Redox Components: Key Regulators of Epigenetic Modifications in Plants

Saravana Kumar R. M., Yibin Wang, Xiaopan Zhang, Hui Cheng, Lirong Sun, Shibin He * and Fushun Hao *

State Key Laboratory of Cotton Biology, Key Laboratory of Plant Stress Biology, School of Life Sciences, Henan University, Kaifeng 475004, China; saravana80@126.com (S.K.R.M.); 18238213127@163.com (Y.W.); xiaopanzhang@163.com (X.Z.); 15194627687@163.com (H.C.); sunlr9208@henu.edu.cn (L.S.)
* Correspondence: sbhe@henu.edu.cn (S.H.); haofsh@henu.edu.cn (F.H.); Tel.: +86-371-23881387 (F.H.)

Received: 27 November 2019; Accepted: 18 February 2020; Published: 19 February 2020

Abstract: Epigenetic modifications including DNA methylation, histone modifications, and chromatin remodeling are crucial regulators of chromatin architecture and gene expression in plants. Their dynamics are significantly influenced by oxidants, such as reactive oxygen species (ROS) and nitric oxide (NO), and antioxidants, like pyridine nucleotides and glutathione in plants. These redox intermediates regulate the activities and expression of many enzymes involved in DNA methylation, histone methylation and acetylation, and chromatin remodeling, consequently controlling plant growth and development, and responses to diverse environmental stresses. In recent years, much progress has been made in understanding the functional mechanisms of epigenetic modifications and the roles of redox mediators in controlling gene expression in plants. However, the integrated view of the mechanisms for redox regulation of the epigenetic marks is limited. In this review, we summarize recent advances on the roles and mechanisms of redox components in regulating multiple epigenetic modifications, with a focus of the functions of ROS, NO, and multiple antioxidants in plants.

Keywords: epigenetic modifications; DNA methylation; histone modification; chromatin remodeling; redox regulation; reactive oxygen species; nitric oxide; antioxidants

1. Introduction

Epigenetic modifications refer to the mitotically- or meiotically-inheritable changes in gene expression that are not affected by the DNA sequence itself, mainly including DNA methylation, histone modifications, chromatin remodeling, and histone variants in plants and other organisms [1,2]. They can change chromatin architecture, affect DNA accessibility, and gene activity, thereby regulating many molecular processes, like the transcription of genes, and replication, repair, and recombination of DNA [1–4]. They play vital roles in controlling growth and development, including cell differentiation, regeneration, reproduction, flowering, and senescence, and governing plant acclimations to various environmental stimuli, such as pathogen infection, drought, high salinity, extreme temperature, heavy metal stresses [1,3–7]. Most epigenetic modifications are reversible, and under the control of multiple factors including different developmental cues, diverse environmental stresses, phytohormone signals [1,8,9]. Among these, redox components are of great importance [10–12].

Redox components consist of numerous oxidants and antioxidants. In plants, the primary oxidants are reactive oxygen species (ROS), for example, hydrogen peroxide (H$_2$O$_2$), superoxide radical (O$_2^{-*}$), singlet oxygen (O$_2$), and hydroxyl radicals, and reactive nitrogen species, including nitric oxide (NO), peroxynitrite, nitrogen dioxide radicals. [13]. The main antioxidants include enzymatic antioxidants (e.g., superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), glutathione peroxidase (GPX), glutathione reductase (GR)), and nonenzymatic antioxidants
These oxidants and antioxidants are able to spatiotemporally change the redox status and influence redox balance, controlling nearly every aspect of cellular processes such as gene expression, biological metabolisms, growth and development, and adaptations to different environmental stresses in plants [13,15–18].

In recent years, many review papers covering the roles and regulatory mechanisms of epigenetic modifications have been published. The relationship between redox metabolites and some epigenetic modifications has also been discussed [8,10–12,19–22]. However, the functions and mechanisms of redox mediators modulating the epigenetic modifications are not comprehensively summarized. In this review, we provide an integrated view how redox components control the epigenetic marks, with a focus of the roles of ROS, NO, and multiple antioxidants in the regulation of DNA methylation, histone methylation, and histone acetylation in plants.

2. Epigenetic Modifications in Plants

2.1. DNA Methylation

DNA methylation typically means the specific post-replication modification over DNA molecules, in which some cytosine bases are methylated at 5’ position to become 5-methyl-cytosine (\(^{5}\text{mC}\)). In plants, methylation occurs in the C base of “CG”, “CHG”, and “CHH” (H represents A, C, or T) contexts [23]. DNA methylation favors the maintenance of genome stability, suppresses gene recombination and mutation, and is essential for the silencing of transposable elements and the regulation of gene expression and splicing [3,24]. DNA methylation inhibits transcriptional initiation, and may have little effect on transcriptional elongation within the gene body [25].

In *Arabidopsis thaliana*, de novo DNA methylation is established through RNA-directed DNA methylation (RdDM) pathway, which involves 21-, 22-, and 24-nt small interfering RNAs (siRNAs) production [3,26,27]. DNA methylation is maintained through three pathways: DNA methyltransferase 1 (MET1) for CG methylation, chromomethylase 3 (CMT3) and CMT2 for CHG methylation, and domain rearranged methyltransferase 2 (DRM2), CMT2, and CMT3 for CHH methylation. The methyl donor is S-adenosyl-l-methionine (SAM) [3,23]. Methyl groups can be removed from DNA through DNA demethylation. Active DNA demethylation is mediated by 5-methylcytosine DNA glycosylases through a DNA base excision repair pathway in plants [3,28]. There exist four 5-methylcytosine DNA glycosylases in *A. thaliana*: repressor of silencing 1 (ROS1), demeter (DME), and Demeter-like 2 (DML2) and DML3 [3,28].

2.2. Histone Methylation and Acetylation

Chromatin is the organized nucleoprotein structure in nuclei where nucleosomes are arranged. Each nucleosome is comprised of two copies of H2A, H2B, H3, and H4 histone molecules, and is wrapped by 145–147 bp double-stranded DNA [29]. The N-terminal tails of histones are subject to various post-translational modifications such as methylation, acetylation, phosphorylation, ubiquitinylation, glycosylation, ADP-ribosylation, and sumoylation. These modifications can alter chromatin structure and gene transcription either by affecting the interaction between histones and the surrounding DNA or by modulating the binding of various regulatory proteins to DNA [1,2,7]. Histone methylation and acetylation have been well characterized. They have wide functions in plant evolution, development, and stress acclimations by facilitating or repressing gene expression [22,30–32].
Histone methylation is confined to lysine and arginine residues located at different positions of histone molecules (H3, H4). The transfer of methyls to histone is catalyzed by histone methyltransferase (HMT) families, which include histone lysine methyltransferases (HKMTs) and protein arginine methyltransferases (PRMTs) [22,33]. The donor of methyl groups for histone methylation is also SAM. On the basis of the number of methyls that occurs over histone molecules, histone methylation can be grouped into mono-, di-, and tri-methylation. Different modifications have distinct effects on gene expression [22,33]. For instance, trimethylation of Lys 27 (H3K27me3) leads to the repression of gene expression whereas trimethylation at Lys 4 (H3K4me3) activates gene transcription in A. thaliana [34,35].

Methyl groups can be removed by histone demethylases (HDMs). In plants, HDMs are grouped into lysine-specific demethylase 1 (LSD1) and Jumonji C domain-containing proteins (JMJs). Both enzymes follow different pathways to demethylate histones using different cofactors. LSD1 pertains to flavin-dependent amine oxidase family whereas JMJs belong to 2-oxoglutarate-dependent dioxygenase family [33,36].

Histone acetylation is the covalent modification in which acetyl groups are transferred from acetyl CoA to the epsilon-amino group of the lysine residue in histone molecules. Such modification causes the neutralization of the positive charge of the lysine, weakens the interaction between the modified histone and DNA, thus, chromatin becomes relaxed [22,37]. Acetylated histones can also recruit other proteins, which regulate chromatin structure [38,39]. Generally, hyperacetylation of histones favors transcriptional activation whereas hypoacetylation of histones causes gene repression [22,37,40]. The levels of histone acetylation are regulated by the antagonistic activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [1,41]. Plant HATs are divided into four classes, including p300/CREB (cAMP responsive element-binding protein)-binding proteins, TATA-binding protein-associated factors, general control nonrepressible 5-related N-terminal acetyltransferases and MOZ, Ybf2/Sas3, Sas2, and Tip60 proteins [41]. HDACs in plants are grouped into three types: reduced potassium dependency 3/histone deacetylase 1 (RDP3/HDA1), silent information regulator 2 (SIR2), and plant-specific histone deacetylase 2 (HD2). SIR2 family proteins (sirtuins) require NAD$^+$ as cofactor, and other HDACs use Zn or Fe ion as cofactors. There exist 18 HDAC members in A. thaliana [41,42].

2.3. Chromatin Remodeling

The regulated change of chromatin structure is termed as chromatin remodeling. It can be changed not only by covalent modifications of histones and DNA, but also by ATP-dependent chromatin remodelers and other chromatin-associated factors. ATP-dependent chromatin remodelers are able to cause the alteration of nucleosome position, destabilization of nucleosomes or displacement of canonical histones by histone variants [43]. Eukaryotic ATP-dependent chromatin remodelers are evolutionarily conserved protein complexes that typically possess a catalytic core: ATPase/helicase of the switching defective2/sucrose non-fermenting2 (SWI2/SNF2) family. They perform functions using the energy provided by ATP hydrolysis [43,44]. In plants, ATP-dependent chromatin remodelers are divided into four major subfamilies, including SWI/SNF subfamily, imitation switch subfamily, chromodomain helicase DNA-binding (CHD) subfamily, and inositol requiring 80/SWI2-related ATPase 1 subfamily [43,44].
3. Redox Components

3.1. ROS and NO

ROS are byproducts of the aerobic metabolism. They act as crucial signaling molecules to mediate and integrate various growth and environmental signals to control plant development, stomatal movement, and acclimation to diverse biotic and abiotic stresses [13,18,45,46]. ROS are generated in distinct organelles or subcellular compartments like chloroplasts, mitochondria, peroxisomes, and apoplasts under normal, especially stressful conditions [18]. Photosynthesis, photorespiration, and mitochondrial electron transport are major sources of ROS. Plasma membrane NADPH oxidase, also known as respiratory burst oxidase (RBOH), is also a key producer of ROS. RBOH-dependent ROS have been demonstrated to be essential regulators of many cellular processes such as seed germination, root formation, tip growth, flowering, stomatal movement, and adaptations to different environmental stimuli in plants [47–52]. Under normal conditions, the concentrations of ROS in tissues are relatively low, and ROS can act as signal molecules. However, under stresses, ROS accumulation in plants increases. When the levels of ROS exceed certain thresholds, oxidative stress occurs. High levels of ROS damage various biological molecules and cell structure, even causing cell death in plants [18,53].

Similar to that of ROS, production of NO is an inevitable process in plant metabolism. NO is synthesized in different compartments of cells including cytosol, chloroplasts, mitochondria, and peroxisomes [54,55]. NO reductases, nitrate reductases, and nitric oxide synthase-like enzyme have been addressed to be important sources of NO in plants. NO is also a key secondary messenger. It independently or synergistically acts with ROS to regulate a wide range of cellular events including vegetative growth, reproductive development, stomatal opening and closure, and responses to diverse biotic and abiotic stresses [16,20,56]. NO and H$_2$O$_2$ can easily enter the nucleus through nuclear pores, and react with nuclear proteins, including histones and transcription factors in plants [15,57,58].

3.2. Enzymatic and Nonenzymatic Antioxidants

Cellular redox status constantly undergoes fluctuations that are balanced by different oxidant and antioxidant systems during plant development and in response to stress cues. Of the enzymatic antioxidants, SOD catalyzes the dismutation of O$_2$$^•$− into O$_2$ and H$_2$O$_2$. CAT, APX, and GPX convert H$_2$O$_2$ into O$_2$ and H$_2$O, whereas GR is responsible for the conversion of the oxidized glutathione to the reduced one [59,60]. Of the non-enzymatic antioxidants, NAD(P)H, GSH, and ASC are critical soluble redox carrier molecules. They can interchange between the oxidized and reduced states (NAD(P)$^+$/NAD(P)H, GSSG/GSH, and Asc/DAsc). Their capacity to gain or lose electrons also makes them versatile carriers to alter the activities of many enzymes implicated in numerous important metabolic pathways and cellular events. NAD(P)H is vital for the transmission of redox signals. By supplying reducing equivalents to GSH and ASC through the Asada–Foyer–Halliwell cycle [61], NAD(P)H can process ROS and reactive nitrogen species [60]. GSH and ASC directly interact with H$_2$O$_2$, and catalyze the conversion of H$_2$O$_2$ to H$_2$O and O$_2$. Under oxidative conditions, GSH-GSSG equilibrium shifts towards oxidized glutathione, leading to S-glutathionylation of proteins, an important redox-modification in plants [60,62,63].
4. Redox Regulation of Epigenetic Modifications

4.1. Redox Regulation of DNA Methylation

Accumulating evidence indicates that redox intermediates govern DNA methylation levels and gene transcription in plants. In general, increases in ROS accumulation cause DNA hypomethylation. In tobacco, addition of \( \text{O}_2^{•−} \) inducer paraquat increases the oxidative stress of cells. The expression of *Glycerophosphodiesterase-Like (NtGPDL)* is upregulated, and CG sites in the coding regions of *NtGPDL* are selectively demethylated [64]. Similarly, treatment of tobacco suspension cells with juglone, a toxic plant secondary metabolite 5-hydroxy-1,4-naphthoquinone, increases the ROS levels in nucleus, nucleolus, cytoplasm, and plasma membrane, accompanied with DNA hypomethylation and programmed cell death (PCD) [65]. Additionally, application of 2,2’-azobis (2-amidinopropane) dihydrochloride, a generator of free radicals, in *Pisum sativum* suspension culture clearly decreases the global DNA methylation levels [66].

Similar to ROS, NO negatively modulates DNA methylation in plants. For instance, treatment of rice seedlings with high concentrations of sodium nitroprusside (SNP, a NO donor) leads to DNA hypomethylation predominantly at the CHG sites, and growth inhibition. In addition, the NO-evoked alterations in DNA methylation can be inherited to the next generation [67]. In another study, application of low concentration of SNP to heat-treated *Lablab purpureus* plants causes the reduction in the levels of \( \text{O}_2^{•−} \) and \( \text{H}_2\text{O}_2 \) and the alteration of DNA demethylation and methylation levels [68]. Additionally, antioxidant nicotinamide, an essential component of NAD(P)H, has shown to induce DNA hypomethylation in *P. sativum* [66].

In plants, three mechanisms for redox regulation of DNA methylation may exist. One mechanism is redox components modulate the synthesis of methyl donor SAM. In plants, SAM synthesis is catalyzed by S-adenosylhomocysteine hydrolase (SAHH)/homologous gene silencing 1 (HOG1), methionine synthase (MS) and S-adenosyl methionine synthase (SAMS)/methionine adenosyltransferases (MAT) [69] (Figure 1). SAHH, MS and SAMS have been demonstrated to be S-nitrosated after treatment with NO donor S-nitrosoglutathione (GSNO) in *A. thaliana*. Activity assay showed that SAMS1 is reversibly inhibited by GSNO [70]. Also, proteomic studies have shown that many of the enzymes involved in SAM synthesis are targets of S-nitrosation and tyrosine nitration [71–73]; and the activity of SAHH is decreased by tyrosine nitration in sunflower [72].

In the SAM cycle, the precursor of SAM is methionine (Met), which is particularly susceptible to oxidation to methionine sulfoxide (MetSo) under stress conditions (Figure 1). Methionine sulfoxide reductases (MSRs) A and B catalyze the reduction of MetSo back to Met [74]. Accordingly, changes in the levels of NAD(H), NADP(H) and GRXs/thioredoxins (TRXs) may affect DNA methylation through controlling the concentrations of Met in cells. NAD(H) and NADP(H) can prevent Met oxidation. In *A. thaliana*, two MSR genes (*MSRB3* and *MSRB8*) are activated under high levels of NAD(H) and NADP(H), and accompanied with an increase in Met content [75]. GRXs/TRXs can donate electrons to MSRs for the catalysis of MetSo reduction [76]. These indicate that NAD(H), NADP(H), GRXs, and TRXs play important roles during the regeneration of Met; accordingly may modulate DNA methylation (Figure 1).
**Figure 1.** Redox components modulate SAM synthesis through folate cycle in plants. Folate cycle begins with the conversion of DHF to THF through DHFR by utilizing the reducing equivalents from NADPH. Methyls derived from THFs (5,10-CH2-THF, 5,10-CH=THF) are synthesized by SHMT and MTHFD, respectively. 5,10-CH=THF is reduced to 5-CH3-THF by MTHFR. The methyl group from 5-CH3-THF is transferred to Hcy to synthesize Met through MS. The produced Met generates SAM through SAMS. SAM donates methyl groups to DNA or proteins through DNA methyltransferase (DNMT)/HKMT/PRMT, and gets converted to SAH. SAH is further processed to Hcy through SAHH/HOG1. The key enzymes influenced by the cellular redox components are: SAMS/MAT, DNMT/HKMT/PRMT, SAHH/HOG1, MS and MSR. K: lysine; R: arginine; Me: methyl. Dashed lines mean uncharacterized regulation.

Additionally, accumulation of Met is dependent on the metabolism of folate, which provides 5-methyl-tetrahydrofolate (5-CH3-THF) for Met synthesis. In *A. thaliana*, impairment of folate production by sulfamethazine treatment has shown to reduce DNA methylation levels [77]. Folate metabolism can also contribute to the maintenance of redox balance by regulating NADPH production, further modulating DNA methylation in plants [78,79]. As shown in the folate cycle (Figure 1), dihydrofolate reductase-thymidylate synthase (DHFR-TS) is a bifunctional enzyme. Its subunit DHFR is located at the N terminus, and catalyzes the conversion of dihydrofolate (DHF) into tetrahydrofolate (THF) by consuming NADPH. THF and 5,10-CH2-THF can be interconverted by the enzyme serine hydroxymethyl transferase (SHMT). 5,10-CH2-THF can also be converted into DHF by TS. Methylene tetrahydrofolate dehydrogenase/methylenetetrahydrofolate cyclohydrolase1 (MTHFD1) is also a bifunctional enzyme, and can convert 5,10-CH2-THF into 5,10-CH=THF, leading to NADPH formation. Mutation in MTHFD1 has been demonstrated to disturb folate metabolism and cellular redox state, and lead to loss of DNA methylation in *A. thaliana* [79]. In the Arabidopsis genome, three DHFR-TS genes exist. DHFR-TS3 inhibits DHFR-TS1 and DHFR-TS2. Overexpression of DHFR-TS3 leads to decreases of DHFR and MTHFD activities, which in turn cause a drop of NADPH/NADP⁺ ratio [78], and likely impact DNA methylation. Further, 5,10-CH=THF is converted by methylenetetrahydrofolate reductase (MTHFR) to 5-CH3-THF, which enters the SAM cycle and serves for homocysteine (Hcy) remethylation to Met by MS.

The second mechanism for redox regulation of DNA methylation is that ROS and NO affect the expression and activities of DNA methyltransferases (DNMTs) and DNA demethylases. In *A. thaliana*, ROS mediate the irradiation-triggered DNA demethylation of bystander aerial plants. Irradiation of the roots markedly decreases the expression of DRM2, and enhances the transcriptional abundances of MET1 and DML3 in bystander aerial plants [80]. Similarly, application of SNP to rice plants induces DNA hypomethylation through down regulation of DNA methyltransferase genes OsCMT2 and
OsCMT3 and upregulation of the DNA demethylase gene OsDME [67]. Yet, it is not clear whether the observed DNA hypomethylation in the SNP-treated plants are due to the regulation of DNA methylase activities or due to the NO-mediated post-translational modification of SAMS.

DNA glycosylases ROS1 and DME have DNA demethylase activity. They catalyze the excision of entire methylated cytosine instead of the methyl group through the base excision repair pathway. ROS1 and DME possess Fe-S cluster assembled structure as their cofactor, and the Fe–S binding motif is essential for their enzymatic activity [81]. Fe-S cluster can gain or lose electrons under different oxidation conditions [82]. Accordingly, redox components may modulate DNA demethylation through impacting the activity of Fe-S cluster assembled DNA demethylases like ROS1 and DEM in plants.

The third mechanism for redox modulation of DNA methylation level is that redox mediators modify the activities of dicer-like4 (DCL4) and RNAse III-like 1 (RTL1), thus affecting the production of siRNAs likely required for DNA methylation through RdDM pathway in plants [83,84]. siRNAs originate from inter- or intramolecular double-stranded RNA (dsRNA) precursors, which are catalyzed by dsRNA-specific endoribonucleases, DCL proteins [85]. In A. thaliana, the products of DCL2, DCL3, and DCL4 are 22-, 24- and 21-nt siRNAs, respectively [27,85]. Apart from DCL-mediated dicing activities, RTL1 also influences siRNA production by cleaving the dsRNA before processing by the DCL proteins, and thus acts as a negative regulator of siRNA production [86]. The roles of DCL4 and RTL1 proteins in siRNA production are depicted in Figure 2. In A. thaliana, the activity of DCL4 is suppressed by sulfur deficiency. The DCL4 activity can be recovered by supplementation with GSH and TRXs. Moreover, immunopurified DCL4 can be activated by recombinant thiorredoxin-h1 with dithiothreitol in vitro, suggesting that DCL4 is under redox regulation. Activation of DCL4 can promote 21-nt siRNA production, and may further promote DNA methylation [83] (Figure 2a). Additionally, Arabidopsis RTL1 has dsRNA binding domains (dsRBD), in which one conserved cysteine (Cys230 in Arabidopsis RTL1) exists. Cys230 has been demonstrated to be crucial for RTL1 cleavage activity. In the presence of GSSG, RTL1 can be glutathionylated at Cys230. Moreover, glutathionylation of RTL1 clearly inhibits its cleavage activity, and the activity of glutathionylated RTL1 can be recovered by two GRX members GRXC1 and GRXC2, indicating that RTL1 is redox regulated (Figure 2b). Moreover, RTL1 negatively regulates siRNA production prior to DCL–mediated cleavage of the siRNA precursors (Figure 2b) [84]. Thus, redox mediators modulate siRNA generation through influencing the activities of DCL4 and RTL1 in plants, and further affect the DNA methylation level.

![Figure 2](image-url)  
**Figure 2.** Redox components regulate DCL4 and RTL1 activities. (a) Processing of siRNA precursors by DCL4 requires dsRNA-binding protein (DRB), especially DRB4. GSH and TRXs are able to restore DCL4 activity from the inactive state. Activated DCL4 promotes 21 nt siRNA production. (b) GSSG/GRXs influence RTL1 activity. RTL1 has RNase III domain and dsRNA binding domains (dsRBD), and acts dimers to perform functions. GSSG treatment results in RTL1 glutathionylation at Cys230 position and inhibits its activity. RTL1 activity is restored by glutaredoxin proteins (GRXs). RTL1 negatively regulates siRNA production prior to DCL–mediated cleavage of the siRNA precursors. The dashed line indicates uncharacterized regulation.
4.2. Redox Adjustment of Histone Methylation

Similar to those of DNA methylation, the methyl groups of histone methylation are also derived from SAM. Thus, redox factors modulating SAM availability also modify histone methylation, as described in the DNA methylation section (Figure 1). In addition to influencing SAM synthesis, redox intermediates also regulate the expression and activity of HMTs and HDMs. For instance, application of S-nitrosocysteine, a NO donor, to Arabidopsis leaves upregulates the expression of Set Domain Group 20, a gene encoding lysine methyl transferase, and PcG Histone Methyltransferase Curly Leaf gene [87], pointing to the important function of NO in modulating the two HMTs. PRMT5 can catalyzes Arg symmetric dimethylation of histones and non-histone proteins in higher eukaryotes [88]. It has been reported that NO positively regulates PRMT5 activity by S-nitrosylation at Cys-125 under NaCl stress in A. thaliana [20]. Treatment with NO donor S-nitrosocysteine also prominently promotes JMJs expression in A. thaliana [87], implying that JMJs are possibly regulated by NO.

4.3. Redox Regulation of Histone Acetylation

Increasing evidence suggests that redox components regulate histone acetylation through affecting acetyl CoA accumulation. It has been addressed that pyruvate conversion to acetyl CoA is catalyzed by pyruvate dehydrogenase (PDH) complex, which uses NAD$^+$ as a cofactor for its catalytic activity (Figure 3). Increases in the ratio of NADH to NAD$^+$ in Escherchia coli inhibit PDH activity, and block the acetyl CoA formation [89]. An in vitro study also revealed that elevation in ratio of NADH/NAD$^+$ is associated with the inhibition of PDH activity in pea [90]. Yet, whether the inhibited PDH activity causes the decreases in levels of acetyl CoA in plants remains to be determined.

Changes in redox reagents also modulate the activities of HATs and HDACs in plants (Figure 3). It has been documented that heat stress promotes the accumulation of O$_2$$^{•-}$ and induces PCD, followed by histone hyperacetylation due to the elevated expression of genes HAT-B and General Control Nondepressible 5 (GCN5) in maize seedlings [91]. Dietzel et al. [92] detected the early nuclear target genes of plastidial redox signals in responding to a reduced light-induced signal of the photosynthetic electron transport chain in A. thaliana, and found that many nuclear genes are not expressed in the redox compromised state transition 7 (stn7) mutants but expressed in WT. Among these, several are epigenetically regulated. Further studies revealed that the redox signal from chloroplasts of WT rather than stn7 activates the nuclear HAT and HDAC, which promote histone acetylation and deacetylation, respectively [92]. Similarly, Arabidopsis mutants accumulated high levels of H$_2$O$_2$ (cat2) and were defective in GSSG to GSH conversion (gr1), showing the differential expression of GCN5-related acetyl transferase gene [93].

In A. thaliana, the expression of many pathogenesis-related (PR) genes is suppressed by HDA19, which deacetylates the histones on PR protein promoters under nonpathogenic condition. Pathogen attack abolishes HDA19 activity, further resulting in the acetylation of PR protein promoters and increased expression of PR-related genes [94]. Pathogen infection induces oxidative burst at a very early time [95]. Thus, the HDA19 activity affected by pathogen attack is most likely regulated by ROS. Indeed, Liu et al. [96] found that salicylic acid (SA) and flagellin 22 (a bacterial protein) trigger ROS production, leading to the oxidation of HDA9 and HDA19 in A. thaliana. The oxidation of the HDACs reduces their activity and further increases the histone acetylation of stress-responsive genes.
DlERF1 and HD delays the fruit senescence, elevates the transcription of DlHD2 factor-like genes. DlERF1 are plant-specific HDACs. The expression of HD2-like gene DlHD2 is associated with H3K9 histone acetylation [98]. Moreover, GSNO or GSH clearly increases whereas NO scavenger shown to induce endogenous NO generation, which represses HDAC activity and stimulates fruit senescence. These data imply that NO modulates fruit senescence possibly through affecting the expression of DlERF2, as well as DNA hypomethylation [67], indicating that NO possibly delays the fruit senescence. Treatment with NO delays the fruit senescence, elevates the transcription of DlHD2, but diminishes the expression of DlERF2. These data imply that NO modulates fruit senescence possibly through affecting the expression of HD gene in longan [99]. Additionally, in A. thaliana, the HD2 type member HDT2 (histone deacetylase 2) and HDT3 have been identified to be S-nitrosylated [100].

In plants, the activities of sirtuin HDACs are dependent on the NAD⁺ level and NAD⁺/NADH ratio [21]. Thus, oxidative stress alters the redox status of NAD⁺, and may further imprint on HDAC activity. In rice, NAD⁺-dependent sirtuin OsSRT1 has been reported to play critical roles in suppressing glycolysis by deacetylating histones and glyceraldehyde-3-phosphatedehydrogenase [97]. Redox mediators likely modulate the catalytic activity of OsSRT1 by affecting NAD⁺ level.

Mengel et al. [98] found that NO donors GSNO and S-nitroso-N-acetyl-DL-penicillamine and glutathionylating reagent GSNG reversibly suppress HDAC activity in A. thaliana. S-nitrosylation has stronger effects than S-glutathionylation on the HDAC activity. In addition, SA has been shown to induce endogenous NO generation, which represses HDAC activity and stimulates histone acetylation [98]. Moreover, GSNO or GSH clearly increases whereas NO scavenger 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide decreases acetylation levels of many H3K9/14ac sites, indicating that NO contributes to the GSNO-triggered hyperacetylation. HD2 proteins are plant-specific HDACs. The expression of HD2-like gene DIHD2 and two ethylene-responsive factor-like genes DIERF1 and DIERF2 enhances during longan fruit senescence. Treatment with NO delays the fruit senescence, elevates the transcription of DIHD2, but diminishes the expression of DIERF1 and DIERF2. These data imply that NO modulates fruit senescence possibly through affecting the expression of HD gene in longan [99].

Figure 3. Redox components influence histone acetylations. In the cytoplasm, glucose is broken down to pyruvate, which enters into mitochondria, and is converted to acetyl CoA through mitochondrial pyruvate dehydrogenase (mPDH) by reducing NAD⁺. Acetyl CoA combines with oxaloacetate (OAA) produced in the TCA cycle to form citrate, which enters cytoplasm. In cytoplasm, citrate is converted back to OAA and acetyl CoA through ATP-citrate lyase (ACL). Acetyl CoA synthesized in the cytoplasm enters into the nucleus as the source supplier of acetyl group for the histone acetylation process. HAT utilizes the acetyl group from acetyl CoA to introduce acetylation marks (Ac) over the lysine residues of the histone tail, thus weakening the contact between DNA and histone and facilitating gene expression. HDAC removes histone acetyl group, leading to chromatin compaction. Different HAT and HDAC enzymes are affected by ROS, NO, and NAD⁺.
4.4. Redox Affecting Chromatin Remodelers and Other Chromatin-Associated Factors

DNA methylation 1 (DDM1) is an important SWI/SNF2 chromatin remodeler, and can shift nucleosome composition and mediate DNA methylation by allowing MET1, CMT2, and CMT3 to access DNA, especially in heterochromatin regions in plants [101]. Mutation of DDM1 leads to a dramatic decrease in DNA methylation in A. thaliana [102]. In rice, exogenous application of SNP results in the downregulation of the expression of OsDDM1a and OsDDM1b, as well as DNA hypomethylation [67], indicating that NO possibly modulates DNA methylation via impacting chromatin remodeling. PICKLE, a CHD3 remodeler, promotes H3K27me3 in A. thaliana [103]. It is identified as a target for tyrosine nitration [73], suggesting that its activity is redox regulated. In A. thaliana, topoisomerase VI (Topo VI) A subunit (AtTOP6A), a chromatin-associated factor, has been demonstrated to mediate singlet oxygen signals from the plastid to the nucleus. Under \(^1\)O\(_2\) accumulation condition, AtTOP6A binds to the promoters of \(^1\)O\(_2\)-responsive AAA-ATPase gene and a set of other \(^1\)O\(_2\)-responsive genes, and directly activates the expression of these genes. Topo VI also regulates the transcription of H\(_2\)O\(_2\)-responsive genes under high light stress. However, changes in the expression of \(^1\)O\(_2\)- and H\(_2\)O\(_2\)-responsive genes modulated by AtTOP6A are different, suggesting that Topo VI is capable of integrating multiple signals produced by ROS in plants under stress [104].

5. Conclusions

Redox mediators, particularly ROS and NO have been emerging key regulators of chromatin remodeling in plants. They greatly influence not only the transcription and activities of multiple enzymes, catalyzing the addition or removal of methyl and acetyl groups in DNA and histones, but also the biosynthesis and supply of methyl and acetyl donors to DNA and histones. Redox-regulated changes in the epigenetic marks shape chromatin organization, further controlling the expression of many genes and other molecular processes, thereby profoundly affecting plant growth and stress responses. In recent years, much progress has been made on the roles of redox mediators in regulating DNA methylation, and histone modifications in plants. However, many reported actions of redox components on epigenetic marks are indirect effects, and the precise molecular mechanisms underlying the processes are largely unknown. Whether epigenetic modification changes are caused by one oxidant without triggering other antioxidants is also poorly described. Moreover, the research works on redox regulation of other epigenetic marks like phosphorylation, ubiquitinylation, glycosylation, ADP-ribosylation, and sumoylation of histone, chromatin remodeling, and siRNA are quite limited to date.

It has been documented that pathogen attack and diverse abiotic stresses significantly modify epigenetic marks [6,8,9]. ROS, NO and other redox components are also central mediators of these environmental stresses [16,18]. Yet whether the stress triggered chromatin modifications are dominantly mediated by the redox intermediates remains to be determined. Additionally, NADPH oxidase, and multiple antioxidant enzymes contribute to ROS generation and scavenging, respectively, and nitrate reductase and NO synthase-like enzymes are responsible for NO biosynthesis in plants [18,47,54,55]. However, whether these enzymes play important roles in epigenetic modifications is unclear. We believe that these problems will be solved in near future with the rapid development of various biotechnologies, including omics, bioinformatics, and gene editing technologies. We also believe that uncovering the molecular mechanisms for redox control of epigenetic changes will greatly help to understand the strategies of plants adapting to ever-changing environmental conditions, and to facilitate cultivating of elite crop varieties with desired characteristics in the coming days.
Author Contributions: Conceptualization: F.H. and S.H.; writing: S.H., F.H., and S.K.R.M.; visualization: S.K.R.M., H.C., and S.H.; editing: X.Z. and Y.W. L.S. is responsible for editing the MS. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Natural Science Foundation of China (31870248 and 31401044), the “111” Project, and the Program for Young Backbone Teachers in Universities of Henan Province (2016GGJS-024).

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ACL ATP-citrate lyase
APX Ascorbate peroxidase
ASC Ascorbate
CAT Catalase
CHD Chromodomain helicase DNA-binding
CMT Chromomethylase
DCL Dicer-like
DDM1 DNA methylation 1
DHF Dihydrofolate
DHFRED Dihydrofolate reductase
DME Demeter
DML Demeter-like
DNMT DNA methyltransferase
DRB dsRNA-binding protein
DRM Domain rearranged methyltransferase
dsRBD dsRNA binding domains
GCN5 General Control Nondepressible 5
GPX Glutathione peroxidase
GR Glutathione reductase
GRX Glutaredoxin
GSH Glutathione
GSNO S-Nitrosoglutathione
GSSG Oxidized glutathione
H₂O₂ Hydrogen peroxide
HAT Histone acetyltransferase
Hcy Homocysteine
HD2 Histone deacetylase 2
HDAC Histone deacetylase
HDM Histone demethylase
HKMT Histone lysine methyltransferase
HMT Histone methyltransferase
HDT2 Histone deacetylase 2
JMJC Jumonji C domain-containing protein
LSD1 Lysine-specific demethylase 1
Met Methionine
MET1 DNA methyltransferase 1
MetSo Methionine sulfoxide
MS Methionine synthase
MSR Methionine sulfoxide reductase
MTHFD1 Methylene tetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase1
MTHFR Methylene tetrahydrofolate reductase
NAD(P)H Pyridine nucleotides
NO Nitric oxide
OAA Oxaloacetate
{O}_2 Singlet oxygen
O_2^− Superoxide radical
PCD Programmed cell death
PDH Pyruvate dehydrogenase
PR Pathogenesis-related
PRMT Protein arginine methyltransferase
RBOH Respiratory burst oxidase
RdDM RNA directed DNA methylation
RDP3/HDA1 Reduced potassium dependency 3/histone deacetylase 1
ROS Reactive oxygen species
ROS1 Repressor of silencing 1
RTL RNAse III-like
SA Salicylic acid
SAM S-Adenosyl-L-methionine
SAMS/MAT S-Adenosyl methionine synthase/methionine adenosyl transferases
SAHH/HOG1 S-Adenosylhomocysteine hydrolase/homologous gene silencing 1
SHMT Serine hydroxymethyl transferase
siRNA Small interfering RNA
SIR2 Silent information regulator 2
SNP Sodium nitroprusside
SOD Superoxide dismutase
stn7 State transition 7
SWI/SNF Switching defective/sucrose non-fermenting
THF Tetrahydrofolate
Topo VI Topoisomerase VI
TRX Thioredoxin
TS Thymidylate synthase

References
1. Pikaard, C.S.; Mittelsten Scheid, O. Epigenetic regulation in plants. Cold Spring Harb. Perspect. Biol. 2014, 6, a019315. [CrossRef] [PubMed]
2. Allis, C.; Jenuwein, T. The molecular hallmarks of epigenetic control. Nat. Rev. Genet. 2016, 17, 487–500. [CrossRef] [PubMed]
3. Zhang, H.M.; Lang, Z.B.; Zhu, J.K. Dynamics and function of DNA methylation in plants. Nat. Rev. Mol. Cell Biol. 2018, 19, 489–506. [CrossRef] [PubMed]
4. Lebedeva, M.A.; Tvorogova, V.E.; Tikhodeyev, O.N. Epigenetic mechanisms and their role in plant development. Russ. J. Genet. 2017, 53, 1057–1071. [CrossRef]
5. Lee, K.; Seo, P.J. Dynamic epigenetic changes during plant regeneration. Trends Plant Sci. 2018, 23, 235–247. [CrossRef]
6. Ramirez-Prado, J.S.; Abulfaraj, A.A.; Rayapuram, N.; Benhamed, M.; Hirt, H. Plant immunity: From signaling to epigenetic control of defense. Trends Plant Sci. 2018, 23, 833–844. [CrossRef]
7. Chang, Y.N.; Zhu, C.; Jiang, J.; Zhang, H.; Zhu, J.K.; Duan, C.G. Epigenetic regulation in plant abiotic stress responses. J. Integr. Plant. Biol. 2019. [CrossRef]
8. Vriet, C.; Hennig, L.; Laloi, C. Stress-induced chromatin changes in plants: Of memories, metabolites and crop improvement. *Cell. Mol. Life Sci.* 2015, 72, 1261–1273. [CrossRef]
9. Yamamuro, C.; Zhu, J.K.; Yang, Z. Epigenetic modifications and plant hormone action. *Mol. Plant* 2016, 9, 57–70. [CrossRef]
10. Shen, Y.; Issakidis-Bourguet, E.; Zhou, D.X. Perspectives on the interactions between metabolism, redox, and epigenetics in plants. *J. Exp. Bot.* 2016, 67, 5291–5300. [CrossRef]
11. Locato, V.; Cimini, S.; De Cara, L. ROS and redox balance as multifaceted players of cross-tolerance: Epigenetic and retrograde control of gene expression. *J. Exp. Bot.* 2018, 69, 3373–3391. [CrossRef] [PubMed]
12. Ageeva-Kieferle, A.; Rudolf, E.E.; Lindermayr, C. Redox-dependent chromatin remodeling: A new function of nitric oxide as architect of chromatin structure in plants. *Front. Plant Sci.* 2019, 10, 625. [CrossRef] [PubMed]
13. Del Rio, L.A. ROS and RNS in plant physiology: An overview. *J. Exp. Bot.* 2015, 66, 2827–2837. [CrossRef] [PubMed]
14. Gupta, D.K.; Palma, J.M.; Corpas, F.J. *Antioxidants and Antioxidant Enzymes in Higher Plants.*, 1st Ed. ed; Springer International Publishing AG: Gewerbestrasse, Switzerland, 2018; pp. 1–162.
15. He, H.M.; Van Breusegem, F.; Mhamdi, A. Redox-dependent control of nuclear transcription in plants. *J. Exp. Bot.* 2018, 69, 3359–3372. [CrossRef]
16. Farnese, F.S.; Menezes-Silva, P.E.; Gusman, G.S.; Oliveira, J.A. When bad guys become good ones: The key role of reactive oxygen species and nitric oxide in the plant response to abiotic stress. *Front. Plant Sci.* 2016, 7, 471. [CrossRef]
17. Chan, Z.; Yokawa, K.; Kim, W.Y.; Song, C.P. ROS regulation during plant abiotic stress responses. *Front. Plant Sci.* 2016, 7, 1536. [CrossRef] [PubMed]
18. Waszczak, C.; Carmody, M.; Kangasjarvi, J. Reactive oxygen species in plant signaling. *Annu. Rev. Plant Biol.* 2018, 69, 209–236. [CrossRef]
19. Shen, Y.; Wei, W.; Zhou, D.X. Histone acetylation enzymes coordinate metabolism and gene expression. *Trends Plant Sci.* 2015, 20, 614–621. [CrossRef]
20. Hu, J.L.; Yang, H.J.; Mu, J.Y.; Lu, T.C.; Peng, J.L.; Deng, X.; Kong, Z.S.; Bao, S.L.; Cao, X.F.; Zuo, J.R. Nitric oxide regulates protein methylation during stress responses in plants. *Mol. Cell* 2017, 67, 702–710. [CrossRef]
21. Hu, Y.; Lu, Y.; Zhao, Y.; Zhou, D.X. Histone acetylation dynamics integrates metabolic activity to regulate plant response to stress. *Front. Plant Sci.* 2019, 10, 1236. [CrossRef]
22. Zhao, T.; Zhan, Z.; Jiang, D. Histone modifications and their regulatory roles in plant development and environmental memory. *J. Genet. Genom.* 2019. [CrossRef] [PubMed]
23. Law, J.A.; Jacobsen, S.E. Establishing, maintaining and modifying DNA methylation patterns in plants and animals. *Nat. Rev. Genet.* 2010, 11, 204–220. [CrossRef] [PubMed]
24. Bartels, A.; Han, Q.; Nair, P.; Stacey, L.; Gaynier, H.; Mosley, M.; Huang, Q.Q.; Pearson, J.K.; Hsieh, T.F.; An, Y.Q.C.; et al. Dynamic DNA methylation in plant growth and development. *Int. J. Mol. Sci.* 2018, 19, 2144. [CrossRef] [PubMed]
25. Bewick, A.J.; Schmitz, R.J. Gene body DNA methylation in plants. *Curr. Opin. Plant Biol.* 2017, 36, 103–110. [CrossRef]
26. Matzke, M.A.; Mosher, R.A. RNA-directed DNA methylation: An epigenetic pathway of increasing complexity. *Nat. Rev. Genet.* 2014, 15, 394–408. [CrossRef]
27. Cuerva-Gil, D.; Slotkin, R.K. Non-canonical RNA-directed DNA methylation. *Nat. Plants* 2016, 2, 16163. [CrossRef]
28. Parrilla-Doblas, J.T.; Roldan-Arjona, T.; Ariza, R.R.; Cordoba-Canero, D. Active DNA demethylation in plants. *Int. J. Mol. Sci.* 2019, 20, 4683. [CrossRef]
29. Luger, K.; Mader, A.W.; Richmond, R.K.; Sargent, D.F.; Richmond, T.J. Crystal structure of the nucleosome core particle at 2.8 Å resolution. *Nature* 1997, 389, 251–260.

30. Ueda, M.; Seki, M. Histone modifications form epigenetic regulatory networks to regulate abiotic stress response. *Plant Physiol.* 2020, 182, 15–26. [CrossRef]

31. He, S.B.; Yan, S.H.; Wang, P.; Zhu, W.; Wang, X.W.; Shen, Y.; Shao, K.J.; Xin, H.P.; Li, S.H.; Li, L.J. Comparative analysis of genome-wide chromosomal histone modification patterns in maize cultivars and their wild relatives. *PLoS ONE* 2014, 9, e97364. [CrossRef] [PubMed]

32. Tan, J.; He, S.; Yan, S.; Li, Y.; Li, H.; Zhang, H.; Zhao, L.; Li, L. Exogenous EDDS modifies copper-induced various toxic responses in rice. *Protoplasma* 2014, 251, 1213–1221. [CrossRef]

33. He, S.B.; Yan, S.H.; Wang, P.; Zhu, W.; Wang, X.W.; Shen, Y.; Shao, K.J.; Xin, H.P.; Li, S.H.; Li, L.J. Comparative analysis of genome-wide chromosomal histone modification patterns in maize cultivars and their wild relatives. *PLoS ONE* 2014, 9, e97364. [CrossRef] [PubMed]

34. Zheng, B.; Chen, X. Dynamics of histone H3 lysine 27 trimethylation in plant development. *Curr. Opin. Plant Biol.* 2011, 14, 123–129. [CrossRef] [PubMed]

35. Binder, A.; Shafigh, S.; Shen, W.H. Histone modifications in transcriptional activation during plant development. *BBA-Gene Regul. Mech.* 2011, 1809, 567–576.

36. Xiao, J.; Lee, U.S.; Wagner, D. Tug of war: Adding and removing histone lysine methylation in *Arabidopsis*. *Curr. Opin. Plant Biol.* 2016, 34, 41–53. [CrossRef] [PubMed]

37. Marmorstein, R.; Zhou, M.M. Writers and readers of histone acetylation: Structure, mechanism, and inhibition. *Cold Spring Harbor Perspect. Biol.* 2014, 6, a018762. [CrossRef] [PubMed]

38. Zhang, C.J.; Hou, X.M.; Tan, L.M.; Shao, C.R.; Huang, H.W.; Li, Y.Q.; Li, L.; Cai, T.; Chen, S.; He, X.J. The Arabidopsis acetylated histone-binding protein BRAT1 forms a complex with BRP1 and prevents transcriptional silencing. *Nat. Commun.* 2016, 7, 11715. [CrossRef]

39. Nie, W.F.; Lei, M.; Zhang, M.; Tang, K.; Huang, H.; Zhang, C.; Miki, D.; Liu, P.; Yang, Y.; Wang, X.; et al. Histone acetylation recruits the SWR1 complex to regulate active DNA demethylation in Arabidopsis. *Proc. Natl. Acad. Sci. USA* 2019, 116, 16641–16650. [CrossRef]

40. Zhang, H.; Yue, M.; Zheng, X.; Gautam, M.; He, S.; Li, L. The role of promoter-associated histone acetylation of *Haem Oxygenase-1* (HO-1) and *Giberellic Acid-Stimulated Like-1* (GSL-1) genes in heat-induced lateral root primordium inhibition in maize. *Front. Plant Sci.* 2018, 9, 1520. [CrossRef]

41. Han, S.K.; Wu, M.F.; Cui, S.; Wagner, D. Roles and activities of chromatin remodeling ATPases in plants. *Plant J.* 2015, 83, 62–77. [CrossRef] [PubMed]

42. Chen, X.; Ding, A.B.; Zheng, X. Functions and mechanisms of plant histone deacetylases. *Sci. China Life Sci.* 2020, 63, 206–216. [CrossRef]

43. Ojolo, S.P.; Cao, S.; Priyadarshani, S.V.G.N.; Li, W.; Yan, M.; Aslam, M.; Zhao, H.; Qin, Y. Regulation of plant growth and development: A review from a chromatin remodeling perspective. *Front. Plant Sci.* 2018, 9, 1232. [CrossRef]

44. Han, S.K.; Wu, M.F.; Cui, S.; Wagner, D. Roles and activities of chromatin remodeling ATPases in plants. *Plant J.* 2015, 83, 62–77. [CrossRef] [PubMed]

45. Song, Y.; Miao, Y.; Song, C.P. Behind the scenes: The roles of reactive oxygen species in guard cells. *New Phytol.* 2014, 201, 1121–1140. [CrossRef] [PubMed]

46. Qi, J.; Song, C.P.; Wang, B.; Zhou, J.; Kangasjärvi, J.; Zhu, J.K.; Gong, Z. Reactive oxygen species signaling and stomatal movement in plant responses to drought stress and pathogen attack. *J. Integr. Plant Biol.* 2018, 60, 67–88.

47. Marino, D.; Dunand, C.; Puppo, A.; Pauly, N. A burst of plant NADPH oxidases. *Trends Plant Sci.* 2012, 17, 9–15. [CrossRef] [PubMed]
48. Ma, L.Y.; Zhang, H.; Sun, L.R.; Jiao, Y.H.; Zhang, G.Z.; Miao, C.; Hao, F.S. NADPH oxidase AtrbohD and AtrbohF function in ROS-dependent regulation of Na+/K+ homeostasis in Arabidopsis under salt stress. J. Exp. Bot. 2012, 63, 305–317. [CrossRef]

49. Jiao, Y.H.; Sun, L.R.; Song, Y.L.; Wang, L.M.; Liu, L.P.; Zhang, L.Y.; Liu, B.; Li, N.; Miao, C.; Hao, F.S. AtrbohD and AtrbohF positively regulate ascorbic acid-inhibited primary root growth by affecting Ca$_{2+}$ signalling and auxin response of roots in Arabidopsis. J. Exp. Bot. 2013, 64, 4183–4192. [CrossRef]

50. Li, N.; Sun, L.R.; Zhang, L.Y.; Song, Y.L.; Hu, P.P.; Li, C.; Hao, F.S. AtrbohD and AtrbohF negatively regulate lateral root development by changing the localized accumulation of superoxide in primary roots of Arabidopsis. Planta 2015, 241, 591–602. [CrossRef]

51. Chen, Q.; Yang, G. Signal function studies of ROS, especially RBOH dependent ROS, in plant growth, development and environmental stress. J. Plant Growth Regul. 2019. [CrossRef]

52. Sun, L.; Zhao, Z.J.; Hao, F.S. NADPH oxidases, essential players of hormone signalings in plant development and response to stresses. Plant Signal. Behav. 2019, 14, 1657343. [CrossRef]

53. Czarnocka, W.; Karpinski, S. Friend or foe? Reactive oxygen species production, scavenging and signaling in plant response to environmental stresses. Free Radic. Biol. Med. 2018, 122, 4–20. [CrossRef]

54. Kolbert, Z.; Barroso, J.B.; Brouquisse, R.; Corpas, F.J.; Gupta, K.J.; Lindermayr, C.; Loake, G.J.; Palma, J.M.; Petřívalský, M.; Wendeheenne, D.; et al. A forty year journey: The generation and roles of NO in plants. Nitric Oxide. 2019. [CrossRef]

55. Del Castello, F.; Nejamkin, A.; Cassia, R.; Correa-Aragunde, N.; Fernández, B.; Foresi, N.; Lombardo, C.; Ramírez, L.; Lamattina, L. The era of nitric oxide in plant biology: Twenty years tying up loose ends. Nitric Oxide. 2019, 85, 17–27. [CrossRef]

56. Sun, L.R.; Yue, C.M.; Hao, F.S. Update on roles of nitric oxide in regulating stomatal closure. Plant Signal. Behav. 2019, 14, e1649569. [CrossRef] [PubMed]

57. Mengel, A.; Chaki, M.; Shekariesfahlan, A.; Lindermayr, C. Effect of nitric oxide on gene transcription—S-nitrosylation of nuclear proteins. Front. Plant Sci. 2013, 4, 293. [CrossRef] [PubMed]

58. Martins, L.; Trujillo-Hernandez, J.A.; Reichheld, J.P. Thiol based redox signaling in plant nucleus. Front. Plant Sci. 2018, 9, 705. [CrossRef] [PubMed]

59. Foyer, C.H.; Noctor, G. Redox signaling in plants. Antioxid. Redox Signal. 2013, 18, 2087–2090. [CrossRef]

60. Soares, C.; Carvalho, M.E.A.; Azevedo, R.A.; Fidalgo, F. Plants facing oxidative challenges—A little help from the antioxidant networks. Environ. Exp. Bot. 2019, 161, 4–25. [CrossRef]

61. Foyer, C.H.; Halliwell, B. The presence of glutathione and glutathione reductase in chloroplasts: A proposed role in ascorbic acid metabolism. Planta 1976, 133, 21–25. [CrossRef]

62. Dalle-Donne, I.; Rossi, R.; Colombo, G.; Giustarini, D.; Milzani, A. Protein S-glutathionylation: A regulatory device from bacteria to humans. Trends Biochem. Sci. 2009, 34, 85–96. [CrossRef]

63. Zaffagnini, M.; Fermani, S.; Marchand, C.H.; Costa, A.; Sparla, F.; Rouhier, N.; Geigenberger, P.; Lemaire, S.D.; Trost, P. Redox homeostasis in photosynthetic organisms: Novel and established thiol-based molecular mechanisms. Antioxid. Redox Signal. 2019, 31, 155–210. [CrossRef]

64. Choi, C.S.; Sano, H. Abiotic-stress induces demethylation and transcriptional activation of a gene encoding a glycerophosphodiesterase-like protein in tobacco plants. Mol. Genet. Genom. 2007, 277, 589–600. [CrossRef]

65. Poborilova, Z.; Ohlsson, A.B.; Berglund, T.; Vildova, A.; Provaznik, I.; Babula, P. DNA hypomethylation concomitant with the overproduction of ROS induced by naphthoquinone juglone on tobacco BY-2 suspension cells. Environ. Exp. Bot. 2015, 113, 28–39. [CrossRef]

66. Berglund, T.; Wallstrom, A.; Nguyen, T.V.; Laurell, C.; Ohlsson, A.B. Nicotinamide; antioxidative and DNA hypomethylation effects in plant cells. Plant Physiol. Biochem. 2017, 118, 551–560. [CrossRef] [PubMed]

67. Ou, X.F.; Zhuang, T.T.; Yin, W.C.; Miao, Y.L.; Wang, B.; Zhang, Y.H.; Lin, X.Y.; Xu, C.M.; von Wettstein, D.; Rustgi, S.; et al. DNA methylation changes induced in rice by exposure to high concentrations of the nitric oxide modulator, sodium nitroprusside. Plant Mol. Biol. Rep. 2015, 33, 1428–1440. [CrossRef]
68. Rai, K.K.; Rai, N.; Rai, S.P. Salicylic acid and nitric oxide alleviate high temperature induced oxidative damage in *Lablab purpureus* L plants by regulating bio-physical processes and DNA methylation. *Plant Physiol. Biochem.* **2018**, *128*, 72–88. [CrossRef] [PubMed]

69. Rahikainen, M.; Alegre, S.; Trotta, A.; Pascual, J.; Kangasjarvi, S. Trans-methylation reactions in plants: Focus on the activated methyl cycle. *Physiol. Plant* **2018**, *162*, 162–176. [CrossRef]

70. Lindermayr, C.; Saalbach, G.; Durner, J. Proteomic identification of S-nitrosylated proteins in *Arabidopsis*. *Plant Physiol.* **2005**, *137*, 921–930. [CrossRef]

71. Puyaubert, J.; Fares, A.; Reze, N.; Peltier, J.B.; Baudouin, E. Identification of endogenously S-nitrosylated proteins in *Arabidopsis* plantlets: Effect of cold stress on cysteine nitrosylation level. *Plant Sci.* **2014**, *215–216*, 150–156.

72. Chaki, M.; Valderrama, R.; Fernandez-Ocana, A.M.; Carreras, A.; Lopez-Jaramillo, J.; Luque, F.; Palma, J.M.; Pedrajas, J.R.; Begara-Morales, J.C.; Sanchez-Calvo, B.; et al. Protein targets of tyrosine nitration in sunflower (*Helianthus annuus* L.) hypocotyls. *J. Exp. Bot.* **2009**, *60*, 4221–4234.

73. Lozano-Juste, J.; Colom-Moreno, R.; Leon, J. In vivo protein tyrosine nitration in *Arabidopsis thaliana*. *J. Exp. Bot.* **2011**, *62*, 3501–3517. [CrossRef]

74. Rouhier, N.; Vieira Dos Santos, C.; Tarrago, L.; Rey, P. Plant methionine sulfoxide reductase A and B multigenic families. *Photosynth. Res.* **2006**, *89*, 247–262. [CrossRef]

75. Petriacq, P.; de Bont, L.; Hager, J.; Didierlaurent, L.; Mauve, C.; Guerard, F.; Noctor, G.; Pelletier, S.; Renou, J.P.; Tcherkez, G.; et al. Inducible NAD overproduction in *Arabidopsis* alters metabolic pools and gene expression correlated with increased salicylate content and resistance to *Pst-AvrRpm1*. *Plant J.* **2012**, *70*, 650–665. [CrossRef]

76. Zhang, H.M.; Deng, X.Y.; Miki, D.; Cutler, S.; La, H.G.; Hou, Y.J.; Oh, J.; Zhu, J.K. Sulfamethazine suppresses epigenetic silencing in *Arabidopsis* by impairing folate synthesis. *Plant Cell* **2012**, *24*, 1230–1241. [CrossRef]

77. Groth, M.; Moissiard, G.; Wirtz, M.; Wang, H.F.; Garcia-Salinas, C.; Ramos-Parra, P.A.; Bischof, S.; Peng, S.H.; Cokus, S.J.; John, A.; et al. MTHFD1 controls DNA methylation in *Arabidopsis*. *Nat. Commun.* **2016**, *7*, 11640. [CrossRef] [PubMed]

78. Couturier, J.; Chibani, K.; Jacquot, J.P.; Rouhier, N. Cysteine-based redox regulation and signaling in plants. *Front. Plant Sci.* **2013**, *4*, 105. [CrossRef]

79. Seta, A.; Tabara, M.; Nishibori, Y.; Hiraguri, A.; Ohkama-Ohtsu, N.; Yokoyama, T.; Haru, S.; Yoshida, K.; Hisabori, T.; Fukudome, A.; et al. Post-translational regulation of the dicing activities of *Arabidopsis* DICER-LIKE 3 and 4 by inorganic phosphate and the redox state. *Plant Cell Physiol.* **2017**, *58*, 485–495. [CrossRef]
85. Fukudome, A.; Fukuhara, T. Plant dicer-like proteins: Double-stranded RNA-cleaving enzymes for small RNA biogenesis. *J. Plant Res.* 2017, 130, 33–44. [CrossRef]

86. Shamandi, N.; Zytnicki, M.; Charbonnel, C.; Elvira-Matelot, E.; Bochnakian, A.; Comella, P.; Mallory, A.C.; Lepere, G.; Saez-Vasquez, J.; Vaucheret, H. Plants encode a general siRNA suppressor that is induced and suppressed by viruses. *PLoS Biol.* 2015, 13, e1002326. [CrossRef]

87. Hussain, A.; Mun, B.G.; Imran, Q.M.; Lee, S.U.; Adamu, T.A.; Shahid, M.; Kim, K.M.; Yun, B.W. Nitric oxide mediated transcriptome profiling reveals activation of multiple regulatory pathways in *Arabidopsis thaliana*. *Front. Plant Sci.* 2016, 7, 975. [CrossRef]

88. Blanc, R.S.; Richard, S. Arginine methylation: The coming of age. *Mol. Cell* 2017, 65, 8–24. [CrossRef]

89. Ojima, Y.; Suryadarma, P.; Tsuchida, K.; Taya, M. Accumulation of pyruvate by changing the redox status in *Escherichia coli*. *Biotechnol. Lett.* 2012, 34, 889–893. [CrossRef]

90. Miernyk, J.A.; Randall, D.D. Some kinetic and regulatory properties of the pea mitochondrial pyruvate dehydrogenase complex. *Plant Physiol.* 1987, 83, 306–310. [CrossRef]

91. Wang, P.; Zhao, L.; Hou, H.L.; Zhang, H.; Huang, Y.; Wang, Y.P.; Li, H.; Gao, F.; Yan, S.H.; Li, L.J. Epigenetic changes are associated with programmed cell death induced by heat stress in seedling leaves of *Zea mays*. *Plant Cell Physiol.* 2015, 56, 965–976. [CrossRef]

92. Dietzel, L.; Glasser, C.; Liebers, M.; Hiekel, S.; Courtois, F.; Czarnecki, O.; Schlicke, H.; Yan, Z.B.; Bornet, T.; Mayer, K.; et al. Identification of early nuclear target genes of plastidial redox signals that trigger the long-term response of *Arabidopsis* to light quality shifts. *Mol. Plant* 2015, 2015, 8, 1237–1252. [CrossRef]

93. Mhamdi, A.; Hager, J.; Chaouch, S.; Queval, G.; Han, Y.; Taconnat, L.; Saindrenan, P.; Gouia, H.; Issakidis-Bourguet, E.; Renou, J.P.; et al. Arabidopsis GLUTATHIONE REDUCTASE1 plays a crucial role in leaf responses to intracellular hydrogen peroxide and in ensuring appropriate gene expression through both salicylic acid and jasmonic acid signaling pathways. *Plant Physiol.* 2010, 153, 1144–1160. [CrossRef]

94. Choi, S.M.; Song, H.R.; Han, S.K.; Han, M.; Kim, C.Y.; Park, J.; Lee, Y.H.; Jeon, J.S.; Noh, Y.S.; Noh, B. HDA19 is required for the repression of salicylic acid biosynthesis and salicylic acid-mediated defense responses in Arabidopsis. *Plant J.* 2012, 71, 135–146. [CrossRef]

95. Wojtaszek, P. Oxidative burst: An early plant response to pathogen infection. *Biochem. J.* 1997, 322, 681–692. [CrossRef]

96. Liu, P.; Zhang, H.; Yu, B.; Xiong, L.; Xia, Y. Proteomic identification of early salicylate- and flg22-responsive redox-sensitive proteins in Arabidopsis. *Sci. Rep.* 2015, 5, 8625. [CrossRef]

97. Zhang, H.; Zhao, Y.; Zhou, D.X. Rice NAD$^+$-dependent histone deacetylase OsSRT1 represses glycolysis and regulates the moonlighting function of GAPDH as a transcriptional activator of glycolytic genes. *Nucleic Acids Res.* 2017, 45, 12241–12255. [CrossRef]

98. Mengel, A.; Ageeva, A.; Georgii, E.; Bernhardt, J.; Wu, K.; Durner, J.; Lindermayr, C. Nitric oxide modulates histone acetylation at stress genes by inhibition of histone deacetylases. *Plant Physiol.* 2017, 173, 1434–1452. [CrossRef]

99. Kuang, J.F.; Chen, J.Y.; Luo, M.; Wu, K.Q.; Sun, W.; Jiang, Y.M.; Lu, W.J. Histone deacetylase HD2 interacts with ERF1 and is involved in longan fruit senescence. *J. Exp. Bot.* 2012, 63, 441–454. [CrossRef]

100. Chaki, M.; Shekariesfahlan, A.; Ageeva, A.; Mengel, A.; von Toerne, C.; Durner, J.; Lindermayr, C. Identification of nuclear target proteins for S-nitrosylation in pathogen-treated *Arabidopsis thaliana* cell cultures. *Plant Sci.* 2015, 238, 115–126. [CrossRef]
103. Ho, K.K.; Zhang, H.; Golden, B.L.; Ogas, J. PICKLE is a CHD subfamily II ATP-dependent chromatin remodeling factor. *Biochim. Biophys. Acta* **2012**, *1829*, 199–210. [CrossRef]

104. Simkova, K.; Moreau, F.; Pawlak, P.; Vriet, C.; Baruah, A.; Alexandre, C.; Hennig, L.; Apel, K.; Laloi, C. Integration of stress-related and reactive oxygen species-mediated signals by Topoisomerase VI in *Arabidopsis thaliana*. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 16360–16365. [CrossRef]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).