Journal of Advanced Research 42 (2022) 99–116

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Original Article

# Redox status of the plant cell determines epigenetic modifications under abiotic stress conditions and during developmental processes

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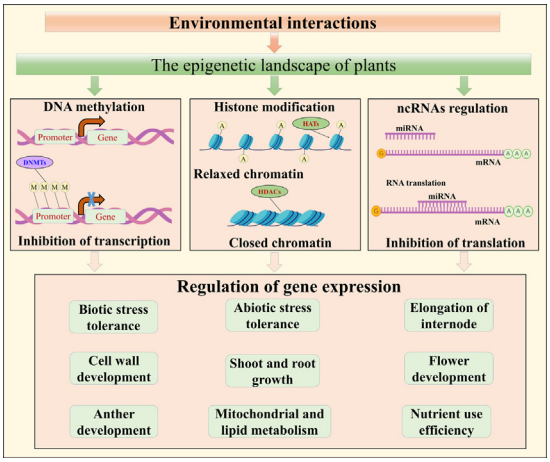
## HIGHLIGHTS

- The redox status of the cell influences enzymes involved in plant epigenetic modifications.
- The redox homeostasis in the cell is difficult to sustain because of unequal production of oxidant molecules.
- Intracellular epigenetic modifications in plants mitigate damage response during stress.
- High-throughput techniques have greatly advanced redox-mediated gene expression discovery.
- The integrated view of the redox status and epigenetic changes in plants are still scarce.
- We show opportunities for smart use of the redox status of the cell in development of the plant.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

*Article history:*
Received 22 January 2022
Revised 30 March 2022
Accepted 12 April 2022
Available online 28 April 2022

## ABSTRACT

*Background:* The oxidation-reduction (redox) status of the cell influences or regulates transcription factors and enzymes involved in epigenetic changes, such as DNA methylation, histone protein modifications, and chromatin structure and remodeling. These changes are crucial regulators of chromatin architecture, leading to differential gene expression in eukaryotes. But the cell's redox homeostasis is difficult to sustain since the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS)

Peer review under responsibility of Cairo University.

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https://doi.org/10.1016/j.jare.2022.04.007
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*Keywords:*
Redox status
Oxidative stress
Epigenetic modifications
miRNA biogenesis
Chromatin rearrangement
Abiotic stress tolerance

is not equal in plants at different developmental stages and under abiotic stress conditions. Exceeding optimum ROS and RNS levels leads to oxidative stress and thus alters the redox status of the cell. Consequently, this alteration modulates intracellular epigenetic modifications that either mitigate or mediate the plant growth and stress response.

*Aim of review:* Recent studies suggest that the altered redox status of the cell reform the cellular functions and epigenetic changes. Recent high-throughput techniques have also greatly advanced redox-mediated gene expression discovery, but the integrated view of the redox status, and its associations with epigenetic changes and subsequent gene expression in plants are still scarce. In this review, we accordingly focus on how the redox status of the cell affects epigenetic modifications in plants under abiotic stress conditions and during developmental processes. This is a first comprehensive review on the redox status of the cell covering the redox components and signaling, redox status alters the post-translational modification of proteins, intracellular epigenetic modifications, redox interplay during DNA methylation, redox regulation of histone acetylation and methylation, redox regulation of miRNA biogenesis, redox regulation of chromatin structure and remodeling and conclusion, future perspectives and biotechnological opportunities for the future development of the plants.

*Key Scientific Concepts of Review:* The interaction of redox mediators such as ROS, RNS and antioxidants regulates redox homeostasis and redox-mediated epigenetic changes. We discuss how redox mediators modulate epigenetic changes and show the opportunities for smart use of the redox status of the cell in plant development and abiotic stress adaptation. However, how a redox mediator triggers epigenetic modification without activating other redox mediators remains yet unknown.

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## Introduction

Gene expression is the part of the central dogma of cells supporting plant growth and development throughout the plant life cycle, but spatiotemporal gene expression depends on several factors: gene structure and organization and epigenetic processes. Epigenetic changes, such as DNA and histone proteins modifications, are crucial regulators of chromatin architecture, leading to differential gene expression. These changes are transient, thus playing a vital role during plant development and for abiotic stress adaptation [1]. Epigenetic-mediated gene expression undergoes dynamic changes such as switching stress and cell-specific genes on or off [2]. Epigenetically-induced phenotypic variations are generally inheritable without affecting the primary DNA sequence [3].

However, the internal cellular environment, particularly the oxidation-reduction (redox) status of the cell, influences enzymes involved in epigenetic changes, thereby controlling the activities of several transcription factors and other enzymes. For instance, enzymes involved in histone acetylation homeostasis require primary metabolites as substrates or cofactors whose levels are seriously influenced by the redox status of the cell [4]. The redox status also influences enzymes involved in methyl group donor and methyl group acceptor, which determine methylation efficiency. In recent times, redox-mediated gene expression discovery and its associations with epigenetic modifications is established in plants. Accruing evidence indicates that altered the redox status of the cell reform the cellular functions and epigenetic changes and regulates a wide range of functions in plants than previously understood. This occurs in all stages of plant growth and development, including adaptations to stresses [5]. However, despite the importance of the redox status of the cell, except for a few reviews [4–7], there is a lack of organized literature on redox-related epigenetic changes in plants. Therefore, in this review, we attempt to highlight the role of cellular redox status in epigenetic changes in plant systems, especially in addressing abiotic stress tolerance, vernalization and stem cell development.

## Redox components and signaling

The redox status is balanced by interactions of oxidant and antioxidant systems in the cell. The maintenance of the redox status of a living cell is dynamic because of the continuous production of oxidant molecules, reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Supplementary Table 1). In plants, ROS production occurs in various cellular components (Fig. 1), such as in chloroplast during photosynthesis, in mitochondria during electron transport, in peroxisomes during photorespiration, and in the plasma membrane [8]. As with ROS, RNS generation is also ineluctable. RNS is generally derived from nitric oxide (NO). RNS is also generated within different cellular compartments by the action of enzymes such as NO reductase, nitrate reductase and nitric oxide synthase-like enzymes [9]. Both oxidant molecules regulate important cell signaling processes in cell differentiation, multiplication and migration and programmed cell death [10]. Though ROS and RNS are both maintained at optimum levels by scavenging systems (antioxidants), excessive oxidant production occurs when cells are stressed and derails the redox status, triggering an oxidative stress response; however, these species get reduced, counterbalancing oxidative processes to maintain the cell's redox status [11]. During cellular processes, cellular redox status is an important indicator of a healthy plant system. Changes in the cell's redox status influence or alter nuclear gene expression in several ways such as direct modification, transcription factor activation, epigenetic modification, etc. [4].

Although oxidative stress due to the accumulation of excessive ROS and RNS is highly harmful to plant biological systems, optimum levels of ROS and RNS are necessary for regulating gene expression for stress tolerance. For instance, in *Arabidopsis*, mutants deficient in ROS production (knockout-NADPH oxidase D protein) were reported to be more sensitive to light stress [12]. Phytohormones like salicylic acid (SA) accomplish their activity by changing the redox status of the cell when the appropriate balance of reactive species is lost. For example, during salt stress, SA promotes the generation of endogenous ROS and NO and modulates their function [13].

### *Soluble redox carriers*

During redox homeostasis, intracellular communication between various cellular compartments is performed by soluble molecules known as redox/electron carriers such as nicotinamide adenine dinucleotide (NADH), glutathione (GSH) and ascorbate

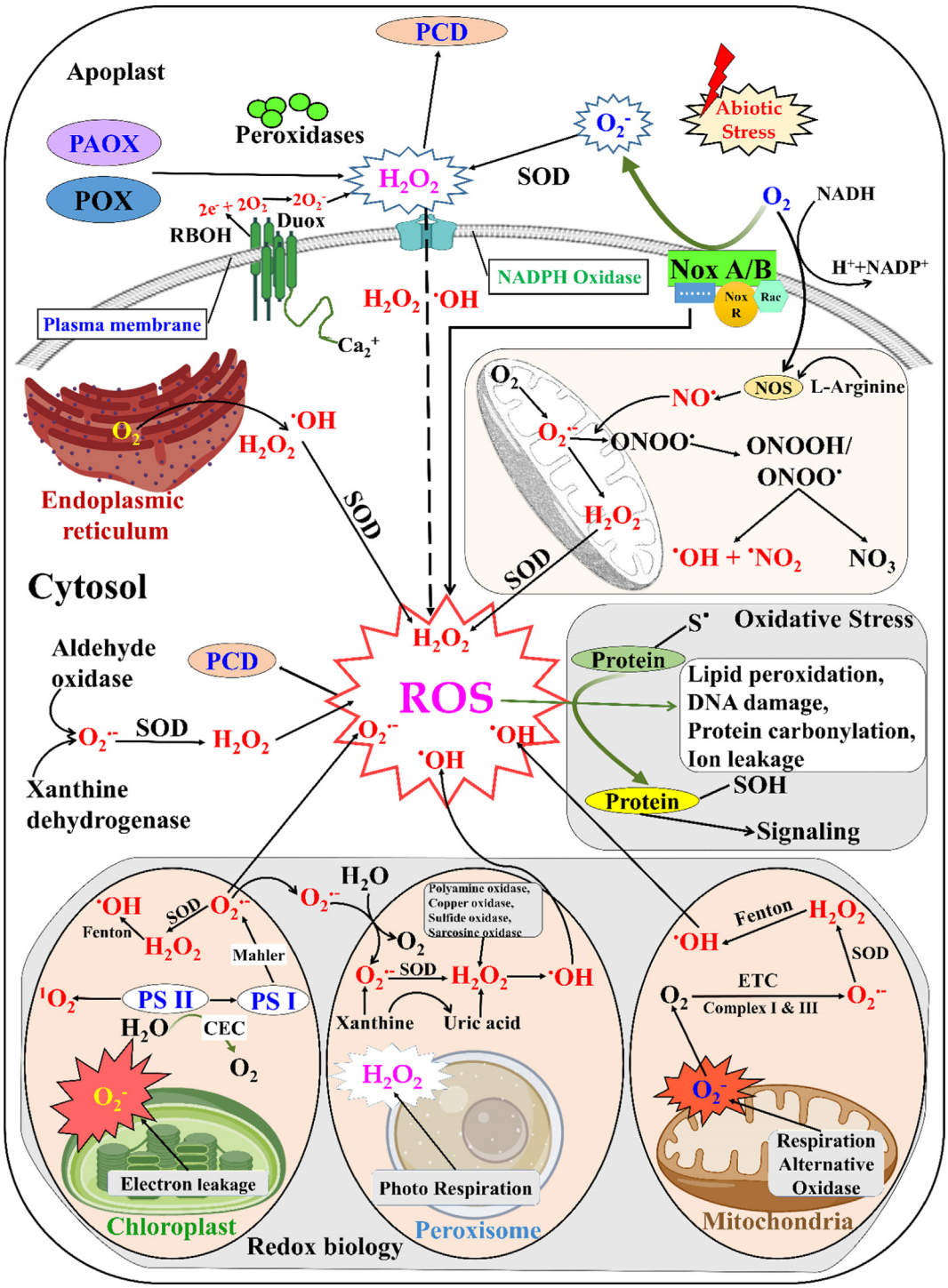


**Fig. 1.** Redox process of cellular state. Different reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in plants under abiotic stress to regulate gene expression for stress tolerance. ROS and RNS generation are activated during abiotic stress in the apoplastic space, chloroplasts, mitochondria, and peroxisomes. For instance, first, superoxide ($O_2^{\cdot-}$) is generated by plasma membrane NADPH (nicotinamide adenine dinucleotide phosphate reduced) oxidases, and $O_2^{\cdot-}$ is immediately dismutated to hydrogen peroxide ($H_2O_2$) by superoxide dismutases (SOD) in the corresponding organelles. Peroxidases (POX) and polyamine oxidases (POAX) are other sources of apoplastic $H_2O_2$ generation [14]. These organelles also have mechanisms to detoxify the $H_2O$; however, oxidative stress and programmed cell death (PCD) occur if ROS and RNS generation is beyond the homeostatic range.

(Asc) [15]. These molecules can quickly switch between reduced and oxidized states through the exchange of electrons (gain or loss of electrons). Thus, redox couples or redox guardians are essential for maintaining redox homeostasis and cellular metabolism. Redox pairs of these carrier molecules, such as NADH/$NAD^+$, GSH/glutathione disulfide (GSSG) and Asc/dehydroascorbic acid (DHA), play a significant role at various plant growth stages and when plants are exposed to stress.

The imbalance of redox couples or preventing reactions of the redox pairs of these carrier molecules renders the cell more vulner-

able to ROS. For example, *Arabidopsis* failed to develop past the embryonic stage without GSH whose function depends on the redox status of the cell [16]. The GSH:GSSG ratio is high in most cell organelles in plants growing under normal conditions but is altered by oxidative stress that increases the accumulation of GSSG to enhance stress tolerance. Thus, the GSH:GSSG ratio is related to the intracellular availability of $H_2O_2$. The glutathione reductase (*gr1*) mutant, encoding the peroxisome/cytosol enzymes, decreased the accumulation of GSSG in *Arabidopsis* leaf tissue, preventing survival [17]. Plants with NADPH deficiency also produced low GSH:GSSG ratios in the vacuole or endoplasmic reticulum, reviewed by Noctor et al. [18]. In tobacco lines, DHAR overexpression and knockdown respectively increased and decreased extractable foliar activity. The knockdown lines altered the Asc/DHA ratio in leaves under oxidative stress. Further, the GSH/GSSG ratio was higher in the DHAR overexpressed lines. A higher foliar level of Asc protected plants against oxidative stress [19]. Thus, redox carriers can act as markers of redox status and change the redox status of the cell.

Changes in the redox status of the cell induce several epigenetic modifications, including post-translational modifications (PTMs) in histone molecules [4], and either mitigate or mediate a response to damage during stress. The redox potential conditioned by the carrier molecules plays an important role in plants. For instance, an increase in NAD accumulation in a cytoplasmic male sterile II (CMSII) mitochondrial mutant of *Nicotiana sylvestris* was found to impart increased defense response and improved ozone tolerance [20]. By measuring the redox status using a redox-sensitive biosensor, namely reduction-oxidation sensitive green fluorescent protein (roGFP), Vivancos et al. [21] found that GSH plays a vital role in cell cycle progression in *Arabidopsis*. Similarly, an ascorbate deficient, vitamin C defective (*vtc*), mutant of *Arabidopsis* was reported to exhibit mild oxidative stress in the nucleus together with the arrest of cell cycle progression [22]. In the following sections, we summarize and discuss how the redox status of the cell affects epigenetic changes, regulation of miRNA biogenesis, chromatin remodeling and their collective role in abiotic stress tolerance.

## Redox status alters the post-translational modification of proteins

The PTMs of the gene product determine the ultimate phenotype of any gene expression. PTMs introduced by oxidative stress mediate the epigenetic pathway, thereby leading to altered phenotypes [23]. For instance, in *Arabidopsis*, a comparative expression study between the wildtype and a redox compromised mutant *stn7* (*state transition 7*) showed that many nuclear genes were not expressed in *stn7* mutants in response to high-light treatments. Further, in wild-type plants, redox signals that arose from the chloroplast could activate two enzymes, nuclear histone acetyltransferase (HAT) and histone deacetylase (HDAC), to promote histone methylation/demethylation. Since methylation and demethylation are two interchangeable processes integral to epigenetic gene expression, the observations on the *stn7* mutant are further evidence that redox signals alter gene expression through epigenetic and other regulatory pathways [23].

In *Lablab purpureus*, the induced elevation of $O_2^{\bullet-}$ and $H_2O_2$ after high-temperature treatment could be reversed by the application of SA and sodium nitroprusside (SNP), an NO donor. This reversal also showed a concomitant increase in the expression of antioxidant enzymes such as catalase (CAT), ascorbate peroxidase (APX), superoxide dismutase (SOD) and glutathione peroxidase (GPOX). Further, with the application of SA and SNP in high-temperature treated plants, the level of DNA methylation and demethylation was found to be higher than when SA and SNP were not applied [24].

Since PTMs are controlled by the redox status of the cell, protein conformations are adversely affected under oxidative stress. Oxidative stress-mediated PTMs can regulate cell cycle progression, and the maintenance of DNA methylation through cell division is a ubiquitin-dependent process. For instance, in wheat, exposure of seedlings to cadmium (Cd), methyl viologen and $H_2O_2$ induced oxidative stress and led to ubiquitylation of the cell cycle control protein, E2F/Rb related (RBR) transcription factors (TFs), leading, in turn, to the loss of protein function [25]. RBR/E2F association with chromatin factors (HDAC) plays a crucial role at every G1/S transition and participates in transcriptional regulatory complexes related to epigenetic changes [26], thus activating the cellular defence system. Further, the microenvironment and redox potential available to key amino acids determine cross-talk between protein and redox molecules. Generally, cysteine (Cys) and methionine (Met) residues are highly susceptible to reactive molecules. These findings indicate that redox changes affect epigenetic processes in plants and influence gene expression. The intrinsic mechanisms of redox changes during stress conditions in altering gene expression, particularly through epigenetic ways, are still not completely understood.

## Intracellular epigenetic modifications

Intracellular modulations leading to epigenetic changes commonly occur in the nuclear matrix. PTMs introduced at the chromatin region constitute some of the major epigenetic focal points of the cell. Chromatins are organized nucleoprotein structures in the nucleus where the nucleosomes are arranged. Each nucleosome comprises histone proteins and DNA [27]. Each histone molecule ends with an N-terminal tail composed of various amino acids. These tails are where various PTMs occur. Various modifications were reported in histones, such as 13 types in H2A, 12 in H2B, and 21 each in H3 and H4 [28–30]. The most common histone-level PTMs are lysine acetylation, methylation, arginine methylation, citrullination, SUMOylation, carbonylation, phosphorylation, ubiquitylation, ADP ribosylation, proline isomerization and cytosine glutathionylation [28,31–34]. These PTMs are known to alter gene expression by modulating transcriptional regulatory protein binding and/or by influencing histone-DNA interactions. Among these PTMs, acetylation and methylation are well-characterized epigenetic events. Following heat treatment, Wang et al. [35] reported increased acetylation and decreased methylation in maize with increased ROS accumulation. The decreased methylation was concomitant with nucleolar enlargement, implying chromatin decondensation [36]. Wang et al. [35] found that demethylation among H3K9 histones increased superoxide scavenging by loosening DNA-histone contact points favoring gene expression.

## Redox interplay during DNA methylation

Under stress conditions, changes in hormonal levels affect the redox status of the cellular system and are accompanied by changes in DNA and histone methylation. Maintenance of DNA methylation depends on (i) methyl source supplier, (ii) DNA methyltransferase (DNMT) activity, and (iii) DNA demethylase (DME) activity (Supplementary Fig. 1) [37]. In general, DNA methylation occurs at the promoter region and halts transcription. However, there are exceptions wherein methylation enhances gene transcription. This happens in the gene, *repressor of silencing 1* (*ROS1*), wherein the methylation of the promoter improves transcription. *ROS1* is an endonuclease III domain nuclear protein with

bifunctional DNA glycosylase/lyase activity [38]. *ROS1* acts only against methylated but not on unmethylated DNA, which establishes its DNA repair role. *ROS1* requires a direct connection with the Fe-S assembly, which is highly influenced by the redox status of the cell [5].

Generally, increased accumulation of reactive species such as $O_2^{\bullet-}$ is reported to reduce DNA methylation. In tobacco cells, increased oxidative stress due to exposure to various inducers, such as aluminium, paraquat, salt and low temperature, activates the expression of glycerophosphodiesterase-like (NtGPDL) proteins. NtGPDL proteins are already demonstrated to be responsive to aluminium stress. Analyzing the methylation pattern through bisulfite methylation mapping at the genomic loci of the *NtGPDL* gene showed selective demethylation of the CG site in the coding region. Further, irrespective of the stress inducer, the promoter region was found to be unmethylated. Choi and Sano [39] proposed that plant responses to environmental stresses are partly regulated through epigenetic modifications such as DNA hypomethylation. Subsequent studies also confirm that increase in oxidative stress conditions could lead to DNA hypomethylation [40]. Treatment of tobacco suspension culture with a naphthoquinone allelopathic toxin, Juglone (5-hydroxy-1,4-naphthalenedione), was reported to induce overaccumulation of ROS with simultaneous DNA hypomethylation [41]. Similar accompaniment of DNA hypomethylation under oxidative stress induced by the treatment of *Pisum sativum* suspension culture with nicotinamide (precursor to $NAD^+$) was reported by Berglund et al. [42]. Nicotinamide treatment was found to increase the level of GSH. Although epigenetic changes induced by increased GSH levels are well documented in animal and human cells [43], information regarding GSH-induced epigenetic alterations remains scarce in plants. Treatment of rice plants with a higher concentration of SNPs, NO donors, caused DNA hypomethylation [44]. Besides chemical stress inducers, physical factors, such as irradiation, were also found to induce demethylation. In *Arabidopsis*, irradiation of roots induced different methylation patterns on aerial plant parts, ranging from hemi-methylated to non-methylated, accompanied by ROS accumulation [45].

Epigenetic gene silencing in plants is established through the RNA-directed DNA methylation (RdDM) pathway involved with the production of small interfering RNAs (siRNA) [37]. Production of siRNA is mediated through the dicing activity of Dicer-like (DCL) proteins and the cleavage activity of RNase III-like (RTL) proteins. Both these proteins have conserved cysteine residue at the 230th position and are highly susceptible to oxidative stress conditions. In *Arabidopsis*, RTL2 regulates the expression of genes through the production of siRNA. *In situ* mutagenesis studies have shown that the cysteine 230 position is essential for cleavage leading to siRNA production. Incubation of RTL1 with GSH or GSSG was found to abolish RTL1 activity and prevented siRNA production by the glutathionylation of cysteine 230 under oxidative stress [46]. Similarly, regulation of DCL activity by SA and the redox status of the cell was established by Seta et al. [47], who found that DCL4 activity was enhanced by SA application through the accumulation of GSH. They concluded that the dicing activities of DCL3 and DCL4 were regulated by inorganic phosphate and the redox status of the cell, suggesting that homeostasis of gene silencing occurs according to the growing environment.

### *Regulation of SAM synthesis*

The most common methyl source supplier in biological systems is S-adenyl methionine (SAM). SAM synthesis is established through (a) folate and (b) methionine cycles, as depicted in Fig. 2. The source of the methyl group for SAM production is the folate molecule. Folate enters through folate cycle pathways that involve bifunctional enzyme-like dihydrofolate reductase-thymidylate synthases (DHFR-TS) [4]. DHFR-TS helps in the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF) by consuming the reducing equivalent from NADPH. Gorelova et al. [48] have shown that *Arabidopsis* DHFR mutants are incapable of assimilating folates. From folates, different derivatives are produced by different enzymes (Fig. 2). Homology-dependent gene silencing 1 (HOG1) is an enzyme that catalyzes the conversion of S-adenosyl homocysteine (SAH) to homocysteine (Hcy). During this process, SAM acts as a methyl donor for DNA methylation. In this manner, the Hcy/SAM cycle provides a constant supply of methyl groups for DNA methylation. The role of folate in driving this cycle is crucial, as observed in *Arabidopsis*, wherein impairment of folate production by sulfamethazine treatment was found to reduce DNA and histone methylation [49].

The folate cycle is the supplier of the methyl group to methionine and to the SAM cycle. It is found that enzymes involved in SAM synthesis through the folate cycle are regulated through the redox status of the cell or by using reducing equivalents (Table 1). Some of these enzymes, such as HOG1 [50] and MS [51] were found to undergo nitrosylation, the covalent modification of redox-sensitive cysteine residues by NO, suggesting that these enzymes are redox-regulated. Furthermore, during developmental processes and/or under stress, methionine undergoes oxidization to become methionine sulfoxide (MetSo), which, in turn, reverts to methionine by methionine sulfoxide reductase (MSR) activity, consuming NADPH in the process [52]. Evidence indicates that MSR enzyme activity is also redox-regulated in the cell. In *Arabidopsis*, GSH treatment was found to down-regulate MSR accumulation [53]. *In vitro* studies have shown that glutathionylation of MSR at the cysteine position plays a vital role in methionine regeneration. Lindermayr et al. [54] described nitrosylation of SAMS at the cysteine 113 position, following its incubation with nitrosoglutathione (GSNO), which abolished SAMS activity in *Arabidopsis*. They concluded that SAMS activity is influenced by the redox status of the cell. The redox status of the cell modulates DNA methylation by influencing one or more factors related to DNA hyper or hypomethylation. The fact that methylation efficiency depends on the reaction conditions between methyl group donors and acceptors, such as DNA or histones, suggests that the redox status of the cell can influence both donor and acceptor systems to induce epigenetic changes.

### *Regulation of DNA methylation/demethylation*

The redox status of the cell influences DNMT activity, inducing changes in methylation patterns. A methylation indicator, the presence of oxidative stress, has been shown to increase DNMT expression in plants. In *in vitro* grown birch plants, increased ROS activity in older calli elevated DNA methylation and was accompanied by an increased expression of DNMT genes such as domain rearranged methyltransferase (DRM), methyltransferase (MET) and chromomethylase (CMT) [56].

In demethylation, DNA demethylase activity is performed by DNA glycosylase by excising the entire methylated base instead of the methyl group alone. The removal of the methylated base from the methylated DNA region is accomplished through the base excision repair (BER) pathway. DNA glycosylase has an iron-sulfur (Fe-S) cluster assembly as a cofactor, which aids in gaining or losing electrons under oxidation. The assemblage of the Fe-S cluster with the apoprotein is mediated through the cytosolic Fe-S cluster assembly (CIA) pathway. The CIA pathway engages several scaffold and carrier proteins [57]. *Demeter* and *ROS1* are 5-methylcytosine DNA glycosylases that play a role in fertilization [58]. This Fe-S cluster assembled DNA demethylase is activated during fertilization, following an oxidative burst in the central cell, leaving evi-

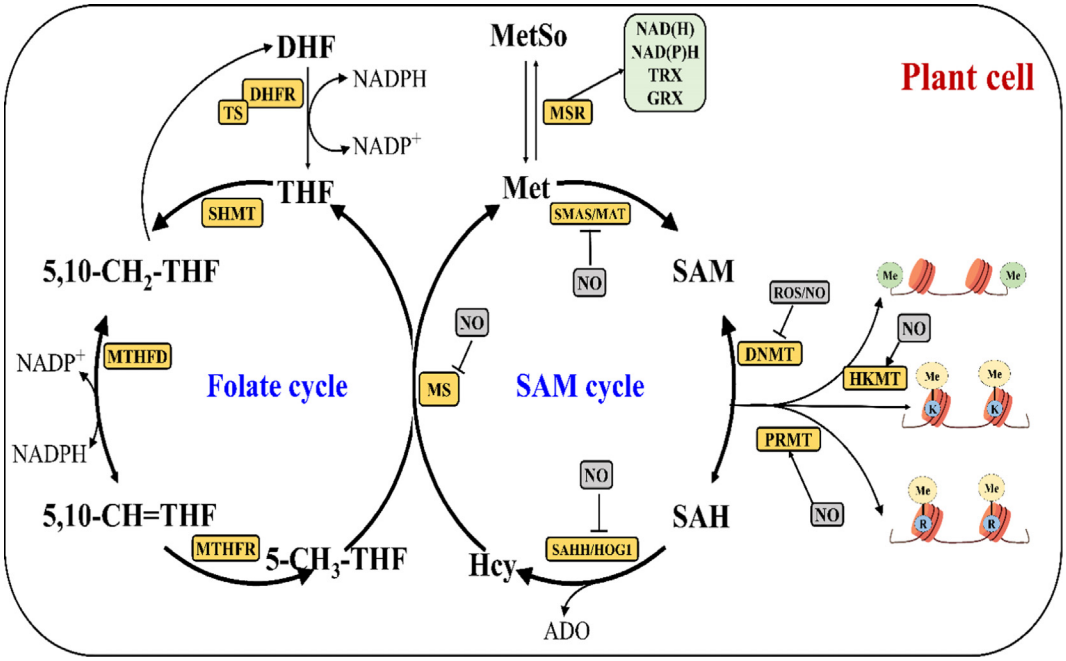


**Fig. 2.** Redox components regulate S-adenyl methionine (SAM) synthesis through the folate cycle in plants. The folate cycle starts with the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF) through dihydrofolate reductase-thymidylate synthase (DHFR-TS) by using reducing equivalents from NADPH (nicotinamide adenine dinucleotide phosphate). Methyl groups gained from THFs (5,10-CH2-THF, 5,10-CH = THF) are synthesized by serine hydroxymethyltransferase (SHMT) and methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase (MTHFD1). Methylenetetrahydrofolate reductase (MTHFR) reduces 5,10-CH = THF to 5-CH3-THF, from which the methyl group is transferred to homocysteine (Hcy) to synthesize methionine (Met) through the methionine synthase (MS) enzyme. Methionine synthesizes SAM through SAM synthase (SAMS), and SAM donates methyl groups to proteins or DNA through DNA methyltransferase (DNMT)/ histone lysine methyltransferase (HKMT)/ protein arginine N-methyltransferase (PRMT) and is converted to S-adenosyl homocysteine (SAH) which is further processed to Hcy through S-adenosyl homocysteine hydrolase/ homology-dependent gene silencing 1 (SAHH/HOG1). Redox components influence the following key enzymes: SAMS/methionine adenosyl transferases (MAT), DNMT/ HKMT/PRMT, SAHH/HOG1, MS and methionine sulfoxide reductase (MSR). K: lysine; R: arginine; Me: methyl. ROS/NO is uncharacterized regulation. GRX, glutaredoxin; TRX, thioredoxin [4]. The schematic representation was adapted from Saravana Kumar et al. [4].

**Table 1**
The list of enzymes involved in DNA methylation affected by the redox status of the cell.

| Epigenetic process and modifying enzyme | Redox status influence on enzymes | Described roles for the epigenetic process | References |
|---|---|---|---|
| Methionine sulfoxide reductase (MSR) | NADP increases the MSR transcript, and GSH helps regenerate MSR | MSR regenerates methionine from the oxidized methionine pool | [52,55] |
| Homologous gene silencing 1 (HOG1) | Nitrosylation of HOG1 | Converts S-Adenosyl homocysteine to homocysteine | [50] |
| Detrahydrofolate reductase | NADPH is converted to NADP | Catalyzes the conversion of dihydrofolate to tetrahydrofolate | [48] |
| Methionine synthase (MS) | Nitrosylation | Converts homocysteine to methionine | [51] |

Note: NADP, nicotinamide adenine dinucleotide phosphate; GSH, glutathione.

dence that conditions similar to oxidative stress are required for demethylase activity.

## Redox regulation of histone acetylation

Histone acetylation, another type of PTM, occurs in the nucleus. In contrast to methylation, acetylation of histones generally facilitates gene expression [59], although some histone methylation is also known to promote gene expression. In the cell, histone acetylation depends on the availability of the substrate, acetyl CoA, and is maintained through the antagonistic activity of two enzymes, HAT and HDAC. As with other PTMs, the activities of HAT/HADC enzymes, as well as acetyl CoA metabolism, are redox-regulated. Currently, several reports establish redox-mediated histone acetylation in plants and animals. Mengel et al. [60] report that, in *Arabidopsis*, treatment with NO or GSNO resulted in the inactivation of the HDAC complex, increasing histone acetylation. During heat-induced programmed cell death, increased accumulation of ROS was found to ensure hyperacetylation by overexpression of HAT in maize seedlings [35]. In sugar beet lines, Causevic et al. [61] have shown that different levels of ROS expression could direct different levels of histone acetylation.

### *Regulation of acetyl CoA*

Acetyl CoA is a thioester between acetic acid and coenzyme A. The prime role of acetyl CoA is to act as an acetyl radical donor, a cofactor for several metabolic pathways in the cell, such as the Krebs cycle and the PTMs such as histone acetylation. Acetyl CoA

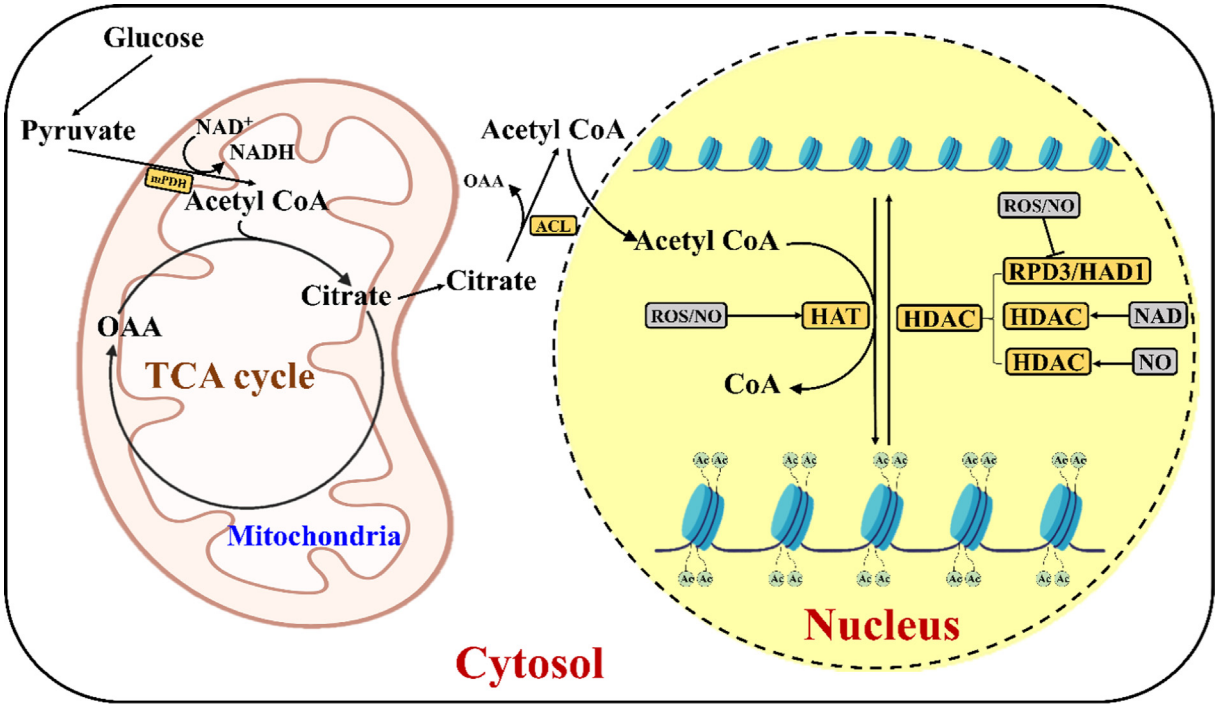


**Fig. 3.** Acetyl CoA synthesis in the mitochondrial matrix and the regulation of histone acetylations by redox components. In the cytoplasm, the breakdown of glucose produces pyruvate, which enters the tricarboxylic acid (TCA) cycle that occurs in the mitochondria. Then, pyruvate is converted to acetyl-CoA through mitochondrial pyruvate dehydrogenase (mPDH) by reducing NAD +. Combining with acetyl-CoA, oxaloacetate (OAA) formed in the TCA cycle produces citrate. After entering the cytoplasm, citrate is converted back to OAA and acetyl-CoA through ATP-citrate lyase (ACL). Synthesized acetyl-CoA enters the nucleus and provides the acetyl group to the histone acetyltransferase (HAT) for histone acetylation. After receiving the acetyl group, HAT introduces acetylation marks (Ac) over the lysine residues of the histone tail, thereby loosening the nucleosome structure (DNA and histones) and facilitating gene expression. Histone deacetylase (HDAC) removes histone acetyl groups from the histone tail, thus leading to chromatin compaction. ROS, NO, and $NAD^+$ influence different HAT and HDAC enzymes [4]. The schematic representation was adapted from Saravana Kumar et al. [4]

is synthesized in plants in different cellular organelles such as mitochondria (Fig. 3), chloroplast, and peroxisomes. The oxidative stress in cells alters acetyl CoA metabolism, thereby significantly influencing histone acetylation [62]. In mitochondria, oxidative decarboxylation of pyruvate by the activity of the mitochondrial pyruvate dehydrogenase (mPDH) complex results in the generation of acetyl CoA. Oxidative decarboxylation of pyruvate is an integral step of the glycolysis pathway that occurs before the entry of acetyl CoA into the Krebs cycle. During this process, the PDH complex uses $NAD^+$ as a cofactor for its catalytic activity, converts pyruvate to acetyl CoA and releases $CO_2$ [63]. In *Arabidopsis*, it has been shown that altering the redox status (increased NADH/NAD + ) under *in vitro* conditions inhibits mPDH complex activity [64]. In a 2019 review, Dumont and Rivoal [65] point out that, in *Arabidopsis*, the PTMs of enzymes are involved in the tricarboxylic acid (TCA) cycle in a redox-dependent manner. The inhibition of the redox-dependent TCA cycle increases acetyl CoA and decreases ROS production by increasing citrate concentrations to increase histone acetylation. In roots and seedlings, pyruvate was shown to increase by oxidative stress. This increase impacts TCA cycle inhibition, suggesting that the redox status influences acetyl CoA synthesis.

The other two mechanisms that generate acetyl CoA include fatty acid β-oxidation and amino acid catabolism. Amino acid catabolism involves amino acids such as leucine, lysine, phenylalanine, tryptophan and tyrosine. The catalytic conversion of acetyl CoA into fatty acids is regulated by the enzyme acetyl-CoA carboxylase 1 (ACC1) in animals and plants. The *acc1* mutants of *Arabidopsis* that are defective in fatty acid synthesis are reported to accumulate a high level of acetyl CoA [66]. A high accumulation of acetyl CoA could induce increased histone acetylation [67].

### *Regulation of histone acetyltransferase*

HAT enzymes mediate acetylation by combining with other factors to form a HAT complex, whose activity is affected by oxidative stress. The elongator protein, a component of the HAT complex, is known to mediate ABA response, anthocyanin biosynthesis and oxidative stress tolerance in *Arabidopsis* [68]. In maize, ROS generation occurs in seedlings exposed to elevated salinity conditions in the form of increased electrolyte leakage and $H_2O_2$ production, thus inducing several antioxidant pathway genes [69]. A collateral increase in HAT enzyme expressions, such as *ZmHATB* and *ZmGCN5*, was observed and was accompanied by the upregulation of cell wall synthesis genes, *ZmEXPB2* (expansin-B2) and *ZmXET* (xyloglucan endotransglycosylase). Upregulation of cell wall synthesis genes was mediated by increased acetylation in promoter regions, evidence that HAT enzymes mediate the expression of various stress-responsive genes by modifying their acetylation status during stress [70].

### *Regulation of histone deacetylases*

Available evidence shows that HDAC expression is primarily regulated by the redox status of the cell leading to histone deacetylation (Supplementary Table 2). Different PTMs mediated by the redox status of the cell also affect HDAC activity. HDACs are enzymes with deacetylation activity that are classified based on

both mechanistic similarity and phylogenetic comparison [71]. There are generally two types, the predominant non-sirtuin types and the sirtuin types. Non-sirtuin HDACs have Zn or Fe ions embedded in their structure while sirtuins use $NAD^+$ as a cofactor. A comprehensive phylogenetic analysis of HDAC-like sequences, across sequenced genomes, established that non-sirtuin HDAC enzymes are best classified into three distinct groups, Class I, II, and IV, while the sirtuin-like enzymes remained classified in Class III. Class I HDACs are *HDA1*, *HDA2*, *HDA3* and *HDAC8*; Class II includes *HDAC4*, *HDAC5*, *HDAC6*, *HDAC7*, *HDAC9* and *HDAC10*; Class III includes sirtuin-2 like (*SIRT*) HDACs such as *SIRT1*, *SIRT2*, *SIRT3*, *SIRT4*, *SIRT5*, *SIRT6* and *SIRT7*; and Class IV contains *HDAC11*. *Arabidopsis* HDACs, for example, constitute 18 genes, grouped as *RPD3* (reduced potassium dependency 3)/*HDA1* (histone deacetylase 1) (RPD3/HDA1), *SIR2* (silent information regulator 2), and *HD2*, the plant-specific histone deacetylase 2 [71].

### *Non-sirtuin HDACs*

Non-sirtuins, the major group of HDACs, are predominantly involved in regulating histone acetylation in cells. Under oxidative stress, HDACs are found to be unrecruited from gene repression, driving increased acetylation and consequent gene expression. Ding et al. [72] report that, in rice, during the compatible host-pathogen interaction, the transcript level of *HDT701* (histone 4 deacetylase 701), an *HD2* subfamily gene, is increased, in contrast to its lowered expression during incompatible interaction. They found that transgenic overexpression of *HDT701* led to a reduction in H4 acetylation leading to susceptibility to rice pathogens, salt, drought and osmotic stresses. Decreased H4 acetylation is associated with delayed seed germination [72,73]. The pattern was found to be reversed with the silencing of *HDT701*, whereupon elevated H4 acetylation was observed along with an increased transcription of PRRs and defense genes. Additionally, treating with pathogen-associated molecular pattern (PAMP) elicitors, flg22 and chitin, increased ROS levels in transgenic plants. Increased transcription of defense genes was found to be linked to enhanced acetylation marks in their promoters.

Non-sirtuin HDAC members are redox-sensitive and are produced during different oxidative stress conditions. In plants, HDACs get inactivated under oxidative stress to increase histone acetylation which helps the expression of many abiotic stress resistance genes [74]. There are several reports of redox switch regulation of HDACs such as *HDA1*, *HDA2*, *HDA3*, *HDAC4*, *HDAC5*, *HDAC6* and *HDAC8* during oxidative stress conditions [74].

PTMs involving HDACs either make proteins inactive or loosen contact with the surrounding DNA. Among the deacetylases, *HDA2* is among the most characterized. Ito et al. [75] demonstrated that S-nitrosylation of *HDA2* leads to hyperacetylation. When $H_2O_2$ was administered, S-nitrosylation was induced on *HDA2,* driving histone acetylation. Similarly, S-nitrosylation of *HDAC6*, *HDAC8* was also found to occur under oxidative stress [74]. Plants are also observed to possess *HDA6*, a homolog of human *HDAC1* [76] and yeast *Reduced potassium dependency 3* (*RPD3*) [77]. Plant HDACs work as a complex, and S-nitrosylation of either HDACs or their complexes could result in the inactivation of HDACs [78]. In general, HDACs lack DNA binding properties and, hence, form complexes with large multiprotein sub-units.

Like any other stress response genes, HDACs also undergo PTMs under stress, when the cysteine residue changes to alter protein development, functions and subsequent protein–protein interactions. Mengel et al. [60] have shown that the application of GSH to *Arabidopsis* seedlings grown in a liquid medium increased histone acetylation due to the reduction of HDAC activity. *In vitro* studies have revealed that GSSG mediates protein glutathionylation at the cysteine position. In *Arabidopsis*, the expression of genes related to SA biosynthesis and SA-mediated defense-associated pathogenesis-related (PR) proteins were repressed by an RPD3/HDA1 class deacetylase. In the case of HDA19, which deacetylates the promoter regions, oxidative stress conditions induced by pathogen attack abolish HDA19 activity to drive promoter acetylation leading to SA accumulation and PR protein expression inciting defense response [79]. Later, Liu et al. [80] demonstrated that increased ROS production, after the addition of SA and flg22 into *Arabidopsis* cell suspension cultures, led to the oxidation of two deacetylases, HDA9 and HDA19, improving the acetylation of stress-responsive genes.

Likewise, in *Arabidopsis* under cold conditions, the CULLIN4-based ubiquitin E3 ligase complex promotes HD2C degradation (increased acetylation levels of histone H3), which allows the activation of cold-responsive (*COR*) genes [81]. Further, HD2C interacts with other HDACs to either increase or decrease acetylation levels to regulate stress tolerance. For instance, in *Arabidopsis*, in double mutant plants (*hda6*, *hd2c*, and *hda6*/*hd2c-1*), HD2C directly interacted with HDA6, was bound to histone H3 and was associated with increased histone H3K9K14 acetylation and decreased histone H3K9 dimethylation, thus activating ABA-responsive genes [82]. In addition, HD2C interaction with the BRM-containing SWI/SNF chromatin remodeling complex regulates *Arabidopsis* heat stress response [83]. According to ROS status in the cell, plants require either low or high levels of acetylation to regulate stress tolerance. In *Arabidopsis*, the HDA19-MSI1 complex maintains low levels of acetylation of histone H3 at lysine 9 and fine-tunes ABA signaling [84]. HDA19 formation with other proteins is also important for brassinosteroid signaling to facilitate histone deacetylation of ABI3 chromatin [85], suggesting that the redox status of the cell regulates plant stress tolerance through histone modifications.

### *Sirtuin HDACs*

Sirtuin HDACs use NADH, a redox carrier cofactor molecule known for its deacetylation activity. NADH is a small metabolite transporting reducing equivalents to different cell compartments [71]. NADH shuttles between oxidized ($NAD^+$) and reduced states through electron exchange, mediating different metabolic reactions inside the cell. The transition of NADH between the two oxidation states depends on the redox status of the cell, qualifying it as an indicator of energy and the redox status of the cell. Although the redox status of the cell and its impact on NADH is not well documented in plants, it is widely accepted that, under oxidative stress conditions, the redox status of $NAD^+$ shifts towards a more reduced state. Since the activity of sirtuin HDACs is $NAD^+$ dependent, the cellular $NAD^+$ level and the $NAD^+$/NADH ratio are the major determinants of their deacetylation activity [86]. Generally, sirtuins are assemblers of heterochromatin (silent information) during gene expression. However, sirtuin type class III HDACs are involved in the deacetylation of histones as well as non-histone proteins.

Among seven sirtuin isoforms (*SIRT1-7*), the activity of the *SIRT2* gene involves several PTMs that are redox-mediated. Under oxidative stress, various protein kinases, which introduce PTMs in the *SIRT1*, are activated. Common oxidative stress-induced protein kinases are casein kinase II (CKII) [87], cell division control 2 (Cdc2) [88] and 5′ adenosine monophosphate-activated protein kinase (AMPK) [89]. Phosphorylation of *SIRT2* by protein kinases makes it dysfunctional, leading to increased acetylation. Although *SRT1* expression is promoted under mild oxidative stress condi-

tions, during severe oxidative stress, *SRT1* gets inactivated through PTMs such as glutathionylation [90] and nitrosylation [91]. Additionally, $NAD^+$ depletion under oxidative stress can also suppress *SRT1* activity [92]. In plants, cellular redox status recruits *SIRT* genes to alter the expression of ROS responsive genes through $NAD^+$ mediated activity. Unlike in animal systems, the number of sirtuins reported in plant systems is low [93]. Two *SIRT* genes each are reported from *Arabidopsis* (*AtSRT1* and *AtSRT2*) and rice (*OsSRT1* and *OsSRT2*) [94], and one from durum wheat (*WhSRT2*) [95].

## Redox regulation of histone methylation

Unlike histone acetylation, methylation does not affect the net charge of histone residues but modifies the bulkiness instead. The bulkiness or hydrophobicity between the residues opens up new platforms for the binding of other regulatory proteins. Classified as mono-, di- and tri-methylation, based on the number of methyl groups attached over the histone molecules, different methylations have different effects on the expression of genes. For instance, trimethylation of the 27th lysine residue of H3 (H3K27me3), usually carried out by the polycomb group (PcG) protein, leads to the repression of genes, while trimethylation at the fourth lysine of H3 (H3K4me3), catalyzed by *Arabidopsis* Trithorax (ATX) group proteins, leads to active transcription [96]. Like other PTMs, histone methylation is also affected by various redox components in the cell.

As with DNA methylation, SAM is the source supplier of the methyl group (added to the lysine and arginine residues of histones) for histone methylation. In *Andropogon virginicus*, *AvSAMS* gene expression is induced by different metal toxicities and other oxidative stress conditions [97]. When *Arabidopsis* is transformed with the *AvSAMS* gene, the transgenic plants confirm increased tolerance to aluminum and other metal ions; during aluminum stress, the histone methylation level of the differentially expressed genes was significantly altered compared to the level in wild-type plants. Ezaki et al. [97] also concluded that *SAMS* expression under oxidative stress-regulated histone methylation influences the expression of stress-responsive genes. Since folate is necessary for SAM production and to carry out the methionine cycle, folate inhibitors can play a significant role in controlling methylation. Sulfamethazine is a potential antagonist to folate synthesis in the cell, affecting epigenetic modifications. When applied, sulfamethazine reduces the folate level in plants, thereby reducing DNA and histone methylation [49]. Although stress-mediated histone methylation is known, the details of interconnectivity between oxidative stress and histone methyltransferase/demethylase reactions are seldom detailed.

### *Regulation of histone methyltransferase*

Histone methyltransferases (HMTs) catalyze the addition of one or more methyl groups to histone residues, particularly those of H3 and H4 histones. Using SAM as the methyl donor, histone-lysine N-methyltransferases (HKMT) and histone-arginine N-methyltransferases (HRMT) mediate methylation. Methyltransferase activity is influenced by stress-induced redox modification whereupon the methylome of stress-specific genes is controlled [98]. Depending upon the target residue, HMTs are of two types, lysine-specific HKMT and arginine-specific HRMT.

HKMT proteins possess conserved SET (Suppressor of variegation 3–9, Enhancer of Zeste, and Trithorax) domains for their catalytic activity. The HMTs of the SET domain-containing group (SDG) (SDG-HMTs) is found to be distributed across yeast, plants and animals [99]. SDG-HMTs are known to alter gene expression either at the transcriptional or post-transcriptional level. In mammalian cells, it was shown that ROS regulate the expression of mitochondrial and antioxidant genes by the action of the SET domain (SETD7) group of proteins [100]. Unlike in animal cells, direct evidence interlinking the redox status of the cell with SDG-mediated gene expression is lacking in plant cells. For instance, in *Arabidopsis*, it is well known that exposure to light and carbon alters the redox status of the cell. Li et al. [101] report that methylation patterns in light and carbon responsive genes are altered by SDG8 activity. Belonging to the SDG-HMT group, *Arabidopsis* Trithorax1 (ATX1) mediates $H_2O_2$ signaling. Kaurilind et al. [102] demonstrated that, when *atx* mutants were integrated with *Arabidopsis* catalase 2 (*cat2*) mutants, lesion development in the mutants got suppressed. The lesions in *cat2* mutants are due to the excessive accumulation of $H_2O_2$, which leads to programmed cell death. Lesion suppression by the introduction of *atx* mutants implied that ATX1 mediates $H_2O_2$ signaling in the programmed cell death pathway.

Similarly, HRMT, also known as protein arginine N-methyltransferase (PRMT), regulates different developmental and stress responses in plants. A well-characterized PRMT in *Arabidopsis*, PRMT5, acts as a redox signaling mediator [103]. PRMT5 induces a di-methylation of the third arginine residue of the H4 histone (H4R3me2) and suppresses the expression of the *flowering locus C* (*FLC*) as well as of salt responsive genes [104,105]. Under salinity stress, PRMT5 acts as a signal transducer of NO by methylating histone residues. The NO produced induces S-nitrosylation of PRMT5, thereby inducing its activity. The induced PRMT5 methylates the spliceosome of stress-response pre-mRNA. The change in the methylation status of the spliceosome affects protein splicing activities and leads to the development of alternative splice variants [105]. The production of these alternate variants increases the number of stress-specific gene products. Such post-transcriptional level variations are induced by NO through S-nitrosylation to regulate the production of stress-specific mRNA transcripts [103].

### *Regulation of histone demethylase reactions*

Histone demethylases (HDMs) mediate the removal of the methyl group from histone molecules. HDMs are of two classes, the Jumonji C (JmjC) domain-containing histone demethylase (JHDM) and the lysine-specific demethylase (LSD) [106]. LSD belongs to a flavin adenosine dinucleotide (FAD)-dependent amine oxidase, while JHDM belongs to the ferrous and α-ketoglutarate-dependent dioxygenase family. Both enzymes follow different pathways to demethylate histones and use different cofactors for their activities [107]. The oxidative stress influence on these demethylase enzymes is directed through their cofactors, which, in turn, regulate enzyme activity and are influenced by the cellular environment.

Among the LSDs, LSD1 is the first characterized histone demethylase. It uses FAD as its cofactor [107]. Forneris et al. [108,109] have shown that the demethylation reaction catalyzed by LSD1 is a flavin-dependent oxidative process in which the methylated lysine is oxidized. LSD1 essentially requires protonated nitrogen for its activity and is relatively active over mono- and di-methylated residues. *In vitro* studies have shown that the FAD cofactor in the enzyme donates electrons to the protonated nitrogen atom and becomes reduced with concomitant oxidation of C-N-methylamine. The resulting imine group reacts with a water molecule to form formaldehyde together with the removal of the methyl group. During this process, flavin undergoes redox switching and this property makes it a key player in transcription, cellular signaling and abiotic stress responses [110,111]. Expression analy-

sis has shown that *LSD1* expression is directly proportional to the level of demethylation of mono-/di-methylated lysine residues in histone 3 (H3K4me1/2), leading to higher gene expression.

The second class of HDMs, the JHDMs, catalyzes the demethylation of mono-, di-, and tri-methylated histones in animals and plants [106]. JHDMs remove histone methylation marks while associating with wide functions in plant development [112,113]. The JmjC domain protein of these HDMs harbors ferrous ions and α-ketoglutarate as cofactors for their activities. Oxidation of ferrous to ferric form leads to the inactivation of JmjC containing protein, promoting hypermethylation. Arabidopsis *jmj16* mutants with aberrant JmjC domain-containing protein, Jmj16, accumulate a higher level of ROS accompanied by H3K4me3 hypermethylation [114]. Hypermethylation induces early leaf senescence by increasing the expression of senescence-associated genes such as *WRKY53* (tryptophan (W) - arginine (R) - lysine (K) - tyrosine (Y) 53) and *SAG201* (senescence-associated gene 201), indicating that Jmj16 is essential for maintaining the homeostatic level of ROS during oxidative stress and for subsequent methylation events.

## Redox regulation of miRNA biogenesis

MicroRNAs (miRNAs) are yet another intermediary of gene regulation in plant systems. Most of their activities are epigenetic, such as heterochromatin formation, methylation, histone modification and gene silencing. In plants, evidence from several species indicates a strong interconnection between the redox status of the cell and miRNAs production. The type of oxidative stress was found to influence the expression of specific miRNAs, depending upon the plant species involved (Supplementary Table 3) [115]. In wheat, exposure to ozone was found to induce the expression of 21 ozone-specific miRNAs that are uninfluenced by $H_2O_2$ exposure [116]. Similarly, Jia et al. [117] have shown that the expression of *miR156* was induced by ROS and GSH but not by $H_2O_2$. Apart from these, $H_2O_2$-responsive miRNAs were identified in rice [118], wheat [116] and *Brachypodium* [119]. When exposed to similar levels of $H_2O_2$, there were significant miRNA expression differences between species (Supplementary Table 3). Only two miRNAs (*miR169* and *miR528*) were found to have similar expression levels between rice and *Brachypodium* under similar treatment conditions [118,119]. In apple, the vegetative phase change is under the regulatory control of *miR156*, which is under the control of plastid-nucleus redox signals. When *in vitro* apple shoots were exposed to chemical inhibitors, the expression of *miR156* was found to be concomitantly affected by GSH content and not by $H_2O_2$ level [117]. This shows that redox signaling works upstream of miRNA production.

Despite mounting evidence on the influence of redox elements on miRNA expression (Fig. 4), direct evidence remains scanty on how they influence the expression of different accessory proteins. Mutant plants with defective accessory proteins are compromised in miRNA biogenesis as seen among *Arabidopsis* mutants, *dcl1*, *hen1* and *hyl1* [120]. However, indirect evidence has shown that miRNA synthesis is inhibited by feedback mechanisms on which oxidative stress conditions have a significant influence. When oxidative stress affects *miR162* and *miR168*, their feedback mechanisms also influence the proteins, DCL1 and AGO1, respectively [121,122]. Although the DCL1 protein is involved in the production of *miR162*, it also binds to the stem-loop structure of *miR162*. In turn, in the feedback reaction, the redox-sensitive *miR162* targets and cleaves DCL1 mRNA and pre-mRNAs [122]. In the case of *dcl1* mutants, wherein the functional, active DCL1 protein is absent, *miR162* biosynthesis is impaired. However, in wild-type plants, DCL1 production was restricted by the *miR162* feedback, resulting in *miR162* homeostasis. Similarly, AGO1 homeostasis is also under the feedback regulation of *miR168* [121].

### *Mediation of miRNA expression*

Many oxidative stress conditions mediate the expression of miRNAs (Fig. 5) through the GSH-dependent redox signaling pathway. Cao et al. [116] showed induction of miRNA expression following $H_2O_2$ treatment in wheat. In *Arabidopsis*, Jagadeeswaran et al. [123] have revealed a redox signaling-dependent production of *miR395*, induced under sulfur deficiency. This miRNA is known to target a low-affinity transporter gene, *Arabidopsis sulfate transporter 68* (*AST68*), and three ATP sulfurylases, APS1, APS3 and APS4. Similarly, *miR395* production is found to be promoted under oxidative stress abetted by sulfur deprivation, the mechanism of which remains unknown. Analysis of *miR395* expression within various genetic backgrounds suggests that *miR395* biogenesis involves more pathways than oxidative stress. GSH dependency for miRNA production and expression was evident from the partial impairment of *miR395* production in the GSH deficient cadmium sensitive mutant, *cad2-1* [123]. In the case of an *Arabidopsis* triple mutant, carrying mutations in nitroreductase genes, *ntra* and *ntrb*, along with *cad2*, *miR395* reduction is found to occur by up to 45%. Likewise, redox homeostatic or redox signaling components have been shown to play a vital role in *miR395* biogenesis under different mutant backgrounds. Conversely, some mutants with impaired GSH synthesis were found to have *miR395* production, indicating that *miR395* expression could also be under the regulatory influence of pathways other than the oxidative stress pathway. Apart from this, the expression of *miR398*, which targets Cu/Zn superoxide dismutases, CSD1 and CSD2, was found to be regulated under oxidative stress conditions [123]. Sulfur deprivation-induced oxidative stress was found to leverage a high level of CSD1 accumulation, with concomitant down-regulation of *miR398* expression. Further supporting this, no CSD1 accumulation was observed in the redox signaling mutants. With observations of specific patterns of miRNA expression, possibilities of occurrence of specific mediatory pathways under specific stress conditions cannot be ruled out and require additional experimental evidence.

## Redox regulation of chromatin structure and remodeling

As the carrier of genetic information, chromatin biology is all about the regulation of gene expression for cellular functions related to development and metabolism. Chromatin shuttles between compact and relaxed forms depending on the internal cellular conditions. Structural compaction of the chromatin generally halts transcription, while relaxation drives transcription and gene expression. For example, under low temperature, chromatin dynamics can regulate histone modifications, DNA methylation and ROS status, thereby activating cold-responsive genes [125] (Fig. 6) and flower induction during vernalization. Organizational modification of chromatin may be either covalent such as epigenetic (DNA methylation and histone post-translational modification), or non-covalent via chromatin modifications and remodeling [126]. As a result, the structural organization of chromatin is decided by histone status, histone variants and structure protein remodelers. ATP-dependent chromatin remodeler and poly (ADP-ribosyl) polymerase are two common remodeler proteins (PARP). Histone modifications include multiple changes in the amino acids of histone codes in the histone tail and interactions of regulatory proteins with modified histones are among the functions of histone modifications [127]. Modified histones tend to interact with chromo- and bromodomain proteins, which alter

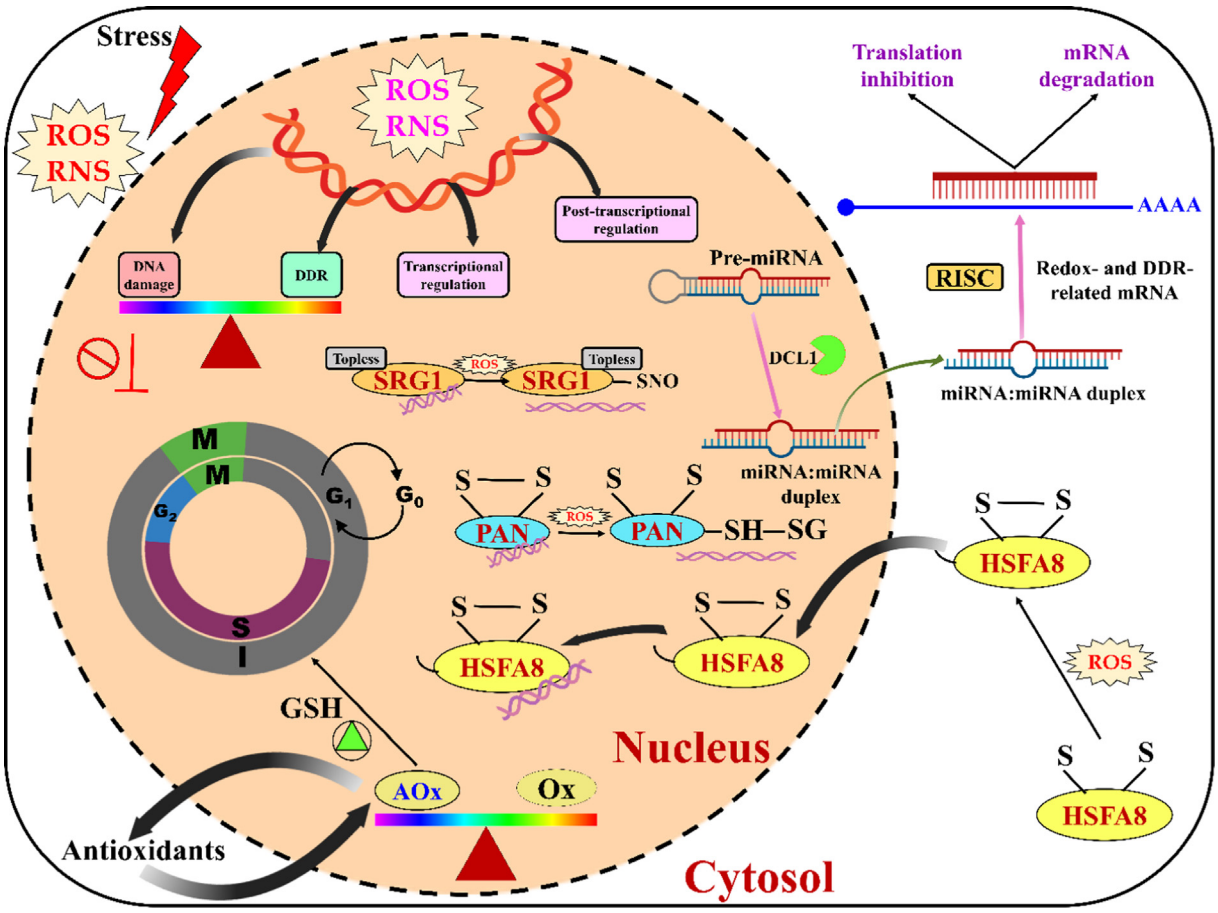


**Fig. 4.** Cellular redox balance-DNA damage response (DDR)-miRNA triangle. Under various stress conditions, increased ROS production is usually present in different cell compartments, such as the nucleus, cytoplasm, etc., through which ROS and redox signals move to regulate gene expression. ROS accumulation in the nucleus can arrest the cell cycle by inducing DNA damage; however, the DDR reduces the negative effects of DNA damage by modulating the activity of microRNAs. To promote the cell cycle according to the redox environment, altered antioxidant and oxidant balance is required in the nucleus. In this circumstance, ROS and redox signals regulate gene expression at transcriptional and post-transcriptional levels. The picture illustrates redox-dependent transcriptional mechanisms involved in the regulation of redox-sensitive TF (SRG1, PAN, and HSFA8) expression to regulate gene expression affected by ROS/RNS. In fact, at the post-transcriptional level, miRNAs can also target mRNAs (redox- and DDR-related target mRNAs) to inhibit the translation of negative regulation of stress tolerance. miRNA, microRNA; ROS, reactive oxygen species; RNS, reactive nitrogen species; AOx, antioxidants; Ox, oxidants; DCL1, DICER-like1; PAN, perianthia; SRG1, SNO-regulated gene1; HSFA8, heat shock factor A8 [115]. The schematic representation was adapted from Cimini et al. [115]

chromatin organization. Furthermore, interacting regulatory proteins have broader roles in DNA repair, recombination, and other plant developmental activities [128]. According to the level of arrangement and active involvement in transcription, Roudier et al. [129] and Wang et al. [130] have classified chromatin into four types: chromatin states 1 to 4 (CS1-CS4). CS1 represents the active state, CS2 the repressive state, CS3 the silent transposon and CS4 the intergenic regions.

### *Regulation of ATP-dependent chromatin remodelers*

ATP-dependent chromatin remodelling complexes (CRC) are nuclear enzymes that mediate the interaction between histones and DNA, to appreciate chromatin plasticity. They are multi-subunit protein complexes that are chromatin modifiers and remodelers and work in harmony to alter chromatin structure. Polycomb group (PcG) and trithorax group (TrxG) proteins constitute chromatin modifiers and interact with remodelers to alter chromatin organization [132]. Both groups of proteins work contrariwise in gene expression, wherein PcG maintains a repressed state, while TrxG maintains an active state. In *Arabidopsis*, PcG interacts with polycomb repressive complex 2 (PRC2) to promote the trimethylation of H3K27 to aid suppression of gene expression, while TrxG derepresses target genes and facilitates gene transcription [133–135]. These ATP-dependent chromatin remodelers utilize energy from ATP and mediate the alteration of histone-DNA modification. In a well-studied remodeler system, switch 2/sucrose non-fermenter 2 (SWI2/SNF2), the protein complex, comprising of protein subunits such as SNF5, SWP73 and SWI3, binds with the promoter region of the gene where different post-translational marks occur [136,137]. Oxidative stress conditions influence the binding of the complex with the promoter and bring in regulatory changes [138–141]. Similarly, gene expression demands are met at various developmental stages when histone modifiers and remodelers alter chromatin structural organization [128,142]. In this review, we restrict the discussions to vernalization and stem cell development which are complex traits that depend on environmental variability.

### *Vernalization*

Plants growing in temperate regions require vernalization, a procedure of flower initiation by exposure of seeds or plants to low temperatures (1–7 °C). Throughout vernalization, flower

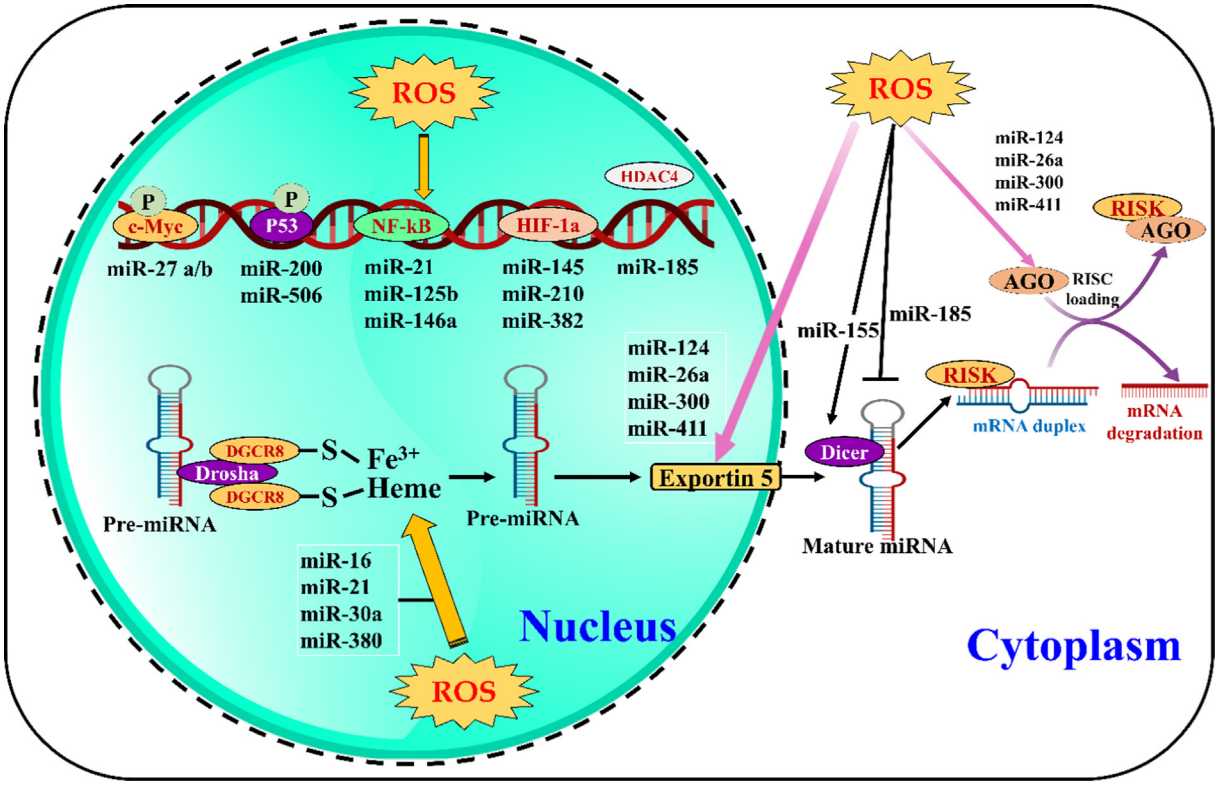


**Fig. 5.** miRNA regulation under oxidative stress. ROS influence miRNA processes in the nucleus and cytoplasm and induce miRNA transcription by triggering transcription factors (TFs), such as c-Myc, p53, NF-κB, and HIF-1α. When TFs bind to the promoter, HDAC4 can suppress the TFs. ROS can regulate the expression of DGCR8, drosha, exportin 5 and dicer enzymes, thereby affecting miRNA biogenesis, translocation and maturation. Arrow and T arrow indicate activation and inhibition, respectively. miRNAs, microRNAs; ROS, reactive oxygen species; HDAC4, histone deacetylase 4; DGCR8, DiGeorge syndrome critical region 8; AGO, Argonaute; RISC, RNA-induced silencing complex [124]. The schematic representation was adapted from Carbonell and Gomes [124]

induction is facilitated through a series of gene expression events that involve chromatin rearrangement from the condensed state to the transcriptionally accessible state. In *Arabidopsis* and several other angiosperms, flowering is under the control of a floral repressor gene, which blocks a series of flowering-related genes to make the plants go into a non-flowering phase. One such gene is *FLC*, which encodes a MADS (minichromosome maintenance factor 1/ agamous (AG)/ deficiens/ serum response factor (SRF)-box TF) to suppress the floral integrator gene, thus upholding the vegetative phase [143]. *FLC* expression is regulated by different epigenetic pathways which are influenced by the redox status of the cell. During vernalization, *FLC* is attenuated by low-temperature exposure, thereby inducing flowering. Other proteins, such as vernalization 1 (VRN1), vernalization insensitive 3 (VIN3), and vernalization 5 (VRN5) /VIN3-like 1 (VIL1), are involved in vernalization [144,145]. *FLC* attenuation occurs through chromatin rearrangement, wherein histone acetylation marks are erased [146–148]. *FLC* repression is mediated through VIN3 proteins, which bind upstream to the *FLC* region [146]. *FLC* repression requires trimethylation of H3K27 residue and deacetylation of H3 proteins; thus, VIN3 encodes for a plant homeodomain (PHD) protein interacting with the PRC2 to induce trimethylation and deacetylation of histone proteins, thereby leading to *FLC* attenuation [149–151]. In *Arabidopsis*, the redox regulation of *VIN3* and *PRC2* expression has been demonstrated and it was found that the expression of *VIN3* is induced by nicotinamide treatment and, also, during hypoxic conditions. Likewise, chromatin-mediated gene expressions at the time of hypoxia are initiated [152] in which ROS and other oxidative stress conditions regulate the activity of PRC2. The PRC2 complex consists of four subunits, among which the *VRN2-PRC2* subunit is responsible for substrate methylation. However, the expression of *VRN2-PRC2* is oxygen level-dependent. So, any change in the $O_2$ level will affect VRN2 activity [153]. NO-regulated protein arginine methyltransferase 5 (PRMT5) induces H4R3 demethylation in *FLC* gene promoter regions to reduce *FLC* expression to suppress flowering [154].

### *Stem cell development*

During plant developmental processes, the redox regulation of chromatin plasticity is well accounted for in plants. The decision for a defined growth is met through stem cells present in the shoot apical meristem (SAM) and root apical meristem (RAM) regions [155,156]. Meristematic activity and cell differentiation in the SAM are maintained by the *wuschel* (*WUS*) genes and in the RAM by *wuschel-related homeobox 5* (*WOX5*) genes. The maintenance of stem cell activity and the differentiation process involve different forms of ROS [157,158]. The accumulation of $O_2^{\cdot-}$ in the stem cell niche increases stem cell activity by activating *WUS* expression, while $H_2O_2$ accumulation in the periphery suppresses stem cell activity and allows for differentiation by inhibiting WUS activity. Both SAM and RAM developments in plants are under regulation by the redox status of the cell. In root cells, an increase in $O_2^{\cdot-}$ was found in the stem cell niche, while, in the periphery, $H_2O_2$ accumulation was found to be high. Thus, throughout stem cell development, redox modulation plays a significant role. Apart from *WOX5* and *WUS*, there are other TFs involved in the stem cell process, such as *plethora* (*PLT*). Encodes for *Apetala 2* (*AP2*) type TFs, *PLT1* and *PLT2*, are involved in the maintenance of the root stem cell niche in *Arabidopsis* [159]. High-level *PLT* expression

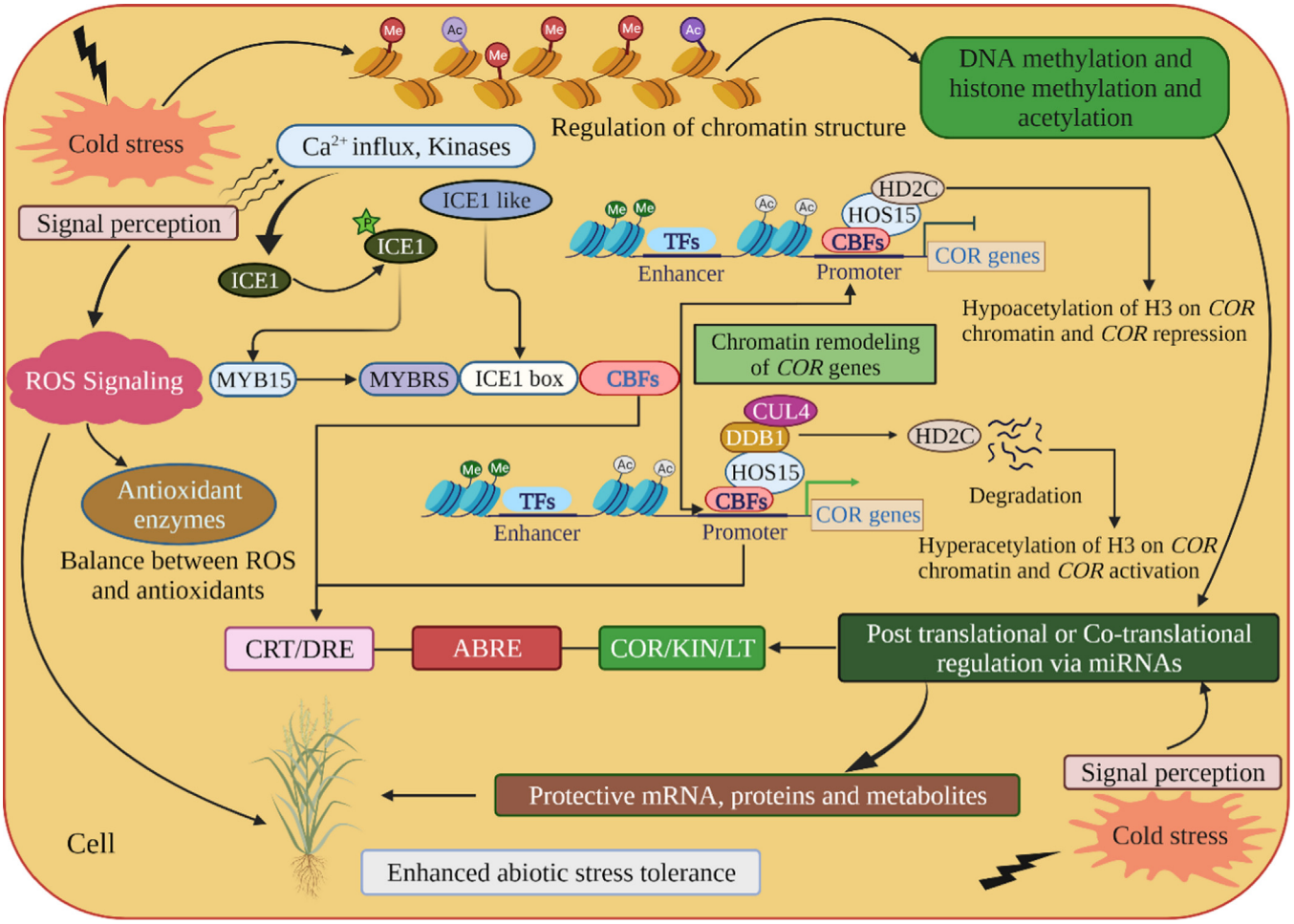


**Fig. 6.** Schematic representation of epigenetic changes at low temperature. Increased levels of ROS and antioxidants under low temperature are associated with chromatin structure which triggers DNA and histone modifications, thereby activating *COR* genes. For example, in normal conditions, the HOS15 and HD2C complex represses *COR* gene expression due to hypoacetylation of H3 on *COR* chromatin. Under cold conditions, histone deacetylase 2C (HD2C) degradation triggers the hyperacetylation of H3 on *COR* chromatin and, thus, activates *COR* genes through CBF TFs. Using the high expression of the osmotically responsive gene 15 (HOS15) as a substrate receptor, the CULLIN4-based ubiquitin E3 ligase complex (CUL4) promotes HD2C degradation. The association of HOS15 with *COR* gene chromatin and HD2C degradation requires Powerdress (PWR), a HOS15-interacting protein. The HOS15/PWR complex and CBF TFs bind to the promoters of *COR* genes [81,131]. Likewise, chromatin changes also activate miRNAs that influence *COR* gene expression through post-transcriptional modification. Cold stress also stimulates calcium influx which triggers protein kinases to activate ICE1. Activated ICE1 suppresses MYB15 and activates the expression of CBFs, thus regulating COR genes. A small star circle represents post-transcriptional modification, such as phosphorylation. ROS, reactive oxygen species; COR, cold-responsive genes; miRNAs, microRNAs; ICE1, an inducer of CBF expression 1; CBF, C-repeat binding factor; CRT, C-repeat elements; DRE, dehydration-responsive elements; ABRE, ABA-responsive element; KIN, cold-induced genes [125].

maintains stem cell activity, while low levels promote cell differentiation [160]. ABA-induced production of ROS is also known to affect the expression of *PLT* [161,162]. In *Arabidopsis*, a pentatricopeptide repeat (PPR) protein, ABA Overly sensitive 8, (ABO8), maintains redox homeostasis. In the case of *abo8* mutants, overaccumulation of ROS represses *PLT1/2* expression [161]. The general control non-repressed 5 (GCN5) protein, belonging to the HAT family, is the first HAT that was found to associate histone acetylation to transcriptional regulation [163,164]. GCN5, along with the adenosine deaminase 2 (ADA2b) transcriptional adapter (for alteration/deficiency in activation 2b), regulates the expression of *PLT1/2* [165]. Among the several TrxG proteins reported in *Arabidopsis*, SDG2 regulates stem cell activity by maintaining H3K4me3 levels. It is observed that the chromatin assembly factor 1 (CAF1) works in a synergetic way along with SDG2 to regulate *PLT1/2* expression [166]. The antagonistic activity of chromatin remodeling factor, *Pickle* (*PKL*), and the PcG protein, Curly leaf (CLF), decides root stem cell activity through the regulation of H3K27me3 [167].

*Regulation of PARP1*

Poly ADP- ribosylation (PAR) is a post-translational modification of histone and non-histone proteins carried out by the enzyme, poly (ADP-ribose) polymerase (PARP) [168]. In this process, $NAD^+$ supplies ADP-ribose and releases nicotinamide as a by-product. Members of this protein possess a catalytic domain, the PARP signature, which catalyzes the addition of ADP-ribose to proteins [169]. Under stress conditions, the activity of PARP is essential to repair DNA [170]. Histone PAR makes the protein more anionic and causes the expulsion of histones from the chromatin structure and, thus, the chromatin will become relaxed [171]. Blocking PARP1 activity through chemical applications leads to a high level of $NAD^+$ accumulation. Under stress, DNA breakage caused by the increased level of ROS accumulation is sensed by PARP which adds ADP-ribose units to the damaged DNA regions, recruiting other damage repair mechanisms [172,173].

In *Arabidopsis* cell culture, a high level of PARP accumulation was found to be more likely to occur during the exponential

growth stage than in the early and older stages of growth. A concomitant increase in $NAD^+$ oxidation and glutathione production were reported when there was a high level of PARP accumulation [174]. Also, elevated *PARP1* expression at the time of DNA damage is caused by oxidative stress conditions [175–177]. Thus, PARP is a major energy consumer during stress response [178,179]. High PARP activity, however, depletes $NAD^+$ content, which compels plants to replenish $NAD^+$ content. For this, plants use other salvage pathways to synthesise $NAD^+$. Thus, the total energy content of the plant system drops, leading to cell death. PARP mutant plants, as well as plants in which PARP1 activity is externally blocked, are shown to be resistant to oxidative stress where energy consumption in the form of $NAD^+$ is protected [178,180]. PARP inhibition enhances the growth of plants as PARP-mediated $NAD^+$ consumption is prevented.

## Conclusion, future perspectives and biotechnological opportunities

Plants adapt to stress conditions with their innate epigenetic rhythms such as DNA methylation, histone modification and chromatin remodeling. Since stress conditions involve redox homeostasis in plants, epigenetic components undergo associated changes, driving crucial regulations of gene expression.

Plant systems have an extensive battery of redox mediators such as ROS, RNS, antioxidants, etc. the interplay of which regulates redox homeostasis. Redox-regulated epigenetic marks are indirect indicators of the redox status of the cell. Thus, redox mediators are emerging key regulators of epigenetic rhythms that regulate the activities of various enzymes controlling various molecular processes involved in plant growth and development under different environments.

The understanding of the functional mechanisms of epigenetic modifications regulated by the redox status of the cell has significantly advanced in recent years; however more remains yet unknown, particularly the precise molecular mechanisms. For instance, how does one oxidant trigger epigenetic modification without activating other antioxidants as well as other redox-regulated epigenetic marks?

Also, epigenetic activities such as sumoylation of histones, phosphorylation, ADP-ribosylation, glycosylation, ubiquitinylation, and chromatin remodeling are relatively under-studied. Chromatin modifications, triggered by redox mediators under various stress conditions, require more investigation. Furthermore, the epigenetic role of enzymes, such as NADPH oxidase and antioxidant enzymes that help in ROS generation and scavenging, and GSH synthesis in the mitochondria, NO synthase-like enzymes and nitrate reductase are yet to be completely understood. Enzymes and transcription factors that are influenced the redox status of the cell require in-depth studies.

Since Epigenetic regulation is complicated since it involves several pathways. Thus, the crosstalk between various components of the epigenetic complex, including co-expression genes, transposable elements, non-coding RNAs, spliceosomes and proteomes, requires investigation, especially with respect to redox-mediated changes. Plant stress memory associated with the redox status of the cell also requires in-depth studies. N6-methyladenosine (6 mA), novel epigenetic modifications of DNA, are adequately understood in plants, but 6 mA associations with the redox status of the cell remain unidentified [181].

Current biotechnological resources and escalating developments offer compelling promise for solutions to the unsolved mysteries of epigenetic development in plants. Recent technological developments such as nanopore sequencing, ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) [182], epitranscriptomics [183], gene editing [184], proteomics, metabolomics, imaging of redox status components [185], etc. are driving discoveries of molecular mechanisms involved in redox-mediated epigenetic changes.

The broader understanding of the epigenetic development of plants will soon recast crop improvement strategies in economically and ecologically important crops and tree species. Therefore, it is necessary to comprehend the epigenetic rhythm of every target species, particularly when related to stress responses where redox-mediated regulations underpin the survival of the organism. This would lead us to grow crop cultivars with improved traits for food and energy security and climate resilience.

## Compliance with Ethics Requirements

*All the authors state that this article does not contain any studies with human or animal subjects performed by the any of the authors and have declared no conflict of interest.*

## Declaration of Competing Interest

*The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

## Acknowledgements

This work was funded by grants from the National Natural Science Foundation of China (grant numbers 31870656 and 31470615) and the Zhejiang Provincial Natural Science Foundation of China (grant number LZ19C160001). MR is also supported by Metasequoia Faculty Research Start-up Funding (grant number 163100028) at Nanjing Forestry University. We would like to extend our sincere gratitude and appreciation to all reviewers for their valuable comments. Fig. 6 was created with BioRender.com.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2022.04.007.

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