSNOR in the control HR cell death [23,65]. Collectively, these findings suggest that AtGSNOR is fundamentally important to multiple aspects of *A. thaliana* immunity [44].

Recently, GSNOR function has been investigated in other dicotyledonous plants. In tomato (*Solanum lycopersicum*) application of a constitutive antisense knockdown strategy against GSNOR transcripts led to reduced fruit and seed development and significantly impaired plant immunity. Conversely, overexpression of GSNOR led to increased SA synthesis, enhanced expression of *pathogenesis-related* (*PR*) genes and elevated basal resistance [66]. Further, following CRISPR/Cas9 mediated knockout of all four alleles of *GSNOR1* in tetraploid *Nicotiana tabacum*, the subsequent plants displayed a spontaneous cell death phenotype with compromised disease resistance against *Pst*DC300 and interestingly, enhanced resistance against *Tobacco mosaic virus* (TMV) [67]. While these plants maintained high levels of SNO as expected of the *gsnor* phenotype, cells undergoing cell death also contained high levels of hydrogen peroxide (H_2O_2). Further, these plants also showed resistance to paraquat, indicating that paraquat resistance in the absence of GSNOR1 function is conserved between *A. thaliana* and *N. tabacum* [65,67].

1.3. GSNOR activity is regulated by S-nitrosylation

The production of NO alone is insufficient to trigger the HR. For effective orchestration of the HR in response to pathogen signals, plants produce a tightly controlled quantity of both NO and ROS [2,68,69]. Evidence of this comes from the observation that dysregulated redox control can both impair and exacerbate cell death [42,44,65,67]. Further, many proteins involved in the production and detoxification of ROS and RNS are regulated by redox-based, PTMs such as *S*-nitrosylation, indicative of the necessity for ROS-RNS crosstalk in initiating immune responses and the maintenance of redox homeostasis. GSNOR is rich in Cys residues, suggesting that GSNOR itself may be regulated by redox-based PTMs [49,70]. Indeed, AtGSNOR has been demonstrated to be *S*-nitrosylated in response to NO treatment both *in vitro* and *in vivo*, resulting in the inhibition of this enzyme [70]. Further, AtGSNOR was later shown to be modified by *S*-nitrosylation on three conserved, solvent exposed cysteines: Cys-10, Cys-271 and Cys-370 following *in vitro* application of NO donors, resulting in inhibition of AtGSNOR activity [50]. Notably, none of these sites are related to the active site of AtGSNOR, suggesting that regulation of AtGSNOR activity via *S*-nitrosylation is controlled allosterically rather than through blocking of the active site [50,70].

Interestingly, *S*-nitrosylation of AtGSNOR1 at Cys-10 leads to its selective degradation through autophagy during hypoxia [71]. *S*-nitrosylation of Cys-10 causes AtGSNOR to undergo a conformational change that exposes an interacting domain of AtGSNOR enabling AUTOPHAGY-REPLATED8 (ATG8) to target AtGSNOR and recruit it to an autophagosome [71]. This mode of inhibition was determined using autophagy inhibitors and *A. thaliana* autophagy knockout lines resulting in increased levels of AtGSNOR, while proteasome inhibitors failed to replicate this outcome [71]. Moreover, this interaction was found to be mediated by a non-canonical catalase 3 (CAT3), which *trans*-nitrosylates GSNOR at Cys-10 via a highly conserved Cys residue of CAT3 (Cys-343), leading to autophagy of AtGSNOR, positively regulating NO signalling [72]. Originally termed REPRESSOR OF AtGSNOR1 (ROG1), a mutation in *ROG1/CAT3* was found to be responsible for rescuing the *atgsnor1* phenotype, which exhibits high nitrosative stress and protein-SNO. Expression of wild-type *CAT3* under its native promoter reverted the phenotype suppressing effect, while a *CAT3*Cys-343-Threonine mutation only partially reverted the phenotype, suggesting that Cys-343 is critical to restoration of the phenotype [72]. Similarly, mutation of *CAT2*, which has significantly higher catalase activity than CAT3 did not recover the phenotype, supporting the conclusion that the *trans*--nitrosylation activity of CAT3 as opposed to its catalase activity is necessary for GSNOR inhibition. CAT3 has been found to interact with a wide range of proteins, perhaps indicating that some of these targets may also be *trans*-nitrosylated. For example, CAT3 can bind cucumber mosaic virus (CMV) 2b during infection of *A. thaliana*, which results in translocation of CAT3 to the nucleus, inducing cell necrosis [73]. Additionally, CAT3 interacts with LESION STIMULATING DISEASE 1 (LSD1), a negative regulator of cell death [74]. The loss-of-function mutation, *lsd1*, results in SA-dependent runaway cell death, perhaps suggesting that CAT3 could inhibit LSD1 via *trans*-nitrosylation to trigger cell death [72]. Collectively, this suggests that AtGSNOR activity is not just inhibited through *S*-nitrosylation but can be selectively depleted through autophagy during abiotic stresses such as hypoxia.

The inhibition of AtGSNOR via *S*-nitrosylation appears first as paradoxical, as AtGSNOR activity is necessary for maintaining a stable GSH: GSNO ratio and preventing nitrosative stress. As such, the inhibition of AtGSNOR during both programmed cell death and increasing cellular GSNO, somewhat contradicts its prescribed functionality during immunity. However, following inoculation of potato with avirulent *P. infestans*, the responding NO burst peaked first at 3 h post inoculation (hpi), then again at 48 hpi and a significant increase in GSNOR activity coincided with the first NO burst and slowly declined over the remainder of the experiment. The lack of GSNOR activity during the second, more potent NO burst at 48 hpi may indicate that GSNOR is regulated via *S*-nitrosylation during prolonged NO exposure, or that other GSNOR regulators become activated during the latter stages of immunity [75]. Moreover, GSH has been demonstrated to denitrosylate GSNOR *in vitro* and GSH synthesis follows both NO treatment and pathogen inoculation, suggesting that increasing GSH during the early stages of immunity could support GSNOR activity [52,55,76].

1.4. GSNOR: an intermediary in ROS - RNS crosstalk

In recent years, the importance of crosstalk between ROS and RNS has been emphasised as a major mechanism by which plants temper their response to pathogens and control the redox status of the cell [47,77]. Here, *S*-nitrosylation serves as a central regulatory mechanism that influences a multitude of protein targets with roles in both the production and detoxification of ROS. To this effect, GSNOR contributes to ROS-RNS crosstalk by controlling the concentration of the GSNO pool and by being responsive itself to oxidative PTMs, such as *S*-nitrosylation, that regulate its activity. GSNOR was recently shown to be directly oxidatively modified by the redox sensor QUIESCIN SULFHYDRYL OXIDASE HOMOLOG 1 (QSOX1) during biotic stress signalling [78]. Following inoculation with the avirulent bacterial pathogen *Pst*DC3000, QSOX1 oxidises and inactivates GSNOR, disabling its activity shortly following the ETI-triggered oxidative burst, attenuating ROS signalling. QSOX1 activity is activated by oxidative PTMs during the redox shift associated with early-stage ROS burst, leading QSOX1 to oxidise target Cys residues of GSNOR thereby increasing protein SNO modifications, triggering the NO signalling network [78].

QSOX1 is therefore likely to serve as an early responder to the oxidative burst with a direct role in initiating NO signalling and an indirect role in perturbing ROS production via a pathogen-induced negative feedback loop [78]. In addition, QSOX1 mediated enhancement of NO signalling leads to *S*-nitrosylation of RBOHD, an NADPH-oxidase and primary source of ROS during the oxidative burst, resulting in inhibition

of its activity [78,79]. RBOHD was shown to be *S*-nitrosylated at Cys-890 during accumulation of SNO, preventing the binding of its co-factor FAD and by extension, inhibiting ROS synthesis in response to attempted pathogen infection, dampening HR development [23]. This is further supported by a recent study where, in the absence of GSNOR activity, the *gsnor1-3* mutant failed to produce sufficient ROS against the oomycete *P. parasitica*, resulting in drastically enhanced disease symptoms. Interestingly, *RBOHD* expression increased in the *gsnor1-3* plants but exhibited significantly lower ROS activity, perhaps owing to the overwhelming availability of GSNO, which likely induces *S*-nitrosylation of RBOHD [23,63]. GSNOR activity has also been linked to the production of H_2O_2 in tomato, where virus-induced gene silencing (VIGS) was utilised to silence *GSNOR* transcripts, resulting in an increase in protein-SNO and perturbation of the heat stress-associated production of apoplastic H_2O_2, disrupting heat tolerance. The authors attribute the reduction in H_2O_2 to downregulation of *Respiratory burst oxidase homolog 1* (*RBOH1*) and possibly inhibition of RBOH1 by *S*-nitrosylation, although the latter was not investigated in this study [80].

A mutation in rice catalase C (*OsCATC*) also resulted in accumulation of high levels of both NO and H_2O_2 under light stress, likely due to lack of CATC mediated H_2O_2 detoxification, resulting in spontaneous cell death. Interestingly, this phenotype was rescued following constitutive expression of rice *GSNOR* and exacerbated by RNA interference (RNAi) of *GSNOR* [69]. These experiments suggest that the overproduction of H_2O_2 inhibits GSNOR activity, which is rescued by expression of *GSNOR* exceeding the inhibitory threshold. Indeed, GSNOR has been demonstrated to be inhibited by H_2O_2 exposure in several independent experiments, reducing its activity in a dose dependent manner, likely through excessive modification of its Zn^{2+} coordinating Cys, resulting in an increase in protein-SNO [81–83]. Interestingly, a mutation in *CAT2* in *A. thaliana*, an ortholog of *OsCATC* [69], results in increased GSNOR activity despite overaccumulation of H_2O_2 and a spontaneous cell death phenotype, exacerbated by long photoperiod stress [76]. Further, *cat2* also displays increased SA accumulation and *PR* gene expression. The increased GSNOR activity is attributed to an almost two-fold increase in *GSNOR* expression contrary to that seen in *oscatc* plants where GSNOR expression is lower than the wild-type line. This suggests that either overaccumulation of H_2O_2 or the absence of *cat2* function may result in induction of *GSNOR* in *A. thaliana* but not in rice. Thus, indicating that AtCAT2 and OsCATC may have evolutionary divergent functions.

Intriguingly, after introduction of the *gsnor1-3* mutation into the *cat2* background, subsequent plants were found to accumulate even higher SNO than the *gsnor1-3* phenotype alone and additionally, the *cat2* spontaneous lesion phenotype was recovered. These plants also exhibited reduced SA accumulation and immune-related gene expression, indicating that GSNOR activity may facilitate immune responses downstream of H_2O_2 in *A. thaliana* [76]. Further, when *cat2* plants were genetically compromised in GSH synthesis following introduction of the *cat2* line into the mutants *pad2* and *cad2*, GSNOR activity was significantly reduced despite similar levels of GSNOR protein and *GSNO* transcripts. Moreover, GSNOR was significantly *S*-nitrosylated in *cat2 pad2*. Collectively, these results suggests that GSH can denitrosylate GSNOR to amplify its activity, placing emphasis on the importance of the GSH/GSSG ratio in activating redox-dependent functions within the cell [76].

Another notable target of *S*-nitrosylation is the $ONOO^-$ scavenger peroxiredoxin II E (PRXIIE), which is inhibited in *A. thaliana* by *S*-nitrosylation during the HR induced by avirulent *Pst* [20]. Consequently, PRXIIE no longer detoxifies $ONOO^-$, leading to an increase in cellular ONOO- and increased protein tyrosine nitration. Further, increased $ONOO^-$, derived from either PRXIIE inhibition, a loss-of-function mutation, or NO donor application, failed to increase HR cell death, suggesting that PRXIIE inhibition is not likely to mediate HR cell death but instead may facilitate control over the effects both ROS and RNS radicals and perhaps enhance tyrosine nitration to convey the effectors of this understudied PTM [20,84].

The H_2O_2 scavenging enzyme ASCORBATE PEROXIDASE 1 (APX1) can be modified by tyrosine (Tyr) nitration on two Tyr residues and by *S*-nitrosylation on Cys-32. In *A. thaliana*, APX1 activity was enhanced via *S*-nitrosylation following application of a nitrosative burst inducer, flagellin 22 (flg22), resulting in increased resistance to oxidative stress. Further, in the mutant line *atapx1-2*, flg22 treatment led to significantly increased expression of two known marker genes relating to the flg22 response, Non-Race-Specific Disease Resistance 1/HIN-like10 (NHL10) and Flagellin-responsive receptor-like kinase 1 (FRK1). Further, this phenotype was rescued by transgene expression of APX1, but not an APX1Cys-32-Serine (Ser) mutant, which prevents *S*-nitrosylation, suggesting that *S*-nitrosylation of APX1 may negatively regulate the immune response to flg22 [85]. Similarly, in pea (*Pisum sativum*), treatment with GSNO and $ONOO^-$ enhanced and inhibited APX1 H_2O_2 detoxifying activity, respectively, the latter of which could reflect inhibition through Tyr nitration [86]. The enhanced activity of APX1 through *S*-nitrosylation may partially explain why *A. thaliana* line *gsnor1-3* is paraquat resistant, as the excessive ROS production induced by this herbicide may be detoxified more efficiently due to increased APX1 *S*-nitrosylation, resulting in high APX1 activity [65,85]. Taken together, this research highlights an essential role for *S*-nitrosylation in the control of the cellular redox state and the triggering of the HR. To this effect, through control of bioavailable NO, GSNOR is a master regulator of SNO signalling.

1.5. *S*-nitrosylation regulates the salicylic acid signalling network

The phytohormone SA plays a critical role in plant immune signalling, helping to trigger the HR and the activation of systemic acquired resistance (SAR) in plants [87,88]. SA synthesis rapidly follows detection of invading pathogens via receptors such as PRRs and NBLRRs, leading to a change in cellular redox status and subsequently, the expression of immune-related genes [87]. SABP3 is a carbonic anhydrase (CA) that can bind SA [19]. The CA activity of SABP3 may relate to the synthesis of lipids and fatty acids in the chloroplast as observed in other CA enzymes [89]. The SA-binding and CA activity of SABP3 are both reduced in the presence of GSNO, suggesting that SABP3 may be a redox-responsive protein. Indeed, SABP3 was demonstrated to be *S*-nitrosylated on Cys-280, decreasing both its SA-binding and CA activity. Interestingly, the subsequent increase in susceptibility to avirulent *Pst*DC3000 in an *A. thaliana* SABP3Cys-280-Ser mutant was associated with impaired CA function, as opposed to SA-binding [19]. As such, the role that SA may play in binding SABP3 has yet to be fully elucidated, but the inhibition of SABP3 by *S*-nitrosylation implies that it serves as a negative feedback loop mechanism that dampens further immune signalling during prolonged NO exposure. *S*-nitrosylation has also been implicated in a multitude of different phytohormone signalling networks, generally interfering with transduction of phytohormone signals or restriction of phytohormone synthesis in response to both biotic interactions [90].

The sharp rise in SA synthesis during immune signalling leads to the initiation of *PR* gene expression, induced by activation of the major transcriptional co-activator of plant immunity, Non-expressor of Pathogenesis-related proteins 1 (NPR1). This transcriptional co-activator localises to the nucleus during SAR and binds to members of the basic leucine zipper (bZIP) family of TGACG motif binding (TGA) transcription factors, thereby enhancing *PR* gene expression [22,91]. In the absence of pathogen challenge, NPR1 is located predominantly within the cytosol in its oligomeric form, bound by covalent disulphide bridges between conserved cysteines, Cys-82 and Cys-156 [22,92]. GSNO can *trans*-nitrosylate Cys-156 *in-vivo* and enhance the formation of intermolecular disulphide bonds between NPR1 oligomers, suggesting that GSNOR activity may indirectly promote SAR through GSNO turnover [22]. During the SA-induced, redox-heightened state, the thiol-disulphide oxidoreductase thioredoxin *h5* (TRX*h5*) reduces the disulphide bonds between NPR1 oligomers in the cytosol, facilitating

NPR1 de-oligomerisation [22]. Further, TRX*h5* can also denitrosylate NPR1, which is thought to further facilitate monomerization by preventing the formation of intermolecular disulphide bonds [18]. In its monomeric form, NPR1 can migrate to the nucleus. Further, interaction with SA induces folding of the NPR1 SA-binding domain, enabling transcriptional enhancement [92]. Interestingly, mutation of NPR1 to NPR1Cys-156-Alanine (Ala) completely prevented the formation of NPR1 oligomers, strongly reducing the formation of dimers and enhancing resistance to *Pseudomonas syringae* pv. *maculicola*, suggesting that Cys-156 is a redox sensor and integral to NPR1 homeostasis [22,92]. Similarly, mutations in Cys-82 and Cys-216 also increases the accumulation of monomers, leading to increased expression of NPR1 associated genes [93].

The NPR1-TGA1 complex binds *activation sequence-1* (*as-1*), which is present in the promoter of various NO-responsive immune-related genes, including *PR1*, *WRKY18*, *WRKY38*, *WRKY62* and *Systemic Acquired Resistance Deficient 1* (*SARD1*) that initiate and modulate SA-mediated immune responses [94–97]. TGA1 and TGA4 contain redox sensitive Cys residues and in this context, TGA1 has been demonstrated to be *S*-nitrosylated and *S*-glutathionylated by GSNO, with these modifications proposed to enhance TGA1 DNA binding activity and protect TGA1 from other oxidative modifications [24]. However, recently the significance of TGA1 and TGA4 redox modifications has been called into question, suggesting these PTMs of TGA1 may not be necessary for the transcriptional enhancement activity [98]. Although further experiments may help confirm this posit [99].

Recent structural analysis of the NPR1-TGA3 complex has revealed that the transcriptional activation form consists of dimeric NPR1 proteins engaged with two TGA3 dimers, suggesting that NPR1 may bridge these transcription factors into an enhanceosome [92]. However, NPR1 binding to TGA3 has thus far not been demonstrated to be redox dependent and may not be mediated by *S*-nitrosylation of TGA3 [24]. The behaviour of NPR1 is contrasted by NPR3 and NPR4, two closely related proteins, that instead repress TGA-related gene expression. However, SA binding to NPR3/4, suppresses this function, subsequently enabling SA-dependent gene expression [100].

TRXh5 is strongly induced following foliar application of SA, treatment with pathogen elicitors and inoculation with avirulent pathogens, tying its activity to SA-mediated immune responses [18,22,101]. TRX*h3*, may also possess denitrosylase activity but likely at a lower level than that of TRX*h5* and is constitutively expressed, perhaps owing to more general functions associated with cellular homeostasis [18,102]. However, *A. thaliana trxh3* mutants do show impaired *PR* gene expression, suggesting TRX*h3* activity has a role facilitating the SA signalling network [22]. Other than the transcriptional activator NPR1, targets of TRX*h5* mediated denitrosylation have remained elusive. For example, glyceraldehyde 3-phosphate dehydrogenase isoenzyme (GAPDH) activity is inhibited through *trans*-nitrosylation and this activity was not restored by TRX*h5 in vitro*, suggesting that GAPDH is unlikely to be targeted by TRX*h5* for denitrosylation *in-vivo*. Instead, GSH may mediate this process, evidenced by full conversion of GAPDH to its active enzyme state by GSH *in v*itro [103]. However, there is evidence to suggest that TRX*h5* is a potent protein-SNO denitrosylase with a wide set of endogenous targets [18].

The *gsnor1-3* mutant accumulates high levels of GSNO, while the *NO overexpression 1-1* (*nox1-1*) line accumulates excessive L-arginine, a prerequisite for NOS-like mediated NO production. Both mutants display high levels of *S*-nitrosylation, impaired *R*-gene mediated resistance and reduced expression of immune-related genes [18,44,104]. Transgene mediated constitutive expression of GSNOR in these lines rescued the phenotype of *gsnor1* but not *nox1*, while the opposite was true following constitutive expression of TRX*h5*, where the *nox1* phenotype was restored but not that of *gsnor1*. Given that both mutants are compromised in SA synthesis and have lowered TRX*h5* expression, this indicates that the excessive NO produced in the *nox1* phenotype results in the *S*-nitrosylation of a distinct set of proteins from that seen in the *gsnor1* line, which accumulates excessive GSNO. Together, this further establishes both GSNOR and TRX*h5* as critical regulators of NO signalling, however, each of these enzymes appears to exhibit a distinct set of targets and regulatory behaviours [18,104].

The denitrosylation activity of TRX*h5* was demonstrated to be dependent on only one of its two active site Cys residues, where replacement of either Cys-39 or Cys-42 with Ser mutations did not affect its denitrosylation activity. Mutation of both these Cys residues in combination, however, abolished TRX*h5* denitrosylation activity [18]. Additionally, this indicated that TRX*h5* may carry out some of its activity as a *trans*-denitrosylase, indicated by the presence of TRX*h5*-SNO following denitrosylation of target proteins and the absence of TRX*h5*-SNO following incubation with either TRX*h5*Cys-39-Ser or TRX*h5*Cys-42-Ser *in vitro*. Thus, suggesting these Cys residues receive the NO group following *trans*-denitrosylation. Similarly, efficient denitrosylation of alkylated plant protein-SNO by TRX*h5*Cys-42-Ser indicated that TRX*h5* engages in *trans*-denitrosylation of a large subset of protein-SNO *in planta* [18]. TRX*h5* activity is regulated by NADPH-dependent thioredoxin reductase (NTRA), which regenerates reduced TRX*h5*, enabling it to continue its denitrosylase activity. Notably, *A. thaliana ntra* protoplasts treated with an NO donor accumulated considerably more protein-SNO than both wild-type and the double mutant *trxh3 trxh5*, indicating that NTRA is essential to TRX*h* mediated denitrosylation in plants [18].

1.6. Novel emerging mechanisms of denitrosylation

In a recent quantitative proteomic analysis of *A. thaliana* plants lacking GSNOR function, the most significant increase in expression was observed in two proteins belonging to the aldo-keto reductase (AKR) superfamily, AKR4C8 and AKR4C9 [105]. Interestingly, recent reports investigating alternative routes for SNO regulation discovered that human AKR1A1 is linked to NO metabolism and can turn over GSNO in an NADPH-dependent manner, contrasting that of GSNOR, which requires NADH to metabolise GSNO [106,107]. *A. thaliana* AKR4C8 and AKR4C9 were found to have significant homology with human AKR1A1, suggesting they may share functionality associated with GSNO turnover. Interestingly, AtAKR4C8, 9, 10 and 11 all have NADPH-dependent GSNO reduction activity *in vitro* albeit at an efficiency roughly 9-fold lower than that of GSNOR. These results may suggest that in the absence of GSNOR activity, ARK4C enzymes might have a role in regulating NO function [105]. As such, AKR activity may account for the ~10% of retained GSNOR activity observed in *gsnor1-3* mutants [108]. Finally, human AKR1A1 is known to turn over the low molecular weight thiol *S*-nitroso-coenzyme A (SNO-CoA) which can mediate protein *S*-nitrosylation in yeast and humans [106,109]. Accordingly, *A. thaliana* AKR4Cs were found to efficiently degrade SNO-CoA in an NADPH dependent manner at a rate between 3 and 4-fold of their GSNO degradation activity [105]. There are no reports on the ability of SNO-CoA to mediate *S*-nitrosylation in plants but given the efficiency with which *A. thaliana* AKRs can degrade these low molecular weight thiols, this activity may have a role in plant NO signalling associated immune responses.

1.7. S-nitrosylation modulates transcriptional and epigenetic mechanisms

While the link between NO and the induction of immune-related genes has been well established [8,94,110–112], insights into the underpinning molecular mechanisms are only now beginning to emerge and remain difficult to study. *S*-nitrosylation of TGA1 for example, was first proposed to enhance its DNA binding capacity, however, this has recently been disputed (described above) [24,98]. AtMYB30 is a well characterised director of immune-related gene expression and has been reported to be *S*-nitrosylated on Cys-49 and Cys-53, inhibiting its DNA binding ability [113]. The crucial role played by AtMYB30 in the regulation of plant disease resistance is underlined by the finding that

AtMYB30 is targeted by the *Xanthomonas* type III effector XopD, resulting in suppression of AtMYB30-mediated immune responses [114]. MYB30 is also targeted by the E3 ubiquitin ligase MIEL1, facilitating its proteasomal degradation. Inhibition of MIEL1 increased MYB30 accumulation following bacterial infection, triggering the HR [115]. Together, this outlines a role for MYB30 in the positive regulation of the HR and suggests that MYB30 can be reversibly inhibited by *S*-nitrosylation to dampen HR development.

A recently identified zinc finger transcription factor, *SNO-regulated gene 1* (*AtSRG1*), was found to be significantly upregulated by high SNO levels and both virulent and avirulent strains of *Pst*DC3000. Further, SRG1 was demonstrated to be *S*-nitrosylated at Cys-87 in response to the same cues, resulting in cessation of its transcriptional repression activity and dampening immune responses. Also, overexpression of SRG1 enhanced SA synthesis and basal disease resistance but reduced plant stature. In contrast, loss-of-function mutations in *SRG1* compromised resistance and enhanced plant stature. SRG1 may therefore target the promoters of genes coding for one or more immunity repressors contributing to the activation of immune responses. *S*-nitrosylation of SRG1 during the later stages of transient immune activation, inhibited this repressive activity, presumably resulting in the transcription of one or more immune repressors, contributing to a dampening of the immune response [116]. Further investigation of the SRG family led to identification of both SRG2 and SRG3 as positive regulators of SA signalling. Interestingly, SRG3 but not SRG2 was found to be regulated by *S*-nitrosylation, with this modification resulting in the downregulation of immune responses. Interestingly, the combined transcriptional repression activity of the three identified SRG proteins may function in an additive manner, enabling fine tuning of plant immune in response to NO cues. Further, single and double knockout lines of the various combinations of *SRG* genes revealed that loss-of-function of a specific SRG impacts the expression of the other two related *SRG* genes. Most notably, *srg3* was the most impactful, downregulating expression 80% and 70% for *SRG2* and *SRG1*, respectively. Collectively, these three NO-responsive transcriptional repressors constitute a major SNO-controlled mechanism, that enables fine tuning of the immune response [117].

The emerging data is also beginning to uncover epigenetic control mechanisms linked to NO mediated transcriptional regulation. *S*-nitrosylation has been proposed to participate in the modification of histones indirectly, through modification of nuclear proteins that in turn influence the transcription of immune-related genes through chromatin remodelling [118–120]. A major initial piece of evidence for this stemmed from GSNO treated nuclear proteins, extracted from *A. thaliana* cell cultures inoculated with avirulent *Pst*DC3000. The authors purified 117 candidate nuclear localised proteins with SNO modifications, strongly indicating that there may be a significant number of redox-sensitive proteins operating in the nucleus. Interestingly, two of these proteins were identified as HDT2 and HDT3, both type-2 histone deacetylases (HDACs); a unique plant-specific HDAC family also referred to as HD-tuins [121]. HDTs have previously been implicated in the negative regulation of cell death and the control of ROS/NO synthesis in *N. tabacum* in response to the oomycete elicitor cryptogein, indicating that they may have a role in regulating the HR in response to attempted pathogen ingress, but changes to protein function following their *S*-nitrosylation have yet to be studied [122,123].

NO has also been shown to affect histone acetylation in *A. thaliana*, where treatment of protoplasts with GSNO increases the occurrence of histone 3 (H3) and H4 acetylation marks. This effect was reversed following application of the NO scavenger CPTIO and similarly, HDAC activity was restored by dithiothreitol (DTT), which can reverse Cys-NO modifications, together suggesting that high cellular NO can result in HDAC *S*-nitrosylation, with associated inhibition of enzyme activity. Further, treatment with SA similarly inhibited HDAC activity, indicating that immunity-derived NO signalling is likely to function in a similar fashion. Moreover, GSNO caused hyperacetylation on several genes related to immune responses, which increases DNA accessibility. These included *TRXh3* and some *WRKY*, *TGA* and *PR* family members, providing further evidence that HDAC inhibition may facilitate increased immune-related gene expression [124]. The authors hypothesise that NO may act directly on HDACs through *S*-nitrosylation, inhibiting their activity and facilitating acetylation of histones in a manner well documented in mammalian HDACs [124–126]. In contrast, DNA methylation generally serves to suppress epigenetic enhancement of transcription as well as other modifications including transposable element shuffling and gene recombination [127,128]. A study investigating DNA methylation in *A. thaliana gsnor1-3* plants found that the major DNA methylation donor S-adenosylmethionine (SAM) accumulated to substantially higher levels compared to the wild-type Col-0 line. When SAM is demethylated during the transmethylation of DNA, S-adenosylhomocysteine (SAH) is released and behaves as a competitive inhibitor of DNA methyltransferases. As such, a strong indicator of overall DNA methylation in cells can be inferred from the ratio of accumulated SAM to SAH, defined as the methylation index. Interestingly, several proteins involved in the methylation cycle have previously been demonstrated to be *S*-nitrosylated suggesting that GSNOR activity is likely to play a significant role in homeostasis of the methylation cycle [64,120,129–131]. The *gsnor1-3* line accumulated 61% more SAM, increasing the SAM/SAH ratio by 47% suggesting that *gsnor1-3* plant genomic DNA was significantly more methylated in the absence of GSNOR activity. This conclusion was supported by global histone profiling which revealed a significant increase in the presence of the repressive H3K9me2 methylation mark in chromatin from *gsnor1-3* plants. However, this increase in DNA methylation did not correlate significantly with changes in gene expression compared to the wild-type line. The authors suggest that the increased H3K9me2 mark in *gsnor1-3* plants could contribute to the disease-compromised phenotype by reducing transposable element shuffling, which may be necessary for immune responses [108].

The arginine methyltransferase PRMT5 in *A. thaliana* was also shown to be *S*-nitrosylated on Cys-125, enhancing its methyltransferase activity on the spliceosome. PRMT5 has a critical role in mediating stress-related pre-RNA splicing, particularly in response to salt stress. Interestingly, salt stress induces a NO burst in affected plant cells, which results in *S*-nitrosylation of PRMT5. Further, in *gsnor1-3* plants, PRMT5 becomes *S*-nitrosylated resulting in constitutive activation of stress-related pre-RNA splicing [132]. PRMT5 is also involved in the methylation of histone H4R3 to generate the repressive mark H4R3sme2, but *S*-nitrosylation was not found to be a prerequisite for this activity during either unstressed or salt-stressed conditions. Recently however, PRMT5 was found to be critical for the initiation of immune responses against avirulent *P. infestans* isolates in potato (*Solanum tuberosum*). Here, a reduction in the H4R3sme2 repressive mark on immune-related gene promoters followed 3 h after the first peak of the NO burst, which occurred 3 h post infection (hpi). Both GSNO treatment and *P. infestans* inoculation resulted in a decrease of the H4R3sme2 repressive mark and an increase in the H4R3Sme3 active mark at the immune-related genes *R3a* and *HSR203J* at 6 hpi, resulting in their increased expression. Conversely, treatment with a PRMT5-selective inhibitor impaired expression of *R3a* and interfered with the HR following *P. infestans* inoculation [75]. *R3a* and *HSR203J* have a role in race-specific resistance against *P. infestans* and the onset of cell death, respectively [133,134]. Together, this research has uncovered PRMT5 as an important NO-responsive epigenetic regulator with roles in both abiotic and biotic stress responses. Similarly, while elucidation of the nuclear protein targets involved in relaying the NO signal to histones is still in its infancy, there is mounting evidence that dysregulation of protein-SNO signalling has a negative impact on histone epigenetic function with consequences in plant immunity.

1.8. S-nitrosylation regulates proteostasis during plant immunity

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is a multifunctional enzyme with roles in glycolysis and the Calvin cycle. In *A. thaliana* this enzyme has been demonstrated to be a target of *S*-nitrosylation and other oxidative modifications on a reactive cysteine located at the active site, resulting in enzyme inhibition [103]. Moreover, AtGAPC1, a GAPDH isoform, undergoes *S*-nitrosylation following inoculation with avirulent *Pst*DC3000, suggesting a role for NO-regulation of GAPC1 in plant immunity [20,135]. In mammals, orthologous GAPDH has been shown to localise to the nucleus following its *S*-nitrosylation, whereby it stabilises the E3 ubiquitin-protein ligase SIAH1, enabling degradation of nuclear proteins via ubiquitination, triggering NO-dependent programmed cell death [136,137]. A similar pattern of nuclear localisation of the GAPC1 isoform has been observed in *A. thaliana* during the immune response, however, it remains to be determined whether *S*-nitrosylation is a critical prerequisite for this activity, as mutation of the target Cys to Ser, precluding *S*-nitrosylation, did not prevent the nuclear localisation [138]. Moreover, there is still ongoing debate about whether *S*-nitrosylation, as opposed to another oxidative modifications, is the fundamental prerequisite for GAPDH triggered apoptosis in mammals. For example, it may be the case that mere inhibition of GAPDH activity drives its nuclear localisation [139]. Recently, GAPC1 and GAPC2 were demonstrated to interact with autophagy-related protein 3 (ATG3), an E2-like ubiquitin-conjugating enzyme in *N. benthamiana*. Here, overexpression of GAPCs perturbed autophagy while silencing of GAPCs enhanced the HR triggered by either avirulent *Pst*DC3000 or TMV. The interaction between these proteins is antagonised following treatment with the ROS generator methyl viologen, suggesting that oxidative modification of GAPCs could be a factor in preventing interaction with ATG3 to induce autophagy and the HR [140].

SUMOylation involves the attachment of the Small Ubiquitin-like Modifier (SUMO) to target proteins, catalysed by SUMO conjugating Enzyme 1 (SCE1), modulating the function of the target protein. *S*-nitrosylation has also been demonstrated to influence SUMO1/2 SUMOylation, counteracting the suppressive effect on plant immunity of this protein modification, evidenced by constitutive activation of pathogenesis related genes and enhanced pathogen resistance in mutants with dysregulated SUMO1/2 SUMOylation [141,142]. SCE1 was demonstrated to be *S*-nitrosylated on Cys-139 in response to pathogen challenge, leading to the inhibition of SUMO conjugating activities of SCE1 [141] (Fig. 2). Further, mutation of Cys-139 to Ser resulted in drastically compromised immunity against both virulent and avirulent strains of *Pst*DC3000, demonstrating that Cys-139 is a potent redox sensor enabling regulation of SCE1 via *S*-nitrosylation, facilitating

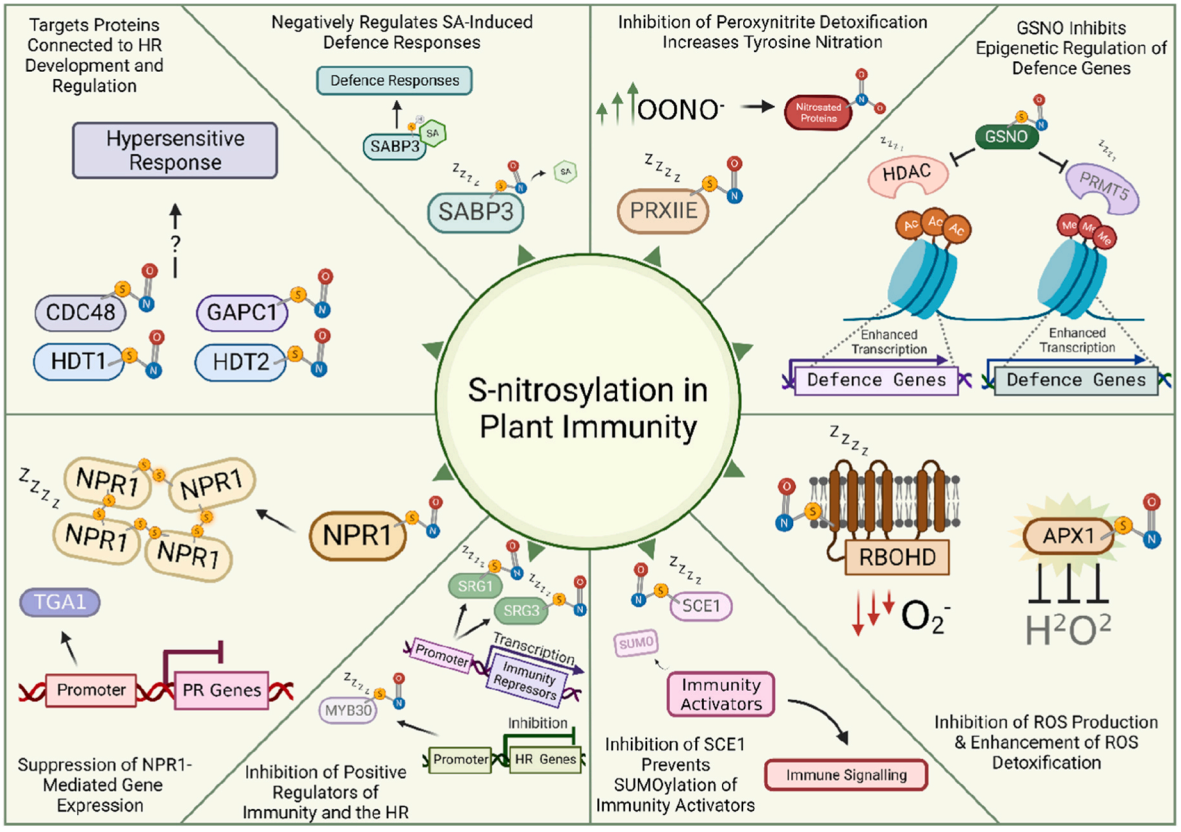

Fig. 2. Overview of Proteins and Pathways Confirmed to be Regulated by *S*-nitrosylation and GSNO During Plant Immune Function.
S-nitrosylation is a major post translation modification where nitric oxide (NO) is relayed between proteins on specific reactive cysteine thiols, often altering protein function and behaviour. During the immune response to pathogens, plants typically engage a nitrosative burst at the site of entry causing a drastic shift in locally available NO, stimulating a wave of S-nitrosylation signalling. Here, enzymes such as S-nitrosoglutathione reductase (GSNOR) and thioredoxin-h5 (TRXh5) regulate the occurrence of S-nitrosylation by reducing the NO donor S-nitrosoglutathione (GSNO) or through direct de-nitrosylation of protein targets. The biphasic nature of the nitrosative burst adds complexity to NO signalling, where different aspects of immunity may be amplified or inhibited during the different phases of the immune response. The diagram summarises the influence of S-nitrosylation over the regulation of plant immunity. Notably, several proteins with suspected roles in hypersensitive response (HR) regulation have been demonstrated to be S-nitrosylated during immunity but their precise role has yet to be elucidated (top left panel). Similarly, several epigenetic regulators were found to be inhibited by GSNO resulting in enhanced defence gene expression, suggesting they may be S-nitrosylated during immunity. Pointed arrows indicate enzymatic activity, release from a promoter region or the continuation of a chain of events, while flat headed arrows indicate an inhibitory effect. Triple arrows indicate an increasing or decreasing concentration. Stacked "Z's" indicate an inactive state. Figure generated in BioRender.com.

SA-dependent immune responses [141].

Cell division cycle 48 (CDC48) is a highly expressed AAA + ATPase (ATPases Associated with diverse cellular Activities) that has a role in the ubiquitin mediated protein degradation network in plants [143]. CDC48 has been repeatedly demonstrated to be subjected to *S*-nitrosylation on multiple different Cys residues in response to exogenous NO treatments, cryptogein and *Pst*DC3000 [37,64,121,144]. A role for CDC48 in plant immunity has been gradually emerging over the years, where CDC48 activity is now increasingly associated with protein turnover and degradation, most notably that of immune receptors and viral proteins, respectively [143]. CDC48 also appears to have a role in orchestrating the HR in response to cryptogein, where overexpression prematurely triggers the HR in tobacco cells. Here, overexpression also results in a failure of these cells to establish increased proteasomal activity as seen in wild-type cells in response to cryptogein [145]. However, there are still major questions regarding the significance of CDC48 *S*-nitrosylation during the immune response because no change in protein behaviour, localisation or interactivity has been demonstrated. One hypothesis suggests that *S*-nitrosylation may inhibit CDC48 ATPase activity, a phenomenon shown to occur *in vitro* [37]. Of note, AtCDC48 interacts with multiple members of the GAP family including GAPC1 and redox regulating proteins such as APX1 and CAT2, suggesting CDC48 may have a role in redox regulation. Further, both GAPC1 and APX1 can be *S*-nitrosylated, suggesting that CDC48 could be involved in an SNO signalling pathway with these proteins during the immune response [143]. Lastly, tobacco cells overexpressing CDC48 were found to contain increased immune-related proteins such as PR1 and WRKY family members, as well as SA-synthesis enzymes, following isolation of ubiquitinated proteins, suggesting that CDC48 may target core components of plant immunity for ubiquitin-mediated degradation [145].

1.9. Pathogen effector proteins are targeted by S-nitrosylation

Interestingly, the bacterial effecter protein HopAI1, was found to be *S*-nitrosylated during pathogenesis on its only Cys residue, inhibiting its phosphothreonine lyase activity. HopAI1 is secreted by *Pst*DC3000 during pathogenesis and binds to plant mitogen-activated protein kinases (MAPKs), interfering with HR signalling and enhancing plant susceptibility [146]. Here, *S*-nitrosylation of HopAI1 during the onset of the HR was demonstrated to inhibit the ability of this effector to bind endogenous MAPKs, likely through a conformation change, leading to restoration of MAPK signalling and completion of the HR [146]. Notably, both bacterial and fungal pathogens produce NO as a virulence factor during pathogenesis, perhaps indicating that these pathogens have adapted to “fight fire with fire” [11]. Collectively, this research demonstrates a new function for *S*-nitrosylation in plant immunity and will hopefully encourage further research aimed at identification of effector proteins that are vulnerable to inhibition by *S*-nitrosylation.

Intriguingly, the secreted proteome of the oomycete *P. parasitica* led to the inhibition of GSNOR both *in vivo* and when applied to *A. thaliana* seedlings, suggesting that *P. parasitica* may possess effectors that target GSNOR during pathogenesis [63]. Since inhibition of GSNOR would likely lead to an increase in protein *S*-nitrosylation due to GSNO accumulation, this suggests that growth of *P. parasitica* may be facilitated by dysregulation of *S*-nitrosylation. Additionally, the fungal toxin victorin, secreted by the necrotrophic fungus *Cochliobolus victoriae* during pathogenesis, was demonstrated to target TRX*h5* directly, inhibiting the activity of this enzyme. Victorin-inhibited TRX*h5* is recognised by an NB-LRR, Locus Orchestrating Victorin Effects 1 (LOV1), triggering cell death. Here however, cell death development exacerbates host susceptibility to *C. vitoriae*, instead of limiting pathogen spread, due to the necrotrophic lifestyle of this fungal pathogen [147–149]. Thus, *C. vitoriae* exploits a key host defence mechanism against biotrophic pathogens to help enable its necrotrophic infection strategy.

2. Conclusions

Since its discovery in plants, *S*-nitrosylation has been found to cross-talk with multiple nodes of immune signalling. The discovery that GSNOR activity is regulated by *S*-nitrosylation adds complexity to the role of this enzyme in immunity and outlines an increasing requirement for temporal evidence of protein *S*-nitrosylation during immune responses. Similarly, TRX*h5* is critical to protein denitrosylation and the initiation of plant immunity but has a specific set of protein targets, most of which have yet to be revealed. *S*-nitrosylation is also integral to ROS and RNS cross-talk where it exerts influence on the synthesis of radicals and facilitates a return to cellular homeostasis via redox feedback loops. Recent developments in the field have expanded the reach of *S*-nitrosylation towards new areas of cellular reprogramming, including histone epigenetics and proteostasis, further cementing the NO signalling network as an indispensable central regulator of the plant immunity.

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