Received: 25 January 2018 | Revised: 8 June 2018 | Accepted: 14 June 2018

DOI: 10.1002/jmr.2754

REVIEW

WILEY Journal of Molecular Recognition

A recent advance in the intracellular and extracellular redox post-translational modification of proteins in plants

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Funding information
Consejo Nacional de Ciencia y Tecnología (CONACYT), Grant/Award Number: U0004-2015-1_259915, CB-2014-01_242990 and 257436

Abstract

Plants, as sessile organisms, have acquired through evolution sophisticated regulatory signal pathways to overcome external variable factors during each stage of the life cycle. Among these regulatory signals, two pathways in particular, reactive oxygen species and reactive nitrogen species, have become of significant interest in several aspects of plant biology, underpinning these molecules as critical regulators during development, cellular differentiation, and plant-pathogen interaction. Recently, redox posttranslational modifications (PTM), such as *S*-nitrosylation on cysteine residues and tyrosine nitration, have shed light on multiple protein targets, as they are associated with signal networks/downstream metabolic pathways, capable of transducing the imbalance of redox hemostasis and consequently redirecting the biochemical status under stress conditions. However, most of the redox PTM have been studied only in the intracellular compartment, providing limited information concerning redox PTM in the extracellular matrix of plant cells. Nevertheless, recent studies have indicated the plausibility of redox PTM in extracellular proteins, including cell wall associated proteins. Accordingly, in this review, we endeavor to examine evidence of redox PTM supported by mass spectrometry data in the intracellular and extracellular space in plant cells. As a further example, we focus the last section of this review on illustrating, using molecular dynamics simulation, the effect of *S*-nitrosylation on the structural conformation of well-known cell wall-associated proteins including pectin methylesterase and xyloglucan endo-transglycosylases.

KEYWORDS

cell wall, molecular dynamics simulation, post-translational modifications, proteomics, reactive nitrogen species, reactive oxygen species, *S*-nitrosylation

1 | INTRODUCTION

The improvement of genomic pipelines and platforms has provided the means to witness the completion of several genome sequences of a broad range of plant species, providing invaluable information about the molecular and biochemical foundation of multiple biological processes.[1] However, the genomic data does not contain sufficiently detailed information to define the vital regulatory players in plant biology. This limited the number of predicted proteins based on genomic sequence and RNA processing steps. Moreover, because of the different proteoforms resulting from posttranslational modifications (PTM) from single gene product, the number of proteins from a single genome increases exponentially. Moreover, genetic approaches provide limited information associated with gain and loss of function,

precluding dynamic regulation of cellular processes.[2] By contrast, profiling and characterizing PTM using proteomic tool boxes have shed light on some crucial processes in plant biology, such as the case of plant response to stress and plant immunity.[2-4] Large-scale PTM, including studies of phosphorylation, acetylation ubiquitination, and sumoylation, have revealed critical clues to the perception of biotic/abiotic factors and signal transduction leading to the induction of plant cell defense mechanisms.[5-7] One specific example is the site-directed mutation of the *N*-glycosylation site Asn143 of the external domain of the receptor-like kinase sensing EF-TU. The absence of the *N*-glycan on this protein prevents the plant from perceiving the microbe-associated molecular pattern and reactive oxygen species (ROS) production under biotic stress, consequently affecting the signal transduction of its defense response and plant immunity.[8-10]

Increasing evidence has suggested that the crosstalk between ROS, reactive nitrogen species (RNS), redox PTM, antioxidants, and growth regulator signal pathways play a crucial role during, nitrogen fixation, cellular differentiation, development, fruit ripening, and biotic and abiotic stress. Nonetheless, very few components of these interacting signals have been molecularly characterized.[11-18] In plant cells, the primary sources of ROS and RNS are the chloroplast, mitochondria, peroxisome, and apoplast.[12,19-22] ROS generated in plant cells include singlet oxygen ($^1O_2$), superoxide radicals ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), hydroperoxyl radicals ($HO_2^{\bullet}$), alkoxyl radicals ($RO^{\bullet}$), peroxyl radicals ($ROO^{\bullet}$), and hydrogen peroxide (H_2O_2). Also, RNS comprises nitric oxide (NO), peroxynitrite (NOO^-), dinitrogen trioxide (N_2O_3), *S*-nitrosoglutathione (GSNO) nitrotyrosine (NO_2-Tyr), and nitro-fatty acids (NO_2-FA).[22,23] Recent studies have reinforced the interconnection between ROS and RNS at different points. Under abiotic stress, outbursts of RNS drive the regulation of ROS-scavenging enzyme activities by cysteine (Cys) *S*-nitrosylation (SNO) and tyrosine nitration (NO_2-Tyr). Superoxide dismutase (SOD), catalases, and members of the ascorbate-glutathione cycle including ascorbate peroxidase (APX), monodehydroascrobate reductase, dehydroascorbate reductase (DHAR), and glutathione reductase are some examples of ROS-scavenging proteins modulated by redox PTM.[11] In addition, a tight partnership between ROS and RNS has been demonstrated during the hypersensitive response and stomatal closure under water deficit conditions.[24] Nonetheless, most studies of base redox PTM have been directed toward the intracellular compartment, determining that proteins associated with fundamental metabolisms such as photosynthesis, glycolysis, and gene expression are regulated with redox PTM.[12,25] By contrast, limited studies have focused on scrutinizing redox PTM's role in the extracellular matrix, such as the external face of the plasma membrane, apoplast, and cell wall. The overproduction of $O_2^{\bullet-}$ in the apoplast by the NADPH oxidase (plant respiratory burst oxidase homolog, RBOH) with the enzymatic or spontaneous conversion of $O_2^{\bullet-}$ to H_2O_2 during biotic stress and the enzymatic production of NO in the apoplast under abiotic stress suggests that the redox PTM of extracellular proteins is associated with cellular processes such as cellular differentiation, growth, and development.[21,24,26-29] Furthermore, recent comprehensive redox proteomic studies provide the first indication of redox PTM on extracellular protein including several cell wall-associated proteins.[30-32] Notably, cell wall proteins are posttranslationally modified by *N*-glycan/*O*-glycans during their transduction and transportation through the secretory system. Redox PTM on cell wall glycoproteins provide another level of complexity in proteomics studies due to the higher dynamic range of unmodified proteins compared with glycoproteins. Besides, we cannot rule out crosstalk between redox PMT and other extracellular PTM such as glycosylation or phosphorylation.

In this review, we endeavor to catalog redox PTM by describing critical examples of well-characterized intracellular redox PTM and newly proposed extracellular redox PTM. Finally, we provide a base molecular dynamics simulation of the Cys SNO of two essential cell wall proteins, including pectin methylesterase (PME) and xyloglucan endo-transglycosylases (XTH).

1.1 | Redox PTMs

ROS and RNS can affect the proteome of plant cells by providing a redox-sensitive post-translational modification (PTM) that can result in several outcomes, including the inactivation, upregulation, translocation, oligomerization, and proteolytic processing of gene products.[33-37] In the past decade, we have observed the generation of an extensive compendium of information related to redox base PTM, including protein targets associated with several biochemical and signal pathways and molecular functions. Of particular note are enzymes associated with carbon metabolism, including glycolysis, TCA cycle, Calvin-Benson cycle, starch biosynthesis, and critical members of the ascorbate-glutathione cycle, as well as plasma membrane proteins, receptors, MAP kinases, and transcription factors. Several excellent studies have described the importance of target proteins of redox base PTM located in different intracellular compartments, such as the cytoplasm, mitochondria, chloroplast, and peroxisome, and focusing on various contexts in plant biology. In this section, we endeavor to classify critical examples of proteins determined with redox base PTM in the intracellular and extracellular compartment of plant cells. We focused on redox PTM information validated with the mass spectrometry approach.

1.2 | Intracellular redox PTMs

1.2.1 | Carbonylation

Carbonylation is an irreversible redox PTM associated with protein oxidation. In this PTM, reactive carbonyl species (RCS) such as aldehydes and ketones, which are downstream products of ROS, are added to the protein as a result of multiple redox factors. In addition, metal-catalyzed oxidation happens when metal ions interact with H_2O_2, generating a highly reactive hydroxyl radical, which oxidizes amino acid side chains (residues of Lys, Pro, Arg, and Thr) or creates a cleavage in the proteins with the generation of carbonyl groups. Lipid peroxidation and glycation/glycoxidation can also generate RCS, which can induce protein carbonylation under abiotic stress. In most cases, heavily carbonylated proteins form aggregates associated with proteolysis.[33,38] Mano et al,[39] by combining affinity-trapped proteins using antibodies against specific RCS (4-hydroxyl-(E)-2-nonenal) and iTRAQ analysis, were able to identify and determine the relative accumulation of 17 carbonylated proteins in Arabidopsis leaves under salt stress and continuous illumination. Furthermore, aldehyde-

reactive probe and streptavidin affinity chromatography and iTRAQ analysis allowed the identification of 22 additional protein targets of ROS. Proteins such as germin-like protein subfamily 3 member 1 (AT1G72610), luminal-binding protein 2 (AT5G42020), and nitrile-specifier protein 5 (AT5G48180) were identified in significantly higher proportion in leaves of plants under salt stress compared with control treatments. Although carbonylation sites were not reported, identified proteins were predicted with different subcellular locations including the cytosol, chloroplast, peroxisomes, and apoplast.

1.2.2 | Methionine oxidation

Methionine (Met) oxidation by H_2O_2 is one of the most well-known redox PTMs in proteins. The product of this PTM is the methionine sulfoxide (MetO), which conferred a lower grade of hydrophobicity of modified proteins. The MetO can be reversed by methionine sulfoxide reductases.[40] Surprisingly, very few proteomics studies have been directed to profiling Met oxidation. The most representative screening of Met oxidation in vivo was carried out in the leaves of Arabidopsis seedlings by comparing wild types with catalase 2 knock-out lines (H_2O_2 over-producers). In this proteomic study, 403 posttranslationally modified proteins with MetO were identified. Among these proteins, two glutathione *S*-transferases (GSTF9 and GSTT23) showed a drastic reduction of their enzymatic activity upon oxidation.[41]

1.2.3 | Persulfidation

The H_2O_2-dependent PTM comprises reversible intra and intermolecular disulfide bonds (S-S), reversible and highly unstable sulfenylation (-SOH), irreversible sulfinylation ($-SO_2H$), and *S*-sulfonylation ($-SO_3H$).[34,35] Furthermore, persulfidation (SSH) is a redox PTM where H_2S modifies oxidase Cys thiols (eg, SOH) of proteins. Under extreme oxidative stress, SSH can form the reversible $RSSO_3H$, which allows the restoration of free thiols and prevents the generation of irreversible SO_2H and $-SO_3H$. Therefore, SSH is a protective PTM against oxidative, metal, and abiotic stress. Waszczak et al[42] developed a YAP1-based sulfenic acid trapping pipeline coupled to a tandem affinity purification tag to profile in vivo the sulfenome in Arabidopsis cell suspension cultures. In doing so, they were able to identify 97 sulfenylated proteins under oxidative stress. Among these posttranslationally modified proteins, the DHAR2 showed that –SOH at the Cys20 drastically negatively affects its enzymatic activity. Recent proteomics studies point out that at least 5% of the Arabidopsis proteome is persulfidated.[31] Proteins that are targets of SSH include cytosolic glyceraldehyde-3-phosphate dehydrogenase (GAPDHC1, AT3G04120), APX, glutamine synthetase, and the abscisic acid receptors PYRABACTIN RESISTANCE 1 (PYR1) and PYR1-LIKE PROTEIN 1 (PYL1). The identification of these persulfidated proteins suggests that this PTM is associated with proteins in several biochemical pathways.[43] More detailed analysis showed that SSH modification of Cys32 on APX1 positively regulates the catalytic activity of this enzyme,[44] while SSH modification of Cys160 on GAPDHC1 induces the nuclear location of this protein.[45] By contrast, the enzymatic activity of GAPDHC1 is negatively affected when its catalytic Cys149 is modified by *S*-glutathionylation (*S*-SG). This PTM can be reversed by glutaredoxins and thioredoxins and might also provide a protective mechanism to irreversible $-SO_2H$ and $-SO_3H$ of Cys149.[46]

1.2.4 | *S*-glutathionylation

Under oxidative stress, glutathione (GSH) is converted to oxidized glutathione (GSSG) or can react with NO to generate GSNO. The former product promotes *S*-SG and the formation of S-S between near Cys residues via thiol-disulfide exchange, and the latter can induce *S*-SG and SNO.[47-50] In addition, mixed disulfides are generated when protein thiols are oxidased to sulfenic acid with a subsequent reaction with GSH. *S*-SG is a reversible PTM, where glutaredoxins and the GSH regeneration system play a crucial role.[51] In general, the detection of *S*-SG is carried out by tracking an increase of 305.11 Da of the molecular mass of Cys targets and tandem mass spectrometry (MS/MS) can provide solid evidence of this redox PTM. Target proteins of *S*-SG include cytoplasmic triosephosphate isomerase (cTPI) and chloroplast putative aldolase and thioredoxin F (TRXf), which are among the first proteins reported in plants that can undergo *S*-SG.[47,52] Furthermore, the Cys149 of recombinant A4-glyceraldehyde-3-phosphate dehydrogenase (A4-GAPDH) from Arabidopsis undergoes reversible *S*-SG and irreversible oxidation under treatment with GSSG and H_2O_2, respectively. Both PTM negatively affect the activity of A4-GAPDH. By contrast, the presence of the substrate and cofactor of this enzyme protects the catalytic Cys149 of this glycolytic protein from redox base PTM.[53] It was also found that under in vitro treatment of recombinant Arabidopsis cytosolic annexin (AnnAt1, AT1G35720) with an excess of GSSG, as well as under in vivo analysis (transient expression of annexin in *Nicotiana benthamiana* leaves), as well as under ABA treatment this protein undergoes *S*-SG of Cys111 and Cys239. Modification of this Cys reduces the affinity of this stress-related protein toward Ca^{2+}.[54] The possible regulation of AnnAt1 by *S*-SG could provide a critical mechanism as a link between calcium and ROS signaling under stress conditions. In fact, AnnAt1 overproducing transgenic plants displayed a higher resistance to water deficit than Col-0 wild types. The mitochondrial glycine decarboxylase complex is another example of a protein posttranslationally modified with *S*-SG. Treatments with different concentrations of GSNO of the partially purified decarboxylating subunit showed the *S*-SG of Cyc402, Cys463, Cys98, Cys943, Cys777, and Cys1022. The enzymatic activity of glycine decarboxylase complex (GDC) is negatively affected by treatments with GSNO, sodium nitroprusside (SNP), and the bacterial elicitor harpin. However, an in vivo experimental approach will be necessary to corroborate the regulation of GDC by *S*-SG or other redox PMT under stress conditions.[55]

Arabidopsis protein crude extracts treated with GSSG-biotin after reduction with DDT, analyzed by 2D-PAGE and peptide mass fingerprinting, provided information about the associated *S*-SG of Cys residues of several proteins. A closer examination of recombinant candidate proteins allowed the corroboration of the occurrence of *S*-SG on the Cys residues of the active sites of DHAR (Cys20) and zeta-class glutathione transferase (Cys19).[56] Similarly, in vitro analysis of recombinant TRXf and cTPI treated with oxidants (*N*-ethylmaleimide, H_2O_2, diamide, and GSSG) in the presence or absence of GSH provided robust information suggesting the

occurrence of *S*-SG in the Cys60 of TRXf, and the occurrence of Cys218 and Cys127 in cTPI. SO_2H and SO_3H were also detected in Cys127 of cTPI.[47,51] Interestingly, both Cys residues of cTPI can be modified by SNO.[57] Furthermore, Arabidopsis 3′-phosphoadenosine 5′-phosphate (PAP) phosphatase (SAL1) has been suggested as an oxidative stress sensor in the chloroplast. SAL1 modulates the levels of PAP during the retrograde signaling pathway, regulating the expression of plastid-redox-associated nuclear genes. Interestingly, SAL1 regulation is based on dimerization of monomers induced by intermolecular S-S between Cys167-Cys190 under oxidative bursts (H_2O_2 and $O_2^{\cdot-}$) and by the *S*-SG of Cys110 and Cys190 by the redox couple GSH/GSSG.[58]

Recently, Arabidopsis transgenic cell suspension cultures with a constitutive expression of nucleoside diphosphate genes (NDPK1, 2, and 3) provided a feasible system to uncover by affinity-purification protein and metabolite partners of these proteins. By using these transgenic lines, it was possible to co-purify and identify new partner proteins of NDPK1, 2, and 3. In addition, it was possible to co-elute glutathione *S*-transferases (GSTs) and reduced GSH with the NDPK1 complexes. Interestingly, NDPK1 undergoes *S*-SG on Cys43, which was corroborated by MS/MS. However, it is unknown if this finding implicates *S*-SG in NDPK1 in oxidative stress signaling.[59] Also, in vitro *S*-SG of Cys353 and Cys408 in the cytoplasmic domain of BRI1-associated receptor-like kinase 1 by glutaredoxin, C2 inhibits its kinase activity to such an extent that *S*-SG may transduce and regulate external signals associated with the extracellular matrix, including the apoplast and cell wall.[60] Altogether, *S*-SG, in addition to protecting Cys residues against irreversible oxidation, may provide a redox signaling mechanism in plants.

1.2.5 | S-nitrosylation

After almost two decades of study, NO has been confirmed as a key signal player in many plant biological processes. In plants, NO can be synthesized from arginine by a still-unidentified NO synthase and from nitrate by the nitrate reductase. Also, plasma membrane-bound nitrate reductase reduces nitrate to nitrite in the apoplast and, to some extent, nitrite further reduces to NO by nitrite: NO oxidoreductase. Furthermore, NO is produced by a non-enzymatic reaction by the reduction of apoplastic nitrate under acidic pH conditions.[26,61,62] Also, polyamine metabolism is associated with the connection of NO.[63] Exogenous application of polyamines and related monoacid precursors induces the production of NO.[64] By contrast, plant hemoglobins (Hb) have been considered an efficient scavenger of endogenous NO under stress conditions.[65] In fact, in barley, overexpression of the non-symbiotic hemoglobin gene HvHb1, which oxidizes NO to NO_3^-, showed increased resistance to drought conditions with concomitant reduction of NO content, ethylene biosynthesis, and higher production of putrescine and spermidine.[66] Altogether, the content of NO in plant cells is finely regulated under stress conditions, providing refined signal transduction through PTM of target proteins. As a matter of fact, overaccumulation of NO or exogenous exposure of NO-donor compounds such as SNP and GSNO can induce the reversible SNO on Cys residues that might play a key role in modulating the activity of essential enzymes.[38,67,68]

SNO is the most studied modification on thiol groups in plant proteins and comprises the reversible covalent addition of NO to Cys residues.[48,69] In addition, the content of GSNO, which is considered the primary NO reservoir, modulates the proportion SNO on proteins. Also, the content of GSNO in cells is regulated by the enzymatic activity of *S*-nitrosoglutathione reductase (GSNOR).[70] Moreover, in Arabidopsis, SNO negatively regulates the activity of GSNOR, thus providing a feedback regulation of this redox PTM.[71] Recently, the scrutiny of mutants with defective ectopic differentiation of vessel cells allowed researchers to suggest that GSNOR played a key role in the NO metabolism associated in some cases with defects in the activation of the *S*-nitrosylated (Cys-264 and Cys-320) vascular-related NAC-domain7 (VND7) transcription factor.[72]

The biotin switch assay, or variations of this method, have been used to purify SNO proteins, and biotinylated tryptic peptides have been used to track the Cys biotinylation mass of 414.20 Da by MS/MS.[73] Pioneering work in Arabidopsis, where protein extracts from cell suspension cultures treated with the NO-donor GSNO were subjected to the biotin switch method and affinity chromatography on a neutravidin matrix, paved the way to proteomics studies.[67,68] Furthermore, proteins extracted from plant leaves treated with NO gas were subjected to the biotin switch method, and affinity purified proteins were then analyzed by proteomics. This approach allowed the identification of several *S*-nitrosylated proteins associated with stress, signaling, and cellular proliferation.[68] Recent proteomics studies related to profiling of *S*-nitrosylated proteins under abiotic stress in different subcellular compartments, such as the mitochondria, peroxisome, and apoplast, underpin the SNO as a potential regulator associated with several biological processes.[19-21] Biochemical characterization of candidate proteins, such as glyceraldehyde-3-phosphate dehydrogenase and methionine adenosyltransferase 1 (MAT1), glycine decarboxylase, peroxiredoxin II E and II F, have suggested that SNO on specific Cys residues has negatively affected the enzymatic activity of the proteins as mentioned earlier.[55,74-77] Moreover, it has been suggested that SNO at Cys-147 on the active site of Arabidopsis type-II metacaspase (AtMC9) suppresses its activity.[78] This inhibition is carried out with the immature protein, while the mature AtMC9 is unaffected due to the occurrence of another Cys-29 residue located near the catalytic groove that can rescue the function of SNO-Cys147.[78] Moreover, studies in Arabidopsis have shown that SNO regulates the cytoplasmic oligomerization of PNR1, which is a key protein regulator associated with abiotic stress.[79] Moreover, SNO negatively regulates the activity of AtRBOHD by modifying the Cys890 under microbial infection. The NADPH-dependent oxidase AtRBOHD has been determined as a crucial factor connected to the induction of ROS during the hypersensitive response. Limiting the activity of AtRBOHD by SNO provides a negative feedback control of the hypersensitive response, underpinning the role of SNO in the plant immune response.[24,80]

Accumulative data has shown crosstalk between NO and plant growth regulators. For instance, the SNO on Cys140 of the Arabidopsis auxin receptor TRANSPORT INHIBITOR RESPONSE 1/AUXIN SIGNALING F-BOX (TIR1/AFB) induces the interaction of this receptor with the transcriptional repressors AUXIN/INDOLE-3-ACETIC ACID (Aux/IAA). This interaction promotes the degradation of Aux/IAA and

activates genes associated with the auxin signal pathway.[81] Another illustrative example is ABA overproduction under drought stress. In this condition, two main molecular events take place including the activation of the sucrose nonfermenting 1 related protein kinase 2s (SnRK2s), a vital component of ABA signal pathways, and the overproduction of NO associated with the SNO of SnRK2s on its Cys137. This modification inhibits the kinase activity of SnRK2s, suggesting a negative feedback loop regulation of ABA signaling.[82] In addition to the ABA signaling pathway, SNO also modulates cytokinin signaling through the modification of the histidine phosphotransfer proteins1 (AHP1) on its Cys115. During the perception of cytokinin, receptors undergo activation by autophosphorylation. AHP1 transduces the activation signal to downstream elements. However, under a higher concentration of NO, such as in Arabidopsis mutant's *nox1* and *gsnor1–3* during stress, the SNO of AHP1 inhibits its phosphorylation and consequently decreases cytokinin signaling.

Hu et al[32] reported the most comprehensive site-specific nitrosoproteomic study in plants, corroborating most studies mentioned earlier and also providing new relevant information such as the importance of SNO in chlorophyll metabolism, photosynthesis, and related pathways. Furthermore, this comprehensive study was able to suggest putative consensus sequences of SNO where acidic amino acids seem essential for this redox PTM. However, due to the high dynamic range of SNO proteins, the low-abundance and well-characterized SNO proteins mentioned earlier could not be detected by this study.[32]

1.2.6 | Tyrosine nitration

Protein nitration is a marker of nitro-oxidative damage and abiotic stress in plant cells.[83,84] The overaccumulation of nitric oxide radical (•NO) reacts with the superoxide anion ($O_2^{\bullet-}$), generating peroxynitrite ($ONOO^-$), which reacts with one of two equivalent ortho carbons of the aromatic ring Tyr to produce 3-nitrotyrosine (Tyr-NO_2).[85,86] Due to the fact that Tyr is prone to phosphorylation, the crosstalk between phosphorylation and Tyr-NO_2 might regulate multiple signal transductions. However, proteomic studies focusing simultaneously in these two PTM have not been conducted in plant cells.

Previous reviews have described some examples of proteins posttranslationally modified by Tyr-NO_2 and are supported by MS/MS data, including *O*-acetylserine (thiol) lyase A1 (Tyr302), glyceraldehyde-3-phosphate dehydrogenase (Tyr318), Methionine synthases (Tyr287), (NADP-isocitrate dehydrogenase (Tyr392), and PSBA (D1) of Photosystem II complex (Tyr262) (see Corpas et al[84]). In general, 2D-SDS-PAGE gels and immunodetection of Tyr-NO_2 and LC-MS/MS analysis of tryptic peptides by tracking an expected increase of 45 Da in mass have provided the essential tools to profile proteins modified by Tyr-NO_2. Surprisingly, robust protocols to dig deeper into this redox PTM have not been established. The active work in this field provides us with new vital examples.

Immunodetection of peroxisome protein by antibodies raised against NO_2-Tyr displayed the occurrence of this redox PTM. Among candidate proteins, detailed analysis of the recombinant peroxisomal NADH-dependent hydroxypyruvate reductase nitration on Tyr198 by $ONOO^-$ reveals significant inhibition of this protein in Arabidopsis.[87] In addition, recombinant SOD from different organelles, including mitochondrial Mn-SOD1 (MSD1), peroxisomal CuZn-SOD3 (CSD3), and chloroplastic Fe-SOD3 (FSD3) treated with $ONOO^-$, inhibited the activity of these ROS scavenging enzymes in different degrees. Mass spectrometry and site-directed mutagenesis studies showed that nitration on the Tyr63, located very close to the active site manganese of MSD1, significantly inhibits the enzymatic activity of this protein.[88] Downregulation of SOD can lead the overaccumulation of $O_2^{\bullet-}$ that can react with NO to produce $ONOO^-$ which in turn inhibits SOD, generating a self-amplification loop. By contrast, the regulation of the amount of $ONOO^-$ is carried out by the reductase activity of peroxiredoxins II E (PrxII E) from Arabidopsis. However, SNO inhibits the $ONOO^-$ detoxification activity of PrxII E.[74]

The negative regulation of SNO and Tyr nitration on the activity of proteins associated with the ascorbate-glutathione cycle, such as DHAR and monodehydroascrobate reductase, as well as the dual control including the decreased (Tyr nitration) and increased enzymatic activity (SNO) of APX, strongly suggest an interaction between antioxidant systems and NO. This interaction has been reviewed in detail elsewhere.[11]

1.3 | Redox PTMs in the extracellular matrix

Most studies mentioned earlier provide examples suggesting the redox PTM are implicated in several intracellular biochemical and signal pathways associated with the chloroplast, mitochondria, and cytosol. By contrast, to the best to our knowledge, limited studies related to redox PTM have been conducted in the extracellular matrix (such as the external face of the plasma membrane, and the apoplast, cell wall, rhizosphere, and cuticle).[21,89] Nonetheless, the apoplast is the ideal cellular compartment to generate and transduce ROS/RNS signals due to its specific physiological conditions, such as the marginal redox buffering capacity, overproduction of H_2O_2 with prolonged half-life, and spontaneous production of NO by nitrite reduction.[90]

Previous studies have demonstrated that NO, GSNO NO_2-Tyr, and GSNOR are detected in the epidermal cells, cell wall, and vascular tissues, supporting a possible role in long-distance signaling.[4,91] These molecules and enzyme showed a variable pattern of accumulation under abiotic stress in plant species. In some cases, such as in sunflower hypocotyls, the level of NO drastically decreased after wounding stress, while in pea, potato, and Arabidopsis leaves, the opposite was found.[4,92-94]

It is noteworthy to mention that most of the extracellular proteins, including a broad range of proteases, soluble apoplastic enzymes, and several cell surface receptors, are enriched with cysteine thiols that can form disulfide bridges, which provide superior stability and protection against oxidant and proteolytic activities.[95,96] Several mechanisms associated with the cleavage of disulfide bridges or the increase of thiolate anions (free Cys) in extracellular space have been described, including dithiol-disulfide exchange, alkaline hydrolysis, acid-based assisted hydrolysis, and apoplast alkalinization under biotic and abiotic stress.[96-98] Moreover, extracellular thioredoxins, protein disulfide isomerase and quiescin-sulfhydryl have been identified as the major player in the thiol/disulfide interconversion under stress conditions.[95,99,100] Consequently, one of these mechanisms could

potentially increase free cysteine in the extracellular space under stress, which can be prone to post-translational modification with ROS or RNS, modulating the function of the proteins of the apoplast, plasma membrane receptors, and cell walls.[97,101] In fact, accumulative evidence suggests that redox signaling is perceived in the apoplast by still unknown plasma membrane receptors, probably cysteine-rich receptor-like kinases, and the signal is transduced by inducing secondary ROS production in the chloroplast, which in turn induces the expression of nuclear genes by a not-well-understood retrograde signaling.[97,102]

Recent redox base proteomics studies have displayed that in most cases, redox modified proteins are mainly located in the chloroplasts, nucleus, cytosol, and mitochondria. By contrast, a lower number of redox modified proteins has been predicted in the extracellular compartment. However, previous studies showed the occurrence of SNO and NO_2-Tyr in apoplast proteins associated with abiotic stress, proteolysis, and cell wall metabolism.[21,89] In addition, Mano et al[39] showed that apoplastic proteins, such as germin-like protein subfamily 3 member 1 (AT1G72610) and peroxidase (POX) 34 (AT3G49120), are overaccumulated and posttranslationally modified by carbonylation under abiotic stress. Previously, Lozano-Juste et al,[30] by combining an immunoprecipitation assay with anti-3-nitroTyr antibody and 2D-SDS-PAGE and LC-MS/MS, carried out the identification of 127 proteins putatively undergoing NO_2-Tyr in Arabidopsis seedlings. Among these proteins, it was possible to identify well-known extracellular cell wall proteins such as pectinesterase-4 (At2g47030), POX 9 (At1g44970) cellulose synthase A catalytic subunit 4 (At5g44030), and 23-kDa cell wall protein (At2g06850), as potential targets of NO_2-Tyr. Moreover, Liu et al,[103] by using a high-throughput quantitative proteomic approach termed OxiTRAQ, were also able to identify extracellular cell wall associated proteins including pectin acetylesterases (O80731 and Q940J8), expansin (Q9LZT5), pectinesterase 1(Q43867), endoglucanase 3 (Q2V4L8), xyloglucan endotransglucosylase/hydrolase protein 4 (Q39099), beta-galactosidase 9 (Q9SCV3), probable polygalacturonase (Q94AJ5), protein COBRA (Q94KT8) and POX 25 (O80822), that undergo reversible redox PTM in Arabidopsis cell suspension cultures. In addition, under H_2O_2 treatment, β-D-glucan exohydrolase-like protein (Q8W112) and expansin B3 (Q9M0I2) were significantly altered in their redox state. The recent establishment of a robust pipeline for the identification of endogenous site-specific SNO proteins in Arabidopsis provided the avenue to understanding redox base PTM more broadly.[32] In this study, Hu et al[32] were able to identify 1195 endogenous SNO proteins; among these was included a small proportion of extracellular and cell wall-associated proteins. By analyzing Arabidopsis Col-0 plants, they were able to identify xyloglucan endotransglucosylase/hydrolase 7(AT4G37800, LDPSSGcGFASK) and cellulose synthase-interactive protein 1 (AT2G22125, SHQcEDTAAR), while in *gsnor1-3* plants (mutants with a significantly increased *S*-nitrosothiol level) it was possible to determine COBRA-like protein 6 precursor (AT1G09790, CCVSLSAFYYQNIVPcPTcScGcSS), pectin methylesterase 3 (AT3G14310, GQIHVEHMcSNALAMIK, GQIHVEHMcSNALAmIK), and PME PCR fragment F (AT5G53370, KDPNQNTGISIHAcK) (Supporting Information in Hu et al[32]). A more recent proteomic analysis of persulfidated proteins in Arabidopsis leaves provided additional evidence of extracellular proteins undergoing redox PTM. Bioinformatic analysis of identified persulfidated proteins indicated that SSH might modify extracellular proteins. Proteins determined to be extracellular included probable pectinesterase/pectinesterase inhibitor (Q94CB1 and Q9LXD9), pectin acetylesterase (O80731 and Q9SFF6), probable pectin lyase (Q9SUP5 and Q93Z25), POXs (Q9SI17 and Q9LHA7), probable xyloglucan endotransglucosylase/hydrolase protein 16 (XTH16, Q8LG58), and polygalacturonase inhibitor protein 1 (Q9M5J9). Although further experimental validation is necessary to corroborate the PTM and subcellular location of candidate extracellular proteins, this study opens the possibility of exploring the regulatory function of SSH during several biological processes.[31] In conclusion, primary components associated with RNS homeostasis are located in strategic sites such as epidermis cell and vascular tissues, suggesting a role for RNS in the extracellular matrix of plant cells and probably as signal molecules.

1.4 | Cell-wall-associated proteins key targets of redox base PTM

The cell wall is an active subcellular zone that is composed of cellulose microfibrils, hemicellulose, pectin (main sugar components), and structural proteins.[104] During the growth of a plant cell, proteins can account for up to 10% of the mass of the cell wall.[105] Also, the cell wall shows an extraordinary variety in composition and function across organs, cells, and species.[105,106] Exogenous application of NO donor SNP can modify cell wall features by modulating the activity of cellulose synthase and altering the content of cellulose, pectin, and hemicellulose of the cell wall; this alteration is associated with changes in root morphology in tomato. Treatment with a lower amount of NO increased the content of cellulose, while higher concentrations displayed opposite effect.[107] Furthermore, overaccumulation of pectin and hemicellulose by SNP (a NO donor) treatment was associated with the enhancement of cadmium tolerance.[108] Under iron deficiency, tomato roots also displayed an increase in the NO level, while upregulation of the activity of PME and diminution of the grade of pectin methylation in the cell wall resulted in free carboxyl groups, which can increase the capacity of iron retention in root apoplast.[109] Therefore, overaccumulation of NO might regulate, via SNO or other redox PTM, the activity of cell-wall-associated enzymes and consequently modify structural domains of the cell wall. Recent comprehensive studies provide the first candidate proteins undergoing SNO, NO_2-Tyr, and SSH.[30-32] 3D structures of well-known cell wall proteins such as PMEs, POXs, xyloglucan endo-transglycosylases (XET), and expansins displayed several cysteine thiols and disulfide bonds that are potential targets of SNO (Figure 1). In fact, in silico prediction with dbSNO and GPS-SNO 1.0 provided a positive determination of several Cys residues with potential S-SNO (Table 1[110]). However, experimental validation is needed to corroborate any bioinformatical prediction of Redox PTMs. For instance, PME catalyzes the de-methyl-esterification of pectin sugars in the cell wall. Several lines of evidence suggest that the level of de-methyl-esterification is associated with cellular expansion and intercellular adhesion.[111,112] Considering that PME activities are inhibited by proteins (PMEIs),[113,114] the PMEIs may directly

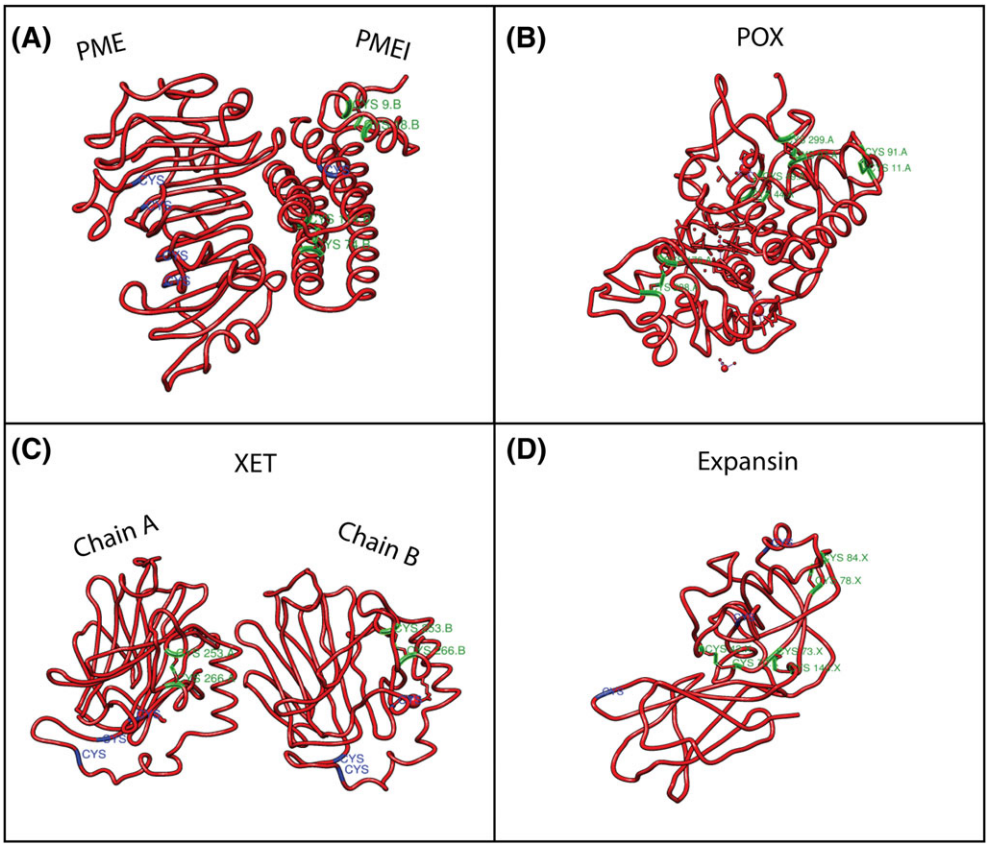

FIGURE 1 A, Structural locations of cysteine thiols and disulfide bonds in cell-wall-associated proteins. The 3D structures were constructed with UCSF chimera platform version 1.6. 3D structures of pectin methyl esterase (PME) and pectin methyl esterase inhibitor from *S. lycopersicum* (PMEI, 1XG2). B, 3D structure of peroxidase from Arabidopsis (POX, 1PA2). C, 3D structure of a poplar xyloglucan endo-transglycosylase (XET, 1UN1). D, 3D structure of β-expansin from *Z. maize* (EXP, 2HCZ). Cysteine thiols are indicated in blue, and disulfide bonds are represented in green

TABLE 1 Bioinformatic prediction of *S*-nitrosylation of cell-wall-associated proteins. GPS-SNO and dbSNO software were used to make SNO predictions[110]

	GPS-SNO			dbSNO (Specificity 95%)	
	Position	Peptide	Score	Position	Peptide
Pectin methyl-esterase (PME, 1XG2, chain A)	166 200	AAVVFQK**C**QLVARK TGTSIQF**C**NIIASSD	22.007 21.518	98 125 266 200	GFILQDI**C**IQNTAGP DMSVINR**C**RIDAYQD AAVVFQK**C**QLVARKP TGTSIQF**C**NIIASSD
Pectin methyl esterase inhibitor (PMEI, 1XG2, chain B)	10 140	NHLISEI**C**PKTRNPS DLKLEDLCDIVLVIS	4.716 21.307	19 75 140	KTRNPSL**C**LQALESD LKGRYET**C**SENYADA DLKLEDLCDIVLVIS
Peroxidase (POX, 1PA2, chain A)	12	ATFYSGT**C**PNASAIV	4.251	12 45 50 92 98 177 209	ATFYSGT**C**PNASAIV IRLHFHD**C**FVNGCDA HDCFVNG**C**DASILLD KTALENA**C**PGVVSCS ACPGVVS**C**SDVLALA HTFGRAR**C**GVFNNRL LSTLQQL**C**PQNGSAS
Xyloglucan endo-transglycosylases (XET, 1UN1, chain A)	207	RSFHIDG**C**EASVEAK	3.598	154 207 216 253	PIRVFKN**C**KDLGVKF RSFHIDG**C**EASVEAK ASVEAKF**C**ATQGARW KYTIYNY**C**TDRSRYP
β-Expansin (EXP, 2HCZ)	0	No site predicted	0	42 58 70 73 84 128 140 156	APDNGGA**C**GIKNVNL PYSGMTA**C**GNVPIFK IFKDGKG**C**GSCYEVR DGKGCGS**C**YEVRCKE RCKEKPE**C**SGNPVTV LNDKIRH**C**GIMDVEF VEFRRVR**C**KYPAGQK VFHIEKG**C**NPNYLAV

regulate the distribution of de-methyl-esterified pectin sugars during somatic embryogenesis (SE). Interestingly, both PMEs and PMEIs are annotated with several cysteine thiols (Figure 1,[115-117]). Interestingly, PME activity is regulated by exogenous treatment of the NO donor GSNO and proteomics studies provide substantial evidence that Arabidopsis PMEs (AT3G14310 and AT5G53370) are posttranslationally modified by SNO (review Supporting Information in Hu et al and Ye et al[32,109]).

Another important example of a direct regulation is the POXs. These *N*-glycoproteins have been associated with cellular proliferation, growth, and differentiation. In roots where the UPB1 transcription factor has been disrupted, POX overexpression has been linked with an increased number of meristematic cells and augmentation of the length of mature cortical cells.[118] On the other hand, in leaves, the expression of POXs through the disruption of the KAU1 repressor has been associated with reduced leaf size.[119] In general, the overexpression of POX with a burst of H_20_2 is associated with the cross-linking of phenolic acids in the cell wall, resulting in the stiffening of the wall and inhibition of growth.[119] On the other hand, the down accumulation of POX-generated •OH- radicals provokes the cleavage of cell wall sugars, leading to cell wall loosening.[118,119] This opposite modulation observed in roots and leaves strongly suggests a fine-tunable regulation of the activity of the pool of POXs present in the extracellular space. In addition, NO has been shown to cause the inhibition and activation of POXs in *Z. elegans* during tracheary and xylem lignification, where the inhibition was attributed to the formation of NO adducts with the heme prosthetic group of POX, while the induction was associated with activation at the transcriptional level due to the occurrence of *cis*-elements known to confer regulation by NO.[120-122] Also, under salt stress, Arabidopsis leaves showed the overaccumulation of carbonylated POX 34 (AT3G49120) in the apoplast.[39] However, experimental studies will be necessary to determine if other redox PTM is essential for the translation and enzymatic regulation of POX.

1.4.1 | Protein modeling of the S-nitrosylation of cell wall-associated proteins

SNO may provide fine-scale and rapid regulation of the POXs, PMEs, PMEIs, XET, and other cell wall-associated proteins, which can define the modification of the cell wall architecture under several biological evens and stress conditions. Therefore, we focused on studying the Cys SNO of two cell wall proteins to gain insight into how this redox PTM might affect the structural conformation of XET (PDB ID: 1UN1) and a PME (PDB ID: 1XG2, chain A). In doing so, we predicted the SNO on Cys by using GPS-SNO, dbSNO, and iSNO-AAPair servers. The results of the predictions with high confidence showed that Cys in the 154 and 200 positions were nitrosylated for XET and MPE proteins, respectively. Also, we performed a molecular dynamics simulation for these two proteins to evaluate the impact of SNO on the protein structure. Alteration of the protein backbone may indicate a perturbation of the functionality of the proteins.

We carried out two simulations for each protein, the first one corresponding to the native protein (no nitrosylation), and the other one corresponding to the protein with SNO. To explore the stabilities of these proteins, the root-mean-square deviations (RMSD) were determined based on the native structures. The native XET reached equilibrium after approximately 100 ns, whereas the SNO-XET showed a high degree of fluctuation during the first 200 ns and then stabilized (Figure 2A). This analysis suggests that Cys nitrosylation causes a destabilization of the structure of XET. The analysis of the hydrogen bond network of Cys 154 reveals that the SNO on this residue disturbs such networks by breaking down several hydrogen bonds in the neighborhood of this residue (Supplementary Figure S1A). This is consistent with observations in the RMSD plot. Principal component analysis (PCA) was used to evaluate structural variation in response to the SNO of Cys 154 in the simulations. The PCA reveals that the ensemble can be divided into five and three major groups along with their principal components, which collectively account for 59% and 48% of the total coordinate mean square displacements for native and SNO (Figure 3A), respectively. Our data suggest that SNO disturbs the dynamics of this protein (Supplementary Video S1 and S2).

However, the results for MPE were the opposite. SNO increases the stability of the protein structure. For example, RMSD analysis reveals that mobility of SNO-PME is less than the native protein (Figure 2B). Hydrogen network analysis showed that upon SNO, the Cys 200 generates more hydrogen bonds than in the native protein (Supplementary Figure S1B). The results of PCA analysis for this protein are consistent with these observations, supporting the assertion that SNO increases its stability (Figure 3B and Supplementary Video S3 and S4). Taken together, the results for both proteins suggest that the effect of SNO on the protein structure is system dependent. Further simulations and analysis of more protein structures will be necessary to obtain a more conclusive view of this phenomenon.

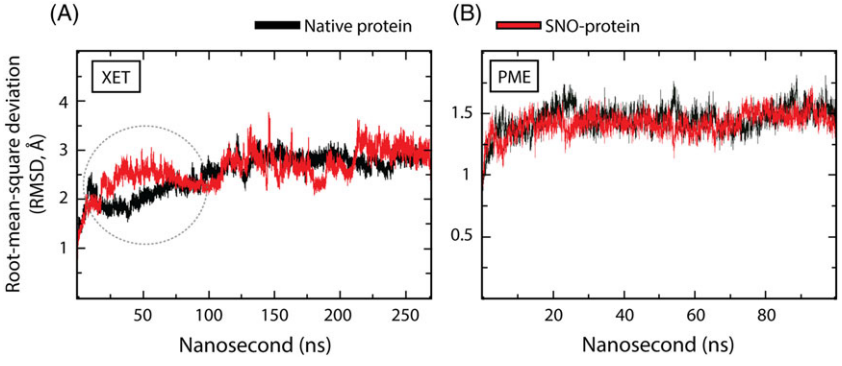

FIGURE 2 Backbone root mean square deviations (RMSD) for A, XET and B, PME proteins during the simulation

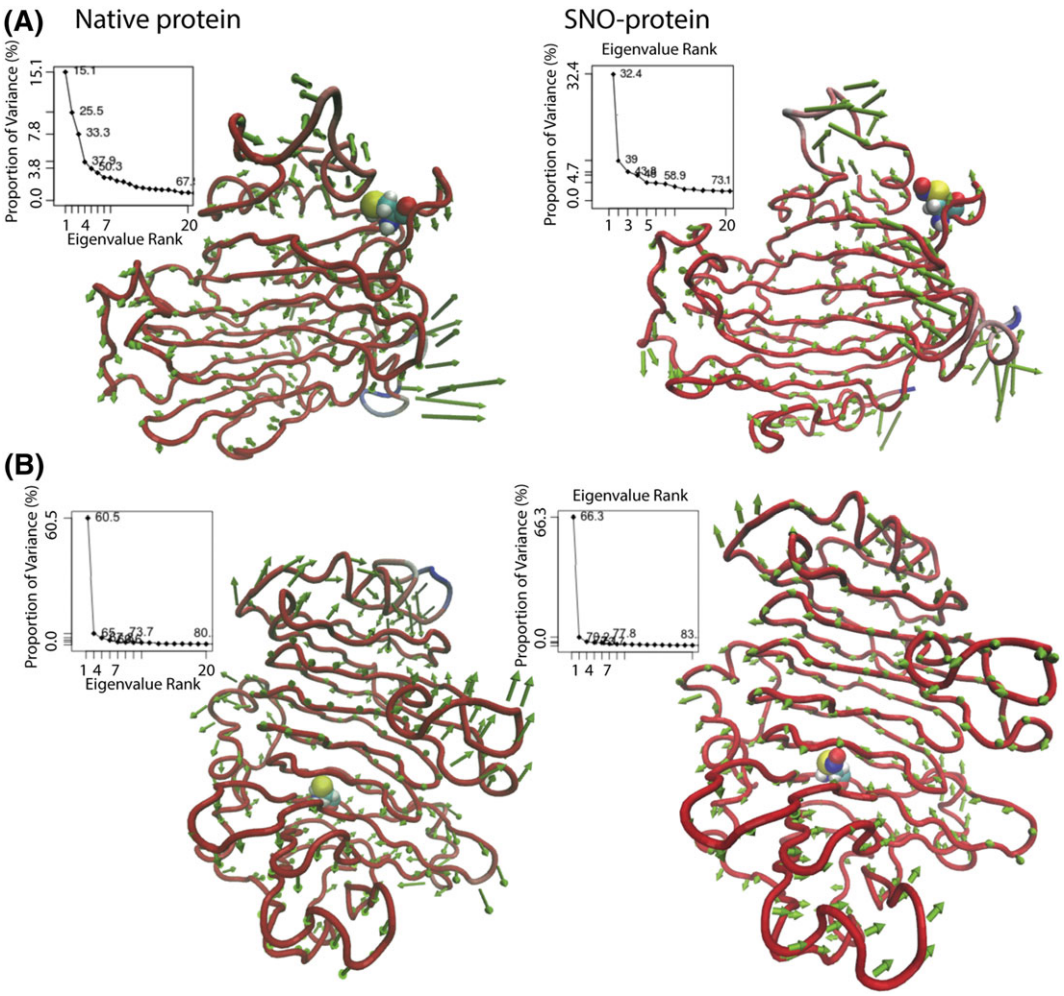

FIGURE 3 PCA results and porcupine plot of principal motion of A, XET and B, PME calculated from molecular dynamics simulation. The length of the arrow in each Cα represents the magnitude of movement, and the direction is from one extreme to the other

2 | CONCLUSIONS

Proteomic studies associated with redox proteomics have provided a glimpse into the diversity and complexity of these modifications. Further analysis should include the establishment of multiple robust pipelines aided by the proteomics toolbox. As mentioned earlier, insufficient comprehensive studies have focused on redox PTM, except the in vivo site mapping of SNO in Arabidopsis. This study was hampered by limitations, such as the high dynamic range of redox-modified proteins, where the few proteins with well-characterized redox PTM are difficult to identify. Surprisingly, this topic has not been studied in plant cells, tissues, and organs. Therefore, the next challenge in this field is to circumvent the high dynamic range of redox posttranslationally modified proteins. Another point to note is the complete characterization of the redoxome, which comprises a comprehensive characterization of all oxidized Cys (oxoforms) residues.[123] GAPDH is a good example that illustrates the oxoforms of Cys160 and Cys149, where the former Cys undergo SSH while the later undergo S-SG and SNO. This multiple redox PTM on GAPDH underpins the fundamental importance of this protein in the primary metabolic processes and indicate various functionalities of this proteins. Nonetheless, we should also consider the crosstalk of oxoforms and other types of PTM such as phosphorylation. Recent reports add extracellular proteins to the extensive list of redox modified proteins. Considering that extracellular proteins, including cell wall proteins, are glycosylated with a broad diversity of glycans, we should expect another level of complexity in analyzing redox PTM and glycosylation. Additionally, the label nature of thiol-redox reactions and the challenge of direct detection of the modified residues, along with the low ionization efficiency of glycopeptides and highly complex glycosylation microheterogeneity and low abundance of relevant proteins, will be the primary hurdles to future research. We expect exciting discoveries shortly considering that extracellular redox PTM is an unexplored subject in plant cells. Our dynamics simulation suggests that SNO can modify the conformation of key proteins, which in turn may shut down or activate the functionality of these proteins such as PME and TEX. However, new technologies will allow us to corroborate our current hypothesis associated with the SNO of cell wall proteins during stress and biological processes. We highlight the lack of proteomic studies to characterize the extracellular redox proteomics in any aspect of plant biology. However, new proteomic pipelines and powerful mass spectrometers will provide the critical tools for unraveling the secrets associated with redox PTM and other modification of proteins.

ACKNOWLEDGEMENTS

Our research was funded by Consejo Nacional de Ciencia y Tecnología (CONACYT, U0004-2015-1_259915 and CB-2014-01_242990 to E. R.M. and 257436 to V.M.L.V.).

CONFLICT OF INTEREST

None declared.

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How to cite this article: Ruiz-May E, Segura-Cabrera A, Elizalde-Contreras JM, Shannon LM, Loyola-Vargas VM. A recent advance in the intracellular and extracellular redox post-translational modification of proteins in plants. *J Mol Recognit*. 2019;32:e2754. https://doi.org/10.1002/jmr.2754