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Review

Redox-regulated transcription in plants: Emerging concepts

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Abstract: In plants, different stimuli, both internal and external, activate production of reactive oxygen species (ROS). Photosynthesis is considered as high rate redox-metabolic process with rapid transients including light/photon capture, electron fluxes, and redox potentials that can generate ROS; thus, regulatory systems are required to minimize ROS production. Despite their potential for causing harmful oxidations, it is now accepted that redox homeostasis mechanisms that maintain the intracellular reducing environment make it possible to use ROS as powerful signaling molecules within and between cells. Redox and ROS information from the chloroplasts is a fine-tuning mechanism both inside the chloroplast and as retrograde signal to the cytosol and nucleus to control processes such as gene expression/transcription and translation. Wide repertoires of downstream target genes expression (activation/repression) is regulated by transcription factors. In many cases, transcription factors function through various mechanisms that affect their subcellular localization and or activity. Some post-translational modifications (PTMs) known to regulate the functional state of transcription factors are phosphorylation, acetylation, and SUMOylation, ubiquitylation and disulfide formation. Recently, oxPTMs, targeted in redox proteomics, can provide the bases to study redox regulation of low abundant nuclear proteins. This review summarizes the recent advances on how cellular redox status can regulate transcription factor activity, the implications of this regulation for plant growth and development, and by which plants respond to environmental/abiotic stresses.

Keywords: photosynthesis; redox; oxidative stress; transcription factors; gene expression; transcription

1. Introduction

Photosynthesis a divided into two types: oxygenic and anoxygenic. In oxygenic photosynthesis, which is carried out by plants and cyanobacteria, oxygen is produced. However, anoxygenic photosynthesis, which is carried out by various, types of green and purple bacteria and produces no oxygen [1]. The origin of oxygenic photosynthesis is estimated to be in the range of 3.4 to 2.3 billion years ago where the oxygen-rich atmosphere of the earth today was initiated [2]. Oxygenic photosynthesis involves two large membrane protein complexes, photosystems I and II (PS I and PS II), which perform the first step in the conversion of the light absorbed from the sun into chemical energy and by producing molecular oxygen and consuming carbon dioxide.

Photosystems contain the reaction centers (the sites where photochemical reactions occur) which are typically divided into groups. PS II has a quinone type reaction center (known as Type II), while PS I has an iron-sulphur (FeS) type reaction center (type I). Moreover, photosystems are connected by an intermediate Cytochrome *b6f* (Cyt*b6f*) super-complex and two electron carriers, the plastoquinone (PQ) that transports electrons between PSII and Cyt*b6f*, and the plastocyanin (PC) which links Cyt*b6f* to PSI [3]. On the other hand, non-oxygenic phototrophic organisms generally contain either a Type II reaction center (e.g. purple Bacteria) or a Type I reaction center (e.g. green-sulphur or Heliobacteria) [1]. A common organization has been assigned for the two photosystems, however, functionally they are organized in two main moieties: a core complex and a peripheral antenna system (light harvesting antenna). During evolution, core complexes have been well conserved evident by the fact that most of the subunits are similar in prokaryotic and eukaryotic photosystems. In contrast, the light harvesting antenna is highly variable where it is composed of peripheral associated membrane proteins in cyanobacteria, the phycobilisomes, and integral LHC membrane proteins in eukaryotic cells [4].

During photosynthesis, the light harvesting antenna to drive electron transport from the low-potential electron donor water to the high-potential electron end-acceptor $NADP^+$ absorbs light. ATP and NADPH representing energy and reduction equivalents are generated which will be subsequently used in carbon dioxide fixation and reduction in the Calvin-Benson cycle, the dark reaction (Figure 1). Changes in abiotic factors such as the intensity and quality of light, the nutrient, the temperature and the water availability have a great impact on photosynthetic efficiency and thereafter on plant yield. When the photon utilization capacity of the chloroplast is overloaded with the photon fluence rate, photosynthesis become inhibited and irreversible damage of the reaction centers i.e. PS II occurs [5,6]. Moreover, elevated excitation pressure increases the production of ROS that will cause damaging effects on protein, lipids and enzymes necessary for the function of the chloroplast and the cell [7,8]. For a long time, ROS accumulation was solely considered indicator of deleterious effects that is termed oxidative stress [9,10]. However, this concept where ROS cause indiscriminate damaging effects became undoubtedly anchored in the literature and the signaling function of ROS was raised as a fundamental principle in cellular communication [11]. Genetic evidence has demonstrated unequivocally that ROS are signaling molecules with important and specific roles in gene expression regulation and that a balance between redox metabolism and ROS formation is needed and that's why cells operate a redox signaling network [12,13]. The network senses environmentally induced redox imbalances and initiates compensatory responses either to readjust redox homeostasis and/or to repair oxidative damage [14]. ROS and redox signals are among several signals that comprise

the retrograde signaling pathways (signals that originate in the organelles, e.g. chloroplast and mitochondria, which modulate nuclear gene expression (NGE). Despite decades of research work on retrograde signaling and the clear ultimate effects on NGE, the initiation and transmission of the signals, as well as their mode of action still a subject of controversy debate [15].

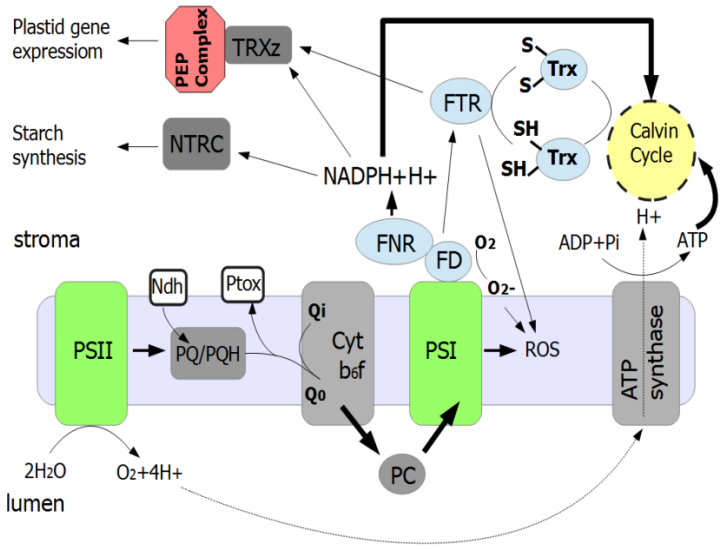

Figure 1. Photosynthetic electron transport chain pathways. Schematic presentation of the thylakoid membrane with PSII, Cyt*b6f*, PSI, and the ATP synthase. Thin continuous lines with arrows show the direction of the electron flow. Linear electron flow (LEF) transport is initiated with the photoinduced water oxidation catalyzed by PSII. Cytb6f, cytochrome b6f; FD, ferredoxin; FNR, ferredoxin-NADP$^+$ reductase; PQ, plastoquinone; PSI, photosystem I; PSII, photosystem

The regulation of gene expression by oxidants, antioxidants, and the redox state has emerged as a novel sub-discipline in molecular biology that has promising wide implications for different organisms. Several redox-dependent mechanisms that control the activity of TFs and that control transcription have been investigated in detail in bacteria and mammals. However, only in the past two decades redox-responsive transcription factors and co-activator proteins have emerged in plants. In this review, we will introduce the recent progress that has been made in plants to identify transcription factors whose activities are directly or indirectly regulated by redox as well as redox-dependent mechanisms that control transcription.

2. Redox signal transduction from the chloroplast to the nucleus (retrograde signaling) and its impact on gene expression

Chloroplasts and mitochondria evolved and became part of the eukaryotic cell through endosymbiosis. During the course of such evolution dramatic reduction in the genome size of these organelles occurred and these organelles became dependent on their eukaryotic host. Currently, the plant plastid genome encodes ~80 proteins and the mitochondrial genome encodes ~57 proteins in the organelles and the rest of ~4000 chloroplast and ~1000 mitochondrial proteins are nuclear-encoded and imported into the organelles from the cytosol [16,17]. Because the organellar genomes encode

now a limited number of proteins and the vast majority of the genes are encoded in the nucleus, there is a requirement for coordinated expression of organellar and nuclear genomes to ensure correct assembly of complexes that contain proteins encoded in each genome [18]. From a historical point of view, the first report, indicating the presence of retrograde signaling and describing the existence of communication between the chloroplast and the nucleus, has been provided by Bradbeer et al [19]. In that report Bradbeer et al. have shown severe decrease in chloroplast protein synthesis associated with decreased expression of nucleus-encoded chloroplast genes using the barley (Hordeum vulgare) chloroplast ribosome-deficient mutant [19]. Subsequent reports using inhibitors of plastid protein synthesis (e.g. streptomycin, lincomycin and chloramphenicol) and various plant species (e.g. mustard, barley, pea and Arabidopsis) confirmed the findings in Bradbeer et al. [20-23].

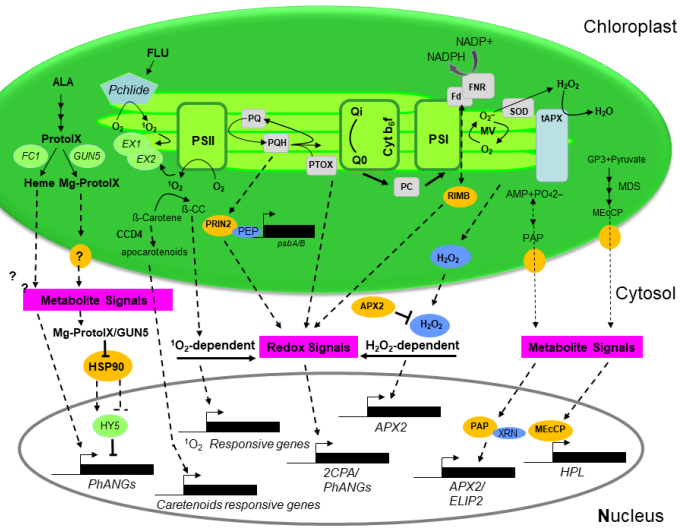

Figure 2. Different retrograde signals from the chloroplast to the nucleus, metabolite related and photosynthesis related, have been described. (1) The chlorophyll biosynthesis intermediates such as Mg-ProtoIX and heme (2) ß-CC, one of the carotenoid oxidation products (3) SAL1-PAP signal (4) MecPP, a precursor of isoprenoids (5) ROS signals, either $^1O_2$ or H_2O_2 signals affect nuclear gene expression and (6) redox signals represented by the redox state of the plastoquinone pool and/or the redox state of the acceptor or the donor site of PSI affects the expression of PhANGs.

Recent advances in recent years have identified several putative retrograde signals and signaling pathways (Figure 2). Pogson et al. classified them into two groups: “biogenic signals” required in the early stages of chloroplast development and “operational signals” in mature plants to cope with the changes in the environment [24]. Some of these retrograde signals include metabolites and metabolic intermediates. Others include photosynthesis-dependent signals [25,26]. In this section we will briefly concentrate on the metabolic retrograde signals and discuss in details the redox-dependent signal transduction pathways.

2.1. Metabolite dependent signals impact on nuclear gene expression

Several metabolites, which are synthesized in the chloroplast and then translocated into the cytosol or to other cellular compartments, have been suggested to be involved in chloroplast-to-nucleus communication. The classical metabolite signaling pathway is associated with tetrapyrrole biosynthesis intermediates [27]. More recently, secondary metabolites such as the isoprenoid precursor methylerythritol cyclodiphosphate (MEcPP) [28], 3′-phosphoadenosine 5′-phosphate (PAP) [29], oxidation products of carotenes, such as the volatile β-cyclocitral [30], and heme [31] have also been discovered and proposed as retrograde plastid signals which affects NGE in plants.

2.1.1. Tetrapyrrole intermediates: the classical retrograde signals that affect expression of photosynthesis-associated nuclear genes (PhANG) in green algae and plants

Mg-ProtoporphyrinIX (Mg-ProtoIX), a tetrapyrrole biosynthesis intermediate in the synthesis of the chlorophyll photosynthetic pigments, have been proposed to act as a plastid signal that regulate the expression of PhANG in algae and plants [32-35]. Isolation of genomes uncoupled (gun) mutants was very helpful in deciphering the retrograde signaling during chloroplast biogenesis [36]. In gun mutants the expression of Light Harvesting Complex b (LHCB) nuclear gene is maintained following chloroplast damage using the herbicide norflurazon (NF) treatment [36]. So far, six guns mutants have been identified and four of them (gun 2−6) have a mutation/lesion in enzymes involved in or associated with tetrapyrroles biosynthesis [34,36-38]. Gun 1 mutant results from a mutation in a gene encoding a chloroplast-localized pentatricopeptide repeatcontaining protein (PPR) that binds nucleic acids [36,39]. The GUN2, GUN3, and GUN5 encode heme oxygenase, phytochromobilin synthase, and the H subunit of Mg-chelatase (CHLH), respectively [39], while GUN4 is a regulator of Mg-chelatase activity [38].

During oxidative stress e.g. after NF treatment Mg-ProtoIX accumulates in the cytosol and act as a mobile signal mediating chloroplast regulation of PhANG [34,40]. However, the specific accumulation of Mg-ProtoIX has been challenged due to the lack of correlation between the metabolite levels and gene expression [41,42]. It is interesting that Zhang et al. reported that oxidative stress induced by NF can induce transient accumulation of tetrapyrroles with concomitant repression of LHCB in adult plants re-addressing the importance of Mg-ProtoIX accumulation in the regulation of PhANG. Interestingly, the authors have shown that following exposure to oxidative stress (NF treatment) accumulation of Mg-ProtoIX/Mg-ProtoIX-ME was rapid and transient [35]. Similar findings were also shown for Mg-ProtoIX/Mg-ProtoIX-ME transient accumulation after methyl viologen (MV) treatment [43].

Although the movement of Mg-ProtoIX into the cytosol is debatable [34,40-42], a possible mechanism of action for Mg-ProtoIX have been described by Kindgren et al. [43]. Mg-ProtoIX binds the cytosolic heat shock 90-type proteins (HSP90) both in vitro and in vivo [43, 44], and that the oxidative stress-triggered GUN phenotype is partially suppressed when HSP90 is down-regulated [43]. Moreover, HY5 was suggested to be part of the GUN5/HSP90 signaling pathway which regulates PhANG expression [43]. This is analogous to the regulatory HSP70-HSP90-HAP1 complex in yeast that responds to heme accumulation and controls the oxidative response [45].

2.1.2. Methylerythritol cyclodiphosphate (MEcPP) is a retrograde signal that affect expression of stress-associated nuclear genes in plants

One major biosynthetic pathway in plants is the isoprenoid metabolism [46]. The isoprenoid precursor methylerythritol cyclodiphosphate (MEcPP) was suggested as a plastid-derived retrograde signal regulating HPL nuclear gene [28]. In a genetic screen designed to identify genes involved in the regulation of hydroperoxide lyase (HPL), a stress-inducible nuclear gene encoding a plastid-localized protein in the oxylipin pathway, constitutively expressing HPL (CEH1) mutant was isolated [28]. The conversion of MEcPP to hydroxymethylbutenyl diphosphate (HMBPP) catalyzed by CEH1, which encodes 1-hydroxy-2-methyl-2-(E)-butenyl4-diphosphate synthase (HDS), is the major step in the methylerythritol phosphate (MEP) pathway [47]. CEH1 mutant results in high levels of MEcPP accumulation, increases in stress-related salicylic acid (SA), increased resistance to the Pseudomonas pathogen and induced the expression of a subset of stress-associated genes, including ISOCHORISMATE SYNTHASE 1, a key plastidial enzyme in SA-biosynthetic pathway, and HPL. Moreover, high light and wounding abiotic stresses increased MEcPP levels which induce the expression of the aforementioned genes [28], demonstrating MEcPP involvement in a retrograde pathway involved in abiotic stresses (operational control) which is distinct from the chlorophyll intermediates (gun) signaling pathway. Indeed, NF treatment of WT and ceh1 seedlings resulted in reduced levels of LHCB transcripts and photo-bleaching. In addition, ceh1 mutant do not alter PhANG expression [28]. This is distinct from the gun mutants which have high levels of LHCB expression in response to NF treatment [21].

2.1.3. SAL1-PAP act as a retrograde signal during high light and drought stress

In a screen for elevated expression of the antioxidant enzyme ascorbate peroxidase (APX2) under low light (LL) and high light (HL), the alx8/sal1 mutant was isolated [48]. In alx8/sal1 mutant 25% of the HL stress inducible genes e.g. APX2 and Early Light Induced Protein 2 (ELIP2), are up-regulated. Moreover, sal1 showed altered metabolome and 50% increased survival under water limiting conditions [48, 49]. SAL1 enzyme, which is localized in both the chloroplast and the mitochondria, is an inositol polyphosphate 1-phosphatase which regulates the steady-state level of 3’-phosphoadenosine 5’-phosphate (PAP) by dephosphorylating it to an adenosine monophosphate (AMP). Interestingly, PAP accumulated 20-fold more in the sal1 mutant and increased by up to 30-fold in wild type plants in response to drought and HL stresses. Accordingly, PAP accumulation triggered changes in the expression of APX2 and ELIP2 nuclear genes [50]. The demonstrated PAP movement between the chloroplast and nucleus [50] probably through the PAPS/PAP chloroplastic antiporter that might be responsible to facilitate the exchange of PAP between the chloroplast and cytosol [51]. PAP most likely regulates nuclear gene expression by altering RNA metabolism mediated by 5-3’exoribonucleases (XRNs) [50]. There are two nuclear-localized XRNs, XRN2 and XRN3 homologues to the yeast Xrn2p/Rat1p. The sal1 and xrn mutants have been shown similar morphological phenotypes [52]. By repressing the activity of XRNs, PAP may stimulate expression of HL and drought-responsive genes, leading to increased tolerance [50].

2.1.4. Carotenoid derived retrograde signaling

Because $^1O_2$ is highly reactive and have short half-life it is unlikely that it functions as a signal that is translocated to the chloroplast envelop, but rather it interacts with a chloroplastic component/molecule, likely close to its site of production, and to act then as a signaling molecule [53]. In plants, β-cyclocitral (β-CC), one of the carotenes oxidation products in the chloroplast act as a stress signal that mediate gene responses to singlet oxygen ($^1O_2$) [30]. Eighty percent of gene expression profiles of the flu mutant ($^1O_2$-responsive genes) [54], are similar to those genes affected in the β-CC plants [30], suggesting that β-CC is an intermediate in the $^1O_2$ signaling pathway. Moreover, the effects of β-CC appear to be specific because the related molecule β-I, a volatile derivative of β-carotene that is accumulated in response to light stress induced oxidation of the carotenoid β-carotene, did not reveal similar results [30]. The β-carotene volatile is a lipid soluble compound which makes it able to cross lipid membranes and therefore it's a strong candidate to function is retrograde chloroplastic signal. Its exact mechanism of action needs further investigation, however at this stage it seems that its impact on nuclear gene expression is independent from the $^1O_2$ signaling pathway within the chloroplast which depends on EXECUTER1 and 2 (EX1/2) [54].

2.1.5. Heme, a derived retrograde signaling, regulates nuclear gene expression in algae and higher plants

Heme, another product of tetrapyrrole biosynthesis, acts as a retrograde signal from the chloroplast to regulate nuclear gene expression in both algae and higher plants [31,55,56]. Feeding experiments with Mg-ProtoIX and heme triggered global changes in the gene expression in Chlamydomonas reinhardtii (almost 1000 genes changed their expression level significantly upon feeding of Mg-ProtoIX or heme) [55]. In Arabidopsis a gain-of-function genetic screen using activation-tagging mutagenesis was used and a candidate mutant (gun 6-1D) was identified [31]. The gun 6-1D encodes and overexpresses the plastid Ferrochelatase 1 (FC1, heme synthase) which leads to the accumulation of PhANGs in the presence of NF. The responses obtained seems to be specific to the activity of FC1 because over-expression of the other chloroplast-localized FC2 did not increase PhANG expression [31]. Biochemical and genetic experiments suggest that increased flux through the heme branch of the plastid tetrapyrrole biosynthetic pathway increases PhANG expression. Moreover, a model was proposed in which heme is exported from chloroplasts to increase PhANG expression. There is no correlation between the gun phenotype and the free heme levels indicating that the signaling heme may be bound to specific targets [57]. One possibility is that heme interacts with cytosolic or nuclear factors similar to the yeast [58]. The other is that heme interacts with heme-binding proteins to regulate gene expression.

2.2. Photosynthesis dependent signals modulate nuclear gene expression

In the context of photosynthesis, chloroplasts act both as source and target of redox regulation [59]. Initiators of retrograde signaling have been proposed for diverse components of the chloroplast. Among them components of the photosynthetic electron transport chain (PETC) [60]. Photosynthetic electron transport (PET) requires the absorption of light by chlorophyll. Then excitation of the pigments and electron transfer reactions in an oxygen rich environment lead to the production of ROS. Moreover, changes in the redox state of PETC

trigger retrograde signaling. The photosynthesis redox-dependent signals are classified into the redox state of the plastoquinone (PQ) pool, the redox state of the acceptor or the donor side of PSI and the accumulation of ROS ($^1O_2$, O_2^- and H_2O_2) [60-63].

2.2.1. The redox state of PQ pool, an early proposed retrograde signal in the control of NGE

More than two decades ago photosynthetic control of nuclear and plastid gene expression has been linked to the redox state of PQ pool. First studies have been demonstrated for cab genes in green algae such as Dunaliella salina and Chlorella vulgaris [64,65]. Inhibitors of electron transport such as 3-(3′,4′-dichlorophenyl)-1,1-dimethyl urea (DCMU) and 3-methyl-6-isopropyl-p-benzoquinone (DBMIB) and different light intensities were used to modify the redox state of the PQ pool. A threefold increase in the amount of cellular chlorophyll occurred in Dunaliella cells within 24 hours of transfer from high light (HL) to low light (LL). More studies with Dunaliella salina and Chlorella vulgaris demonstrated similar acclimatory responses in which photosynthetic adjustment is regulated by the redox poise of inter system electron transport [66,67]. Not only expression of photosynthesis genes encoded in the nucleus, but also expression of some photosynthetic genes encoded in the chloroplast was regulated by the redox state of PQ pool in green algae and higher plants [68]. Analysis of tobacco plants using specific PS-specific light sources (PSI and PSII light) and DCMU and DBMIB inhibitors suggested that the redox state of the PQ pool affects also PhANG (e.g. plastocyanin (petE) gene) in higher plants [69]. Additionally, Oswald et al. [70] investigated the relationship between PET and sugar signaling using transgenic Arabidopsis lines carrying luciferase reporter genes driven by CAB2 promoter or petE promoter. The transcriptional activation of PhANG was found to be dependent on PET but not on the sugar status of the cells which suggested that a redox signal from the plastid overrides the sugar-related expression of PhANG [70]. However, subsequent analysis of cyanobacteria and Arabidopsis using the same PSI and PSII light and inhibitors, demonstrated that the redox state of the PQ pool was not the major source of the HL mediated plastid signal [71-73]. In Arabidopsis only 54 genes were redox regulated directly by the reduction state of PQ and only 2 genes encoded components directly associated with photosynthesis suggesting a weak indication for PQ-dependent regulation of genes for light-harvesting complex proteins [72]. Using microarrays and metabolic profiling to study the role of the redox state of the PQ, Brautigam et al. demonstrated that the reductive redox signal has a faster kinetics than the oxidative signal and that the effect on the transcriptome and metabolome were not complementary [74]. These findings suggested the presence of two different pathways involved in the redox state of the PETC. Although the redox state of PQ is an important part of retrograde signaling, a much more complex signaling mechanism is present rather than a simple switch between oxidized and reduced PQ pool [74]. In addition to redox signals that are generated on the acceptor side of PSII through the action of PQ, Cytb6f complex appears to be critical for redox regulation of genes involved in chlorophyll biosynthesis. The accumulation of GSA, ALAD, HEMA, HLD, CPX1, CHLH1, CTH1 and CHLI transcripts is lost upon illumination of Cytb6f Chlamydomonas mutants [75]. Although at this stage little is known about the specific elements involved, it is suggested that the Cytb6f complex activity through quinole binding to the complex impacts on the activity of STT7 and STN7 protein kinases (which are required for state transitions) [76]. Evidence about PETC redox-dependent retrograde signals that regulate the expression of a large number of genes involved in stress response, metabolism and gene expression was also provided through stn7 [77] but no significant differences in the

expression levels of PhANGs excluding the STN7 kinase direct effect on the transcription of PhANGs in Arabidopsis. Moreover, several hundred miss-regulated genes, in plants lacking the STN7 kinase and mutants with severe PETC over-reduction, were recently identified using Meta-analysis of several studies on NGE [78].

2.2.2. The acceptor availability at PSI, the previously ignored retrograde signal

In heterotrophic organisms and non-photosynthetic compartments of plant cells, thioredoxins (Trx) reduction is provided by NADPH in a reaction catalyzed by an NADPH-dependent Trx reductase (NTR) [79]. In contrast the ferredoxin-thioredoxin reductase /thioredoxin (FTR/Trx) system has been considered the only pathway regulating redox reactions in chloroplasts of photosynthetic plant cells [80]. Redox signals are generated on the acceptor side of PSI through the action of ferredoxins (Fdx), Trx, and NADPH. Trxs are reduced via the FTR in a light-dependent manner, using photosynthetic electrons provided by the PSI electron acceptor Fdx, and are able to reductively cleave disulfide bonds in many stromal target proteins. Thus, modulate their functions i.e. to increase or decrease their activity. Chloroplast Trxs, such as Trx-m, Trx-f, Trx-y, Trx-x and Trx-z [81], chloroplast glutaredoxins (Grx) such as GrxC5, S12, S14, and S16 [82] and chloroplast cyclophilins [83,84] mediate thiol-disulphide redox interchange of various chloroplast proteins like fructose-1,6-bisphosphase (FBPase), a key enzyme of the Calvin–Benson cycle and the most studied target enzyme of the CO_2 assimilation pathway [85], NADP-dependent malate dehydrogenase (NADP-MDH) a key enzyme of the malate valve and represents a classical target of m-type Trxs [86], and peroxiredoxins which are central elements of the antioxidant defense system and the dithiol-disulfide redox regulatory network of the plant cell [87-89]. In the chloroplast, in addition to the light-dependent Fdx/Trx system, a separate Trx system which uses NADPH as electron donor has been identified. This system consists of NADPH-dependent Trx reductase (NTRC) and contains both NTR and a Trx domain on the same protein [90]. Target enzymes of NTRC are AGPase involved in starch biosynthesis [91], the nuclear-encoded 2-Cys peroxiredoxins (2CP) involved in H_2O_2 detoxification [92], and Mg-chelatase I sub-unit [93]. At first NTRC was suggested to function in the chloroplast in a light-independent manner, as a separate thiol-redox system. However, recent finding in planta suggested that NTRC is able to regulate chloroplast FBPase and the Calvin-Benson cycle in response to varying light conditions [94,95]. Although NTRC is a key redox protein responsible for regulatory functions distinct from those of the FTR/Trx system, it was found as an electron donor to Trx-z, an important regulator of chloroplasts gene expression (Figure 1). Moreover, the cooperative control of chloroplast functions via the FTR/Trx and NTRC pathways which is essential for plant viability has been demonstrated [96].

Until the last decade the role of carbon metabolism in chloroplast-mediated signals in nuclear gene expression regulation has been ignored in most studies. Piippo et al. used short-term illumination with different qualities (PSII light that preferentially excites photosystem II and PSI light that excites predominantly photosystem I) and quantities (darkness, low light and high but not excessive light) of light to modulate the redox state of PETC [73]. In their expirements emphasis was focused on the role of the redox state of the PQ pool, the stromal redox compounds, and the CO_2 fixation products as sources of chloroplast signals during the short term treatment period. The genes responding to different light treatments found in their study were among genes involved in protein synthesis and carbohydrate metabolism. Hence, they suggested that the metabolic activity of the

chloroplast could be a source of plastid signals whereas the role of the redox state of the PQ pool in nuclear gene expression appears to be only marginal [73]. Another line of support to these findings came from a study by Baier et al. [97] who reported that the acceptor availability at PSI and the cellular redox poise but not the redox state of the PQ pool control the 2-Cys peroxiredoxin A (2CPA) transcription activity within the nucleus. In all plants analysed so far the expression of 2CP was found to be redox-regulated [87]. Among several enzymatic components of the chloroplast antioxidant system the most detailed analysis of expressional/transcriptional regulation has been performed for 2CPA gene [98-100]. Moreover, a screen for redox-imbalanced (rimb) mutants was set up in Arabidopsis inorder to identify further elements involved in transcriptional regulation of genes for chloroplast antioxidant enzymes [101] using a reporter gene line expressing luciferase under control of the 2CPA promoter [98]. In the rimb mutants, the expression of 2CPA is uncoupled from the redox state of the PSI acceptor side. Identification of the RIMB genes will impact on our understanding of the redox-mediated retrograde signaling pathway(s). Indeed, recently the rimb1 mutation was mapped to a 167 kb region on chromosome1 containg candidate genes and compared the phenotypes of T-DNA insertion lines with rimb1. RIMB1, a major factor involved in redox-regulation of genes for chloroplast antioxidant enzymes and protection against photooxidative stress, was identical to the radical-induced cell death 1 (RCD1), a regulator of disease response reactions and cell death [102].

2.2.3. ROS-dependent signals in the retrograde signaling from chloroplast to the nucleus

HL has been demonstrated to increase the production of ROS and to induce a strong expression of various antioxidant genes, cellular chaperones and heat shock proteins [103,104]. The role of H_2O_2 as signaling molecule in the regulation of gene expression networks in plants has been given special attention and was the focus of several studies [10,105-110]. In Arabidopsis exposure to H_2O_2 resulted in a change of ~1/3 of the transcriptome [111]. Additionally, 113 genes were induced and 62 genes were repressed from those 175 genes regulated by H_2O_2 [107]. Studies of genes involved in H_2O_2 signal transduction, mitogen-activated protein kinases (MAPKs) and various TFs such as NAC, ZAT, and WRKY families have been identified [112, 113]. Moreover, by studying catalase-deficient Arabidopsis plants, Vandenabeele et al. [114] have shown that H_2O_2 was inferred to regulate the expression of genes encoding specific small heat shock proteins and several TFs. The question arises: as a signaling molecule to what extent it is able to diffuse out of the compartments and to cross organelle membranes? This is still debatable and there is no general agreement on the rate and concentration of H_2O_2 production in the cell different compartments [115]. However, Henzler and Steudle and Bienert et al. proposed that H_2O_2 is able to diffuse through membranes, possibly through aquaporins [116,117] and later on Mubarakshina et al. [118] demonstrated that part of the chloroplast-derived H_2O_2 diffuses out of the chloroplasts which might be sufficient to trigger signaling processes i.e. by a change in the expression level of responsive genes. However, it was hypothesized that H_2O_2 itself is unlikely to be the retrograde signaling molecule that directly regulates expression of nuclear-encoded chloroplast genes but rather compartment-specific redox-sensitive components such as oxidized proteins/peptides would act as second messengers or down-stream mediators of such H_2O_2 signaling [119,120]. Most recently, stromules have been proposed to have a role in the translocation of proteins and H_2O_2 from the chloroplast to the nucleus and to be part of retrograde signaling [121].

To study the specific role of $^1O_2$ as a signaling molecule the conditional Arabidopsis flu mutant was used. In the flu mutant induction of $^1O_2$ is allowed in the plastids in a controlled manner. FLU is a

nucleus-encoded plastid protein which acts as a negative regulator of the synthesis of δ-aminolevulinic acid (ALA) in the tetrapyrrole biosynthetic pathway (the chlorophyll (Chl) biosynthesis) [122]. Inactivation of this protein in the flu mutant demonstrates an over-accumulation of protochlorophyllide (Pchlide) in plastids upon transfer to the dark. However, shifting back to the light Pchlide acts as a photosensitizer and generates $^1O_2$. The mature flu plants stopped growing after the release of $^1O_2$, the seedlings bleached and died and the differential regulation of specific sets of nuclear genes [54]. It was also suggested that the $^1O_2$ pathway is active under moderate light stress conditions which could be part of the acclimation response because of the limited cell death occured. Another report demonstrated high levels of $^1O_2$ production in response to norflurazon and lincomycin treatments. Therfore, $^1O_2$ molecule was suggested to be a putative signal for the modulation of NGE in response to these inhibitors supporting a link between $^1O_2$ and GUN1 and ABI4 transcription factors because this regulation is no longer observed in gun1 and abi4 mutants [42]. Screens for flu suppressor mutations that abrogate $^1O_2$-mediated cell death and/or growth inhibition of flu revealed the identification of EXECUTER1 (EX1). EX1 encodes a plastid protein of unknown function and unrelated to known proteins. Moreover, EX1 was shown to be indispensable for the transfer of $^1O_2$ dependent signals that mediate growth inhibition and cell death from the plastid to the nucleus. Inactivation of the EX1 gene in the flu mutant background is not sufficient to fully suppress $^1O_2$-induced changes in nuclear gene expression i.e. inactivation of EX1 attenuated the upregulation of $^1O_2$-responsive nuclear genes but did not fully eliminate the changes [123]. Another plastid nuclear-encoded protein, EX2, has been identified and is also implicated in the changes in signalling of $^1O_2$-dependent nuclear gene expression [124]. When both EXECUTER proteins are inactive in the ex1/ex2/flu triple mutant, most of the $^1O_2$-responsive gene transcripts are close to wild-type level suggesting that the singlet oxygen derived plastid signal requires concerted action of both EXECUTER1 and EXECUTER2 [124]. Another suppressor screen with the flu mutant have led to the identification of dubbed singlet oxygen-linked death activator (soldat) mutants that abrogate $^1O_2$-dependent cell death without affecting Pchlide accumulation. Soldat8 affects a gene encoding the SIGMA6 factor of the plastid RNA polymerase (PEP) while soldat10 affects a gene encoding a plastid-localized protein related to the human mitochondrial transcription termination factor mTERF [125,126]. On the one hand inactivation of SIGMA6 in soldat8 mutants disturbed plastid homeostasis, non-photochemical quenching capacity was reduced drastically and light sensitivity of young soldat8 seedlings was enhanced. Moreover, Suppression of $^1O_2$-mediated cell death in young flu/soldat8 seedlings caused by the initial disturbance of plastid homeostasis seems to be due to a transiently enhanced acclimation at the beginning of seedling development [125]. On the other hand the soldat10 mutation does not interfere directly with the transfer of $^1O_2$-derived signals but disturbs chloroplast homeostasis and suppresses a subsequent $^1O_2$-mediated cell death response in flu seedlings [126]. In short, constitutive acclimation to light stress results in the suppression of $^1O_2$-mediated cell death in soldat8 and soldat10 mutants [125,126]. In the above sections we mentioned that plastids may act as sensors of stress and via plastid-to-nucleus signaling they trigger stress responses, therefore, it is not surprising that the perturbation of plastid homeostasis in soldat mutants is perceived as stress and triggers an acclimatory response.

Overall, by comparing the transcriptional responses to $^1O_2$ and H_2O_2 using the flu mutants and plants treated with MV, transcriptome analyses have differentiated O_2^-/H_2O_2-dependent regulation from $^1O_2$-dependent regulation and demonstrated the specific and the antagonistic effect of these two chloroplastic ROS on gene expression [54,106,111]. However, cross-talk between H_2O_2- and

$^1O_2$-dependent signaling pathways was proposed in which it might contribute to the overall stability and robustness of plants exposed to adverse environmental stress conditions [106].

3. Compartmentalisation is a major factor in ROS/redox signal specificity

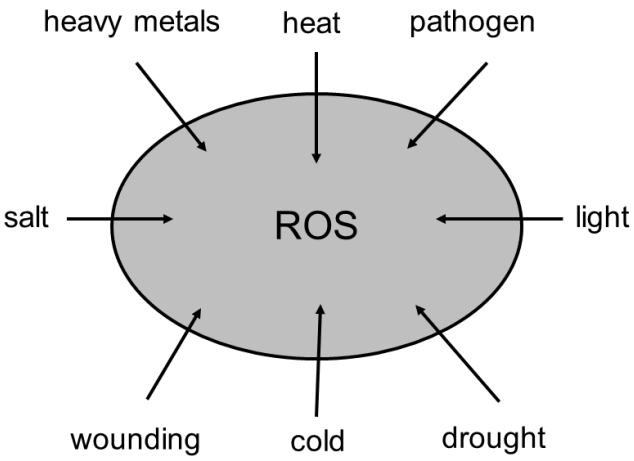

Figure 3. ROS is a signaling molecule during plant response to stress. Schematic representation of the main environmental abiotic and biotic stressors linked to ROS production and signaling.

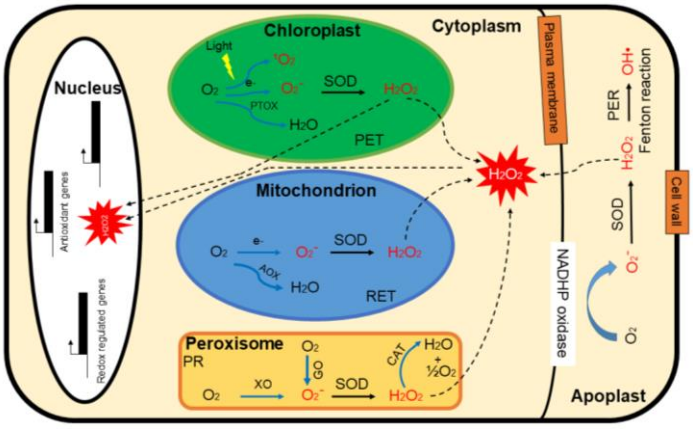

Figure 4. Schematic representation illustrating the major sites of ROS generation in the plant cell. AOX, alternative oxidase; CAT, catalase; GO, glycolate oxidase; PER, peroxidases; PET, photosynthetic electron transport; PTOX, plastid terminal oxidase; RET, respiratory electron transport; SOD, superoxide dismutase; XOD, xanthine oxidase.

Because ROS, which is produced in different sites of the cell, represents a common plant response to almost all environmental stresses (Figure 3) it drives someone's thinking that it could be the primary source of the signaling battery in plants. There are different sources for the production of

ROS within the cell such as the plasma and apoplastic membranes, and in the organelles such as the chloroplasts, mitochondria, and peroxisomes (Figure 4).

The compartmentalization of ROS production within cells, aside from the specificity and selectivity of ROS on their targets, is an important determinant of whether damage or redox signaling occurs. H_2O_2-dependent oxidation of a given protein is likely to occur close to the source of H_2O_2 production so an effective redox signaling can take place. A good example is the protein targets of H_2O_2 generated from plasma membrane NADPH oxidases is likely also located at the plasma membrane. In a similar way, superoxide accumulation in the mitochondrial matrix has different outcomes from superoxide accumulation in the cytosol. Accordingly, both the type of ROS and its local concentration collectively determine whether redox signaling or oxidative-stress-induced damage occurs [59-61]. Thus, for understanding cell redox physiology, ROS generation within specific subcellular compartments and their redox status appear to be of major importance. Additionally, more and more methods for the study of redox compartmentalization have been developed. For example, GSH/GSSG and NAD(P)H/NAD(P)$^+$ redox potentials are quantified by high-performance liquid chromatography (HPLC). However, in order to determine the redox state of several proteins, mass spectrometry and redox Western blotting, in association with labeling of free thiols, are frequently used. Despite the high specificity present in these methods for the redox couple examination and the quantification of both the oxidized and reduced forms, they often require tissue/cell fractionation. Fractionation can result in redistribution and artifactual oxidation/reduction. Molecular biology techniques using epitope-tagged versions of nuclear NLS and NES proteins have been developed to allow measurements without fractionation. Approaches involve fluorescent imaging techniques of ROS and major redox couples within organelles in intact cells or organisms in vivo have been developed more recently.

3.1. ROS/REDOX signal initiation and signal transduction in plants and its impact on NGE

A linear signaling pathway pattern for each stress is unlikely due to the increasing evidences of cross-talk between different signaling pathways. However, if ROS are the points at which different branches of signaling pathways converge then what are the ROS receptors/sensors? the downstream signaling components? the signaling specificity? and the cross-talk between the different signaling pathways? A signal transduction pathway consists of several components starting from the stimulus sensing (sensor/receptor), then the transducer (transmitter) and to the final response.

3.1.1. The receptors or sensors of the redox signals in plants

To activate signaling pathway(s) H_2O_2, O_2^-, and $^1O_2$, as signaling molecules, must interact with a cellular target (receptor/sensor). The life time of ROS is quite short and therefore, the sensor has to be quite efficient and this rises several possibilities about ROS sensing by the plant cell which occurs possibly through different mechanisms (i) receptor proteins that is yet not identified or may be at the apoplastic site of the plasma membrane such as two members of the cysteine-rich receptor-like kinase gene family and a leucine-rich repeat (LRR-RLK) protein in Arabidopsis which are transcriptionally induced after ozone treatment, and thus they could sense ROS through redox modifications of their extracellular domain [127]. Moreover, a tight link between G proteins and ROS in plant signaling has been suggested in which exposure of Arabidopsis leaves to ozone resulted in an oxidative burst which was attenuated or even completely absent in mutant plants lacking Gα

protein or Gβ protein. The study suggested that the extracellular ROS which is produced by ozone in the apoplastic part activate the G protein either directly or indirectly [128]. In fact, NADPH oxidases D and F that receive initial signals from G proteins to mediate ozone responses in Arabidopsis guard cells was suggested [129]. Moreover, AtRbohD and AtRbohF, which are membrane-bound ROS producing enzymes, work in the same pathway with the Gβ subunit of the heterotrimeric G protein for full disease resistance [130]. (ii) Modulation of kinases directly by ROS. Mitogen-activated protein kinases (MAPKs) exist in all eukaryotes and are considered to be evolutionary conserved. MAPKs are interlinked protein kinases: MAP kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK), and MAP kinase (MAPK) where one activates the other by phosphorylation of the tyrosine and therionine residues in the TXY motif. The transmission of oxidative signals is controlled through MAPKs where MAPKs can be activated by accumulation of H_2O_2, or they can trigger an H_2O_2-induced oxidative burst [131]. (iii) ROS activate signaling molecules within the cell or the organelles i.e. redox sensitive compound such as transcription factors such as WRKY, ZAT, RAV, GRAS and MYB. Regulation of TFs by ROS occurs at several levels (i) TF expression up-regulation i.e. increasing mRNA stability and translation; (ii) decreasing TF degradation by inhibiting the ubiquitin E3 ligase complex or by decreasing its association with this complex (iii) Translocation of TFs from for e.g. cytoplasm to the nucleus or by releasing the TF from partners or from membrane anchors and (iv) modulation of DNA binding and/or transactivation potential of TFs, modulation of co-activators or repressors, and by regulating chromatin to activate individual genes.

3.1.2. The transmitters or transducers of the redox signals in plants

Trxs and Grxs as well as the antioxidant enzymes are key players not only in keeping ROS levels low but also may themselves act as signal transmitters [132]. Indeed, König et al. proposed that PRXs can be transducers in redox signaling in plants and animals. They act as floodgates for H_2O_2 under strong oxidative conditions [133]. The mammalian GPX7 functions as an oxidative stress sensor and transmitter. When cells expose to oxidative stress, GPx7 acts as an intracellular sensor that detects redox level and transmits ROS signals to redox-sensitive, thiol-containing proteins to facilitate the regulation of multiple biologic processes [134]. In addition, some TFs were also reported as signal transmitters such as RAP2.4a which acts as an efficient redox-sensor and transducer of the redox state of the cell to the nucleus to control transcriptional activity of chloroplast antioxidant enzymes [99].

3.1.3. The Responses to the redox signals in plants: the expressional/transcriptional level

ROS/redox networks play essential roles in the acclimation of plants to abiotic stresses. A delicate balance of homeostasis is contributed by these signals within the different organelles. Moreover, cross-talk between the different organellar/cellular components is overseen by regulating different biological pathways including gene expression, protein expression and modification for e.g. phosphorylation, energy metabolism in response to stress. ROS-dependent signal propagation as result of abiotic stresses i.e. HL, heat and wounding reqiures RbohD [135]. Cross-talk between the regulatory mechanisms of chloroplast redox signaling and systemic responses dependent on RbohD suggested a great overlap between them although no direct evidence of interaction between these responses was provided [135]. In response to HL and/or fluctuating light changes in PQ pool redox state correlated with expression of antioxidant genes, pathogen defense genes, and thylakoid proteins

phosphorylation. Dark and norflurazon treatments (conditions which suppress chloroplast development) resulted in amplified heat stress-induced apoptotic-like (AL) programmed cell death (PCD) in Arabidopsis cell lines. Knock-out mutant plants dificient in APX1 exhibited increased sensitivity to photo-oxidative stress [136]. Altered gene expression of the stress-induced ZAT10 and ZAT12 in response to HL and increased sensitivity to heat stress was reported in seedlings of abi4 and gun1 mutants which suggested that retrograde signalling could exert influence on abiotic stress response and acclimation through the GUN1-ABI4.

4. Mechanisms of redox-regulated transcription: examples from non-plant and plant organisms

Table 1. *Cis*-elements, transcription factors and their function in possible redox-mediated signaling pathways

Allele	Protein family/subfamily/domain	*cis*-element/DNA binding site	Function	References
Athb-9	Homeodomain (HD)	5'-CTAA(G/C)ATTAC-3'	Role in plant developmental processes	141, 142
At1g30490	TFs/HD-zip III class			
Rap2.4a	AP2/ERF-type TFs/ type	CE3-like motif	Control of 2CPA and other antioxidant	56
At1g36060	Ib-ERF class	5'- CACGCGATTC-3'	genes expression in response to oxidative stress	
AtHSFA8	Heat shock factors (HSFs)	HSE	Responses to abiotic stress	147
At1g67970		5'- AGAAnnTTCT-3'		
ANAC089	NAC family TFs	5'-GCACGTCTAGT-3'	Suppressor of stromal ascorbate peroxidase	149
At5g22290			gene; control of ER-stress induced PCD in plants	
TCP15	bHLH TFs	as-1	Modulation of anthocyanin biosynthesis	154
At1g69690		5'-AATTCAGATCTGTGGG ACC GGGAG-3'		
TGA1	bZIP-TFs/	as-1	Regulation of pathogenesis related (PR)	159
At5g65210	TGA subclass	5'-TCGAGCTGACGTAAG GGATGAC-3'	genes during SAR	
AtbZIP16	bZIP -TFs/G-group	G-box	Regulates early stages of Arabidopsis	163, 168
At2g35530		5'-CACGTG-3'	development	

Whereas redox-regulated transcription is studied extensively in bacteria, yeast and animals (mammalian) systems, our knowledge of redox-regulated transcription in plants is rather limited and only emerging. Recent biochemical, molecular, physiological and genetic studies have revealed parts of these mechanisms in plants and broadened our understanding of how redox signals controlling transcription in plants. An elevation of a specific redox signal may cause redox to either activate or repress the activity of a redox-responding protein (e.g. protein kinase or phosphatase) which then transfer the signal to a TF or it may directly affect target protein like TFs, and thus cause it to activate or repress transcription of target genes, depending on whether the TF itself is a

transcriptional activator or repressor. Some of the downstream target genes of such redox-regulated TF are themselves transcription activators or repressors that affect the expression of many more downstream genes. There are several redox-dependent mechanisms which control TFs activity (i) redox-dependent conformational changes (ii) metal-S-clusters e.g. [Fe-S] cluster (iii) subcellular localization and compartmentation (iv) disulfide formation and other Cys modifications such as S-glutathionylation, S-nitrosylation (v) redox regulation of proteolytic processes (vi) regulation of PTMs such as phosphorylation, ubiquitination and sumoylation (vii) protein-protein interaction (viii) direct redox control of DNA binding [137,138]. The examples shown above are from non-plant and plant systems and in the following sections will describe briefly the non-plant TFs and in details plant TFs. Several of these TFs, their cis-element DNA binding sites, their function and their mechanisms (Table 1) will be discussed.

4.1. Redox-dependent conformational changes

- The bacterial OxyR: a similar mechanism to the plant redox-regulated Rap2.4a

In the prokaryotic cell, e.g. bacteria, which lack the presence of membrane-bound organelles, such as nucleus, chloroplasts, mitochondria etc., a fast response is required and, therefore, it is obligatory to have highly reactive proteins that are able to sense ROS/redox signals and to trigger a response. During stress, bacteria initiate signaling that coordinate the activation of TFs that control the expression of defense-regulated genes. In response to H_2O_2, the redox-regulated TF OxyR, which belongs to the LysR family of TFs, control the expression of the stress responsive genes such as catalase (KatG), alkylhydroperoxide reductase (AhpcF), glutaredoxin (Grx), glutathione reductase (GorA), and the small regulatory RNA (OxyS) in response to elevated levels of hydrogen peroxide. [139,140]. Among the six Cys residues in OxyR, Cys199 and Cys208 are conserved and form a disulfide bond which leads to its activation in responses to H_2O_2. Moreover, it was shown that the tetrameric form of oxidized OxyR binds to target promoters [141-143]. No apparent homologs of OxyR have been found in plants, however, the Arabidopsis Rap2.4a TF similarly play a role in regulating the expression of nuclear-encoded chloroplast antioxidant genes in response to oxidative stress. Rap2.4a, which belongs to activator protein 2/ethylene response factor (AP2/ERF) TF family [144], was isolated from a yeast-one-hybrid screen using a redox-sensitive DNA promoter region that control the expression of 2-cysteine peroxidoxin A (2CPA) gene [98]. Rap2.4a was proposed as redox sensor and/or transducer of redox information in the cell to control the expression of 2CPA and other chloroplast antioxidant proteins [99]. The redox environment leads to profound transitions (dithiol/disulfide) of the quaternary structure of Rap2.4a where under intermediate redox potentials Rap2.4a protein forms homo-dimeric structure by intermolecular disulfide bond and binds to the DNA promoter target and activates transcription. DNA-binding and transactivation activities are impaired under both highly reducing and highly oxidizing conditions. The midpoint redox of Rap2.4a was found to be about −270 mV which is more negative than the midpoint potential of glutathione (−230 mV), but less than that of most thioredoxins (−290 to −300 mV) suggesting that moderate oxidation of the glutathione pool might be sufficient to activate Rap2.4a-dependent gene expression [99]. In high light response, detailed transcriptional profiling and clustering assigned RAP2.4a to a network of extremely fast-responding transcription factors [145,146].

4.2. Metal-S-clusters in functional assem bly

- Bacterial SoxR, SoxS and plant SBP and WRKY

While OxyR is involved in H_2O_2 responses, SoxR and SoxS orchestrate the bacterial response to superoxide. Superoxide modify the activity of SoxR, which, in turn, induces expression of SoxS. *SoxR* is divergently transcribed from *SoxS and* SoxR promoter is embedded within the *SoxS* gene. SoxR binds to *SoxS* promoter as homodimer to prevent enhanced transcription in the absence of an oxidative stress signal. In the absence of an induction signal, SoxR repression in combination with the proteases, Lon and FtsH, results in low levels of SoxS protein, however, oxidation of SoxR [2Fe-2S] cluster converts SoxR to an activator of *SoxS* transcription. When SoxS levels increase, this will lead to increased expression of genes related to DNA repair (such as nfo) and genes involved in detoxification (such as sodA). The activation, as a result of oxidization by the superoxide, has been recently challenged after it has been considered for long time. Superoxide has been shown not to be the oxidizer of SoxR; rather the redox cycling oxidizes SoxR [147-149]. Proteins that carry Fe, Cu, Mn, and Zn metal ions as cofactors mediate diverse biochemical processes, including energy conversion, synthesis, and DNA regulation, reactive oxygen species (ROS) detoxification, as well as signaling events that trigger molecular, cellular, and systemic responses. The well-studied example of the bacterial oxidative stress sensor SoxR with its [2Fe-2S] cluster is compared to the plant-specific TFs that also contain sulfur-based metal-binding sites (Zn), e.g. WRKY proteins and SQUAMOSA promoter binding proteins (SBP) TFs [150,151]. Because metal-S-clusters often serve as redox sensory systems, it is likely these TFs are sensitive to oxidative modifications and redox regulation. Like in the case of WRKY8 [152], expression of WRKY30, WRKY75, WRKY48, WRKY39, WRKY6, WRKY53, WRKY22 was triggered in Arabidopsis in response to H_2O_2 treatment. WRKY63 was suggested to function as an activator in HL stress tolerance where it triggers downstream components that quenches ROS formed by HL stress [153]. CBSX (single cystathionine β-synthase domain–containing proteins), CC-type GRXs (ROXY1 and ROXY2) and SBP TFs, which are targets of miR156 and miR157, were implicated in redox clean up during male reproductive development [154,155].

4.3. Subcellular localization/Compartmentation

- Yeast YAP1, a good example to compare with the plant HSFA8

In unicellular eukaryotic organisms, such as yeast, TFs have been found to respond to ROS and to function in a redox regulated manner. AP1 protein family in yeast (yAP-1) is particularly interesting. S. cerevisiae YAP1 TFs contain a bZIP DNA-binding and dimerization domain. YAP1 exists both in the cytosol in its inactive form and in the nucleus, where it is active. Under non-stress conditions YAP1 is preferentially localized in the cytoplasm however upon cells exposure to oxidative stress YAP1 is quickly translocated to the nucleus [156]. Oxidation of the H_2O_2 sensor Oxidant Receptor Peroxidase 1 (ORP1/Gpx3) triggers a thiol–disulphide relay mechanism that ultimately leads to nuclear accumulation of the yeast YAP1 transcription factor [138]. Like in the case of OxyR, SoxR and SoxS, no apparent homologs have been assigned to the plant system and instead other plant TFs e.g. HSFA8 have been reported to adopt a mechanism that rely on compartmentation. Heat-responsive genes counteract exposure of plants to heat stress. Expression of

heat-responsive genes and heat shock proteins (HSPs) is regulated by the heat shock transcription factors (HSFs) which binds to the heat shock element (HSE; (5′-nAGAAnnTTCTn-3′) in the promoter region of the heat-responsive genes. H_2O_2 have been proposed to possibly directly modify HSFs and induce HSF trimerization [157]. HSFA1A contains one Cys residue within the trimerization domain [158]. The early response to high light has been shown to be mediated by a subset of HSFs where the HSF, e.g. HSFA1D, translocates from the cytoplasm to the nucleus [159]. Furthermore, it has been recently shown that translocation of HSFA8 to the nucleus in response to oxidative stress is mediated through the Cys residue. Indeed, H_2O_2 induced wild-type HSFA8, but not HSFA8 C24S mutant variant, translocations from the cytosol to the nucleus in the protoplasts [160].

4.4. Disulfide formation and other Cys modifications such as S-glutathionylation, S-nitrosylation

- AP-1 involves Cys modification in the DNA binding domain a good example to compare with plant HD-ZIP and

Strong evidences for redox-regulation of mammalian TFs have been demonstrated. Moreover, binding sites of the redox-regulated TFs such as activator protein-1 (AP-1) are present in promoters of genes directly involved in the pathogenesis of diseases e.g. cancer, AIDS, and diabetes. The AP-1 protein family consists of several groups of bZIP TFs subfamilies such as Jun (v-Jun, c-Jun, JunB, JunD), Fos (v-Fos, c-Fos, FOSB, FRA-1, FRA2), small MAF (MAFG, MAFF, and MAFK) and large MAF (cMAF, MAFB, MAFA, and NRL), and ATF/CREB (CREB, ATF1, ATF2, ATF4, ATF5, ATF6a, ATF6b, ATF7, ATF3/LRF1, B-ATF, and ATFa0), JDP1/2). AP-1 regulates several cellular processes such as cell proliferation, survival, differentiation and apoptosis [161]. The AP-1 proteins form heterodimers and bind to target DNA sequences such as TPA-responsive element (TRE; 5-TGAG/CTCA-3) or cAMP response elements (CRE; 5-TGACGTCA-3). One mechanism of AP-1 regulation involves reversible oxidation of specific Cys residues in c-Jun and c-Fos basic regions. The AP-1 activity can be restored in vitro using reducing agents. Furthermore, the DNA-binding activity of AP-1 is suppressed by nitric oxide through S-glutathionylation [162,163].

In plant the homeodomain (HD) containing TFs have been divided into six families, namely (1) homeodomain leucine zipper (HD-Zip); (2) homeodomain with a finger domain (PHD); (3) Bell domain (Bell); (4) zinc finger with homeodomain (ZF-HD); (5) Wuschel homeobox (WOX); and (6) Knotted homeobox (KNOX). Among these the HD-Zip are only present in plants and therefore they were suggested to have plant specific developmental role [164]. Moreover, HD-Zip proteins are divided into four classes, I–IV, where each of them contains several members in the different plant species. Redox regulation has been investigated for members from HD-Zip II and HD-Zip III classes because they contain conserved Cys residues. HAHR1 and HABH-10 that belong to the HD-Zip II of the sunflower (H. annuus) undergo dithiol/disulfide exchanges, which affects their DNA-binding activity evident by using oxidizing, and reducing agents, Cys directed mutagenesis and the use of NADPH/TRX/TR system. The authors suggested that in response to environmental signals a redox-dependent mechanism may operate in the plants to modulate the activity of these TFs [165]. ATHB-9 /PHV of the HD-Zip III class was investigated for the role of the 4 Cys residues in the HD-zip domain and it was shown that the redox sensitivity is conferred from Cys residues located at the positions 23, 38 and 42. Cys23 and Cys38 in ATHB-9 are conserved in all HD-Zip III class. ATHB-9 is actively binding DNA targets in the presence of reducing conditions or thioredoxin

system. Oxidation inactivates ATHB-9 and impairs its DNA-binding activity while TRX reactivate it. Because of sequence conservation, redox-dependent control of target gene expression can be expected in other HD TFs during developmental processes [166].

4.5. Redox regulation of proteolytic processing

- NRF2 and ANAC089

NF-E2-related factor 2 (NRF2) is a member of p45 NF-E2-related proteins (p45 NF-E2, NRF1, NRF2, and NRF3. NRF2 is involved in haematopoiesis, differentiation, proliferation, growth, apoptosis, drug metabolism, and the oxidative stress response. In unstressed (normal) conditions, NRF2 is localized in the cytoplasm where it interacts with Kelch-like ECH-associating protein 1 (KEAP1) which targets NRF2 for rapid degradation by the ubiquitin-proteasome. However, in response to stress NRF2 translocate to the nucleus and heterodimerizes with small masculoaponeurotic fibrosarcoma (MAF) proteins and bind to the Antioxidant Response Element (ARE), a cis-acting enhancer sequence (TCAG/CXXXGC) that is present in the promoter region of NRF2-regulated genes. Moreover, NRF2 was found to possess ARE in its own promoter to initiate its own transcription. It is interesting that KEAP1 contains several active Cys residues that are targets for modification by ROS and electrophiles. Such modification results in dissociation between KEAP1 and NRF2 which allows of NRF2 translocation to the nucleus to regulate gene expression and suggesting that the activity of NRF2 is negatively regulated by KEAP1-dependent cytosolic sequestration pathway [167]. Other mechanisms were suggested to activate NRF2, other than targeting KEAP1, in which oxidation can activate NRF2 through phosphorylation by PKC and PERK that leads to NRF2 dissociation from KEAP1, allowing the free NRF2 to translocate to nucleus [168]. Redox regulation of TFs in terms of shuttling between different compartments i.e. the plasma membrane and the nucleus have been reported for ANAC089. NAC transcription factors have been shown to be involved in responses to biotic and biotic stresses, hormonal signaling and developmental processes. ANAC089 fusion protein localizes to vesicle-like structures and peripheral membranes [169,170]. The reductive signal lead to the translocation of ANAC089 from the membrane to the nucleus [149] where it binds to the oxidative responsive element in the promoter region of sAPX to suppress its gene expression i.e. ANAC089 functions as a negative regulator of sAPX expression if the cell encounters highly reducing conditions [170]. More recently ANAC089 was shown to be an important player in the ER-stress induced PCD which can be summarized as follows: bZIP28 and bZIP60 upregulate ANAC089 gene expression, the ANAC089 translocates from the ER membrane to the nucleus, PCD induction by ANAC089, the ability of ANAC089 to bind the promoter of many downstream targets and finally the evidence deduced from NAC089 knock-down (KD) mutants which suppresses the ER-stress-induced expression of several PCD regulators [171].

4.6. Regulation of PTMs: phosphorylation, ubiquitination, and sumoylation

- NF-κB and ABI5

Nuclear factor kappa B (NF-κB) is a heterodimeric ubiquitous redox-sensitive TF that coordinates regulators of immunity, inflammatory responses, cell proliferation, cellular growth and

development, and apoptosis. The activity NF-kB is dysregulated in a number of chronic inflammatory diseases and certain types of cancers. That's why NF-kB signaling is an attractive target for the development of anti-inflammatory and anti-cancer drugs [172]. The mammalian NF-κB family consists of NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), c-Rel, and RelB which are characterized by the presence of Rel homology domain (RHD). There are three functions mediated by RHD (1) NF-κB DNA binding (2) homo- and hetero-dimerization between NF-κB family members (3) association of the inhibitors of kappa B (IκB) with NF-κB dimers. While NF-kB exists as an inactive cytoplasmic complex with inhibitory kB (IκB) proteins in non-stimulated cells, its transcriptional activation occurs through distinct steps. Different stimuli such as cytokines and ROS leads to NF-κB activation through activation of IκB kinase (IKK) which then phosphorylates IκB resulting in dissociation of NF-κB from the IκB inhibitor and of IκB degradation by ubiquitin/proteasome system. Then unbound NF-κB translocates to the nucleus where it binds to DNA and activates the transcription of target genes [173,174]. In plants, the phytohormone abscisic acid (ABA) regulates plant growth and development as well as response to abiotic and biotic stresses. Cellular responses to ABA are mediated by a suite of transcription factors including members of the B3, AP2, and bZIPs domain families. Abscisic Acid Insensitive 5 (ABI5), a bZIP TF and one of the most studied ABA-responsive TFs, functions as a regulator of abiotic stress responses and integrator of ABA crosstalk with other phytohormones [175]. PTMs such as phosphorylation, ubiquitination, and sumoylation play significant roles in regulating ABI5 and thus ABA signaling. In unstressed conditions, ABI5 is maintained at low levels via degradation by the 26S proteasome. However, upon exposure to stress conditions, proteasome-dependent turnover decreases and ABI5 becomes more stable which leads to its accumulated and then induces expression of ABA-responsive genes required for growth inhibition and stress tolerance [175]. ABI5 degradation by the 26S proteasome depends on the ubiquitination pathway by a number of ubiquitin ligases. Ubiquitin ligases which directly target ABI5 include Keep on Going (KEG), a single subunit RING-type E3, which interacts with the E2 and ABI5 via its RING domain and ankyrin repeats, respectively [176].

While phosphorylation of ABI5, which is necessary for its activation, is mediated by members of the Sucrose Non-fermenting1-related protein kinases (SnRK) 2 and CBL-interacting protein kinase (CIPK) families [177], Serine/Threonine Protein Phosphatase 6 (PP6) dephosphorylates ABI5 and negatively regulate ABA signaling [178]. Moreover, low levels of ABI5 in siz1 mutant compared with wild type in response to ABA treatment suggested that sumoylation regulates ABI5 abundance [179].

4.7. Protein-protein interaction

- Mammalian Ref1-Trx-AP1 and the best studied redox-regulated transcription system in plants NPR1-TGA

Redox effector factor 1 (Ref1) was identified in a search for nuclear factors responsible for the AP-1 TF reduction. Subsequently, Ref-1 was reported to reduce several TFs such as NF-κB, HIF-1α, p53, PAX. The redox regulation of AP-1 depends on a direct interaction between Trx and Ref1 [180]. The scenario is the following: Ref-1 was co-purified with AP-1 and interaction between them was stable. Moreover, TRX is one of the endogenous redox molecules that regulates the AP-1 transcriptional activity through its direct association with Ref1 [181]. Previously, solution structure showed direct association of TRX and the partial peptide of Ref-1 using oligopeptide comprising

amino acid residues 59–71 of Ref-1 and TRX complex [182]. Cys-32 and Cys-35 of TRX, which constitute the catalytic center, were shown to be involved in the association using whole recombinant proteins in in vivo experiments. Moreover, Site-directed mutagenesis Cys-63 and Cys-95 in the redox domain of Ref-1, suggested that they are redox sensitive and can be targets of TRX [181].

TGA TFs belong to the group of bZIP factors binds to the cis element TGACGTGG and they are implicated as regulators of pathogenesis-related (PR) genes [182,183]. Among the 10 TGA genes in Arabidopsis 7 of them (TGA1-TGA7) have been characterized based on their interaction with the nonexpresser of PR gene1 (NPR1). Redox Regulation of the NPR1-TGA1 System is one of the best studied redox-controlled signaling. During systemic acquired resistance (SAR), SA-induced redox change regulates NPR1-TGA interaction [184]. SA-mediated redox changes lead to reduction in the intermolecular disulfide bonds of Cys-156 of NPR1 oligomers to its active monomeric form which is then translocated to the nucleus to fulfill its coactivator function by interacting with TGA1 which is required for the induction of PR genes [185]. SA triggers monomerization of NPR1 by a reduction catalyzed by TRX-h proteins that counter the effect of GSNO-facilitated oligomeri-zation [186]. Among the four Cys residues in TGA1, Cys-260 and Cys-266 form an intramolecular bond in response to oxidation however redox changes do not directly regulate the DNA binding activity of TGA1. However, reduction of this disulfide bond is critical for the interaction between TGA1 and NPR1 [184]. Further investigations suggested that TGA1 Cys-172 and Cys-287 are also redox-responsive and form intermolecular disulfide bond [187]. The authors also demonstrated that the DNA-binding activity of TGA1 was enhanced by GSNO in presence of NPR1. Not only NPR1 and TGA1 proteins were S-nitrosylated with the treatment by NO donor, but also the nuclear translocation of NPR1 was promoted by NO [187]. The plant-specific CC-type glutaredoxins (ROXYs), involved in anther development [188], contains this leucine rich motif which mediates the interactions between ROXYs and TGA TFs [189].

4.8. Direct redox control of DNA binding

Several plants of the TFs are regulated through direct redox control of their DNA inding such as the R2R3 MYB [190]. While vertebrate MYB genes encode proteins with MYB domains formed by three MYB repeats (R1R2R3 MYB), the majority of plant MYB genes encode proteins with only two MYB repeats (R2R3 MYB) most similar to the vertebrate R2 and R3 MYB. Most plant R2R3 MYB domains contain two cysteines, Cys-49 and Cys-53. Cys-53 is located at the equivalent position as Cys-130 in R1R2R3 MYB. In vertebrate MYB TFs Cys-130 was shown to serve as a redox sensor because when it was mutated the DNA binding and transcriptional activities of c-MYB were significantly impaired [191]. It is interesting that Cys-53, established for vertebrate MYB proteins, is not essential for the DNA-binding activity of P1 TF (R2R3 MYB) from maize while Cys-49 acted as the redox sensor [190]. Moreover, Cys-49 and Cys-53 form an intramolecular disulfide bond that can be important for modulating DNA-binding activity [191].

TCP is plant specific family of TFs that share a conserved DNA-binding domain, which contains bHLH motif, called the TCP domain. This family is grouped into class I (TCP-P) and class II (TCP-C) that are involved in plant growth and development [192]. In TCP class I of different plants species, a shared conserved cysteine residue at position 20 within the TCP DNA binding domain (Cys-20) was found. However, this conserved Cys-20 is not present in TCP class II. Interestingly, in vitro assays (EMSAs) suggested that Cys-20 is not required for DNA binding but rather it is responsible for the redox sensitivity of class I TCP proteins and that mutating Cys-20 in TCP15 abolished its redox sensitivity probably though intermolecular disulfide formation [193].

Moreover, H2O2 not only significantly decreased the transcriptional activity of TCP15 in the transactivation assays in yeast but also in the plants [193]. It's interesting that TCP proteins have in the second helix of the DNA-binding domain a leucine-rich short motif (L**LL) which has been shown to mediate protein interactions both in animals and plants.

It is Another group of plant proteins which is under redox control is group G of bZIP TF family [194]. Ten groups are classified in Arabidopsis bZIP family according to sequence similarities of their basic region, conserved motifs, and other features such as the size of the leucine zipper [195]. The G group comprises 5 members namely AtbZIP16, AtbZIP68, GBF1, GBF2 and GBF3 and all of them binds to the G-box cis element [194,196,197]. The G-box element was reported to be enriched in high light regulated genes such as LHCB2.4 [198]. Because LHCB2.4 represents the genes responding to light and/or redox changes, part of its promoter region containing G-box was used to isolate TF(s) targets [194]. Interestingly, the conserved Cys330 in the DNA binding domain of bZIP16, bZIP68 and GBF1 is sensitive to redox treatment and should be reduced for optimal binding of target genes [194]. While Shaikhali et al. reported bZIP16 as transcriptional repressor in the light regulated photomorphogenesis response [194], Hsieh et al. reported bZIP16 as a newly identified G-box binding TF which integrates the light and hormone pathways to promote seed germination and hypocotyl elongation [199]. Subsequently, GIP1 has been identified as a regulator for the TFs bZIP16, bZIP68 and GBF1 in early stages of Arabidopsis seedling development. In response to redox treatments GIP1 undergoes functional switching from redox to chaperone activity [200]. GIP1 was also reported to may act as a transcriptional coactivator of LBD18. LBD18 belongs to plant-specific lateral organ boundaries domain and plays a key role in lateral organ development of plants [201].

5. Redox-regulation of the Mediator complex

The transcriptional regulation in eukaryotes is complex and involve many components such as RNA polymerase II (RNP II), general transcription factors (GTFs), transcription factors and the mediator complex. The mediator complex provides the essential link between TFs and RNP II where it transduces diverse signals to genes involved in different pathways. The first reports on the mediator complex came from the yeast Saccharomyces cerevisiae where about 20 subunits were estimated [202]. Subsequently the mediator complex was identified in almost all organisms. Therefore, a unified nomenclature for the different protein subunits of the mediator complexes across the different species has been proposed. Backström et al. isolated for the first time the mediator complex from Arabidopsis using column chromatography accompanied with immunoprecipitation using antibody raised against MED6 subunit [203]. The authors reported the isolation of 21 conserved and six specific subunits of the mediator complex [203]. Subsequent comparative genomics and bioinformatics work identified the mediator complex in 16 plant species represented across the plant kingdom [204]. In their work, Mathur et al. identified for the first time MED26 subunits that was not identified earlier in any of the plant species. Moreover, Arabidopsis MED32, MED33, MED34, MED35, MED36, and MED37 orthologues were identified in all plant groups [204].

The different mediator complex subunits have been assigned to three modular structures called the head, the middle and the tail modules which form the core of the complex. In addition to these modules, there is a separable kinase or CDK8 module, which consists of CDK8, cyclin C, MED12, and MED13. Depends on the cellular context the mediator complex shuttle between two different states: The Mediator core complex and Mediator core-kinase complex in which the former favors transcription

(the mediator core associates with RNAP II) and the latter represses transcription (the kinase module-bound Mediator complex dissociates from RNAP II). The first studies on the mediator suggested that it is mainly linked to the initiation step of transcription [205,206], however, later on the mediator has be linked to different step in the transcription [207-211]. Specific functions in signaling pathways which are important during development and in response to biotic and abiotic stress have been reported for several plant mediator complex subunits [212-217]. For instance, MED21 has been proposed to function in defense against necrotrophic pathogens through interaction with HUB1 [218]. MED14, MED15, and MED16 are considered as key players in plant defense signaling crosstalk [219]. MED18 and MED20 have been recently suggested as factors that confer susceptibility for Fusarium oxysporum infection in Arabidopsis [220]. MED12 and MED13 regulates early embryo patterning [221]. Cell number during primordia initiation is controlled by SWP/MED14 [222]. PFT1/MED25 has been shown to regulate flowering, jasmonate signaling, light signaling and photomorphogenesis and biotic and abiotic stress tolerance [212,213,216,223].

It is interesting that both the mediator complex and ROS/redox regulate transcription during growth, development and stress, however, no direct linkage between them have been reported until recently [224-230]. Analysis of npr1 single mutant and tga6 tga2 tga5 triple mutant suggested that NPR1 and the TGA factors (TGA2, TGA5, and TGA6) are essential positive regulators of SAR [231-232]. Later on, induction of SAR was abolished completely in med16/sfr6 mutant plants similar to that in npr1 and tga6 tga2 tga5 triple mutant suggesting that MED16 is an essential positive regulator of SAR [234]. The decreased levels of NPR1 protein in med16 mutants suggested that MED16 may regulated SA signaling and basal immunity at least partly through modulating NPR1 accumulation [234]. PFT1/MED25 was suggested to control ROS balance in roots and is critical for root hair differentiation and elongation probably by regulating the expression of redox-related genes, the Class III peroxidases [224]. In their working model the authors suggested that, possibly, PFT1/MED25 induces the expression of class III peroxidases where H_2O_2 is produced in the elongation zone. On contrary, NADPH oxidases produces O_2^- in the meristematic zone. When a threshold concentration of the distribution of H_2O_2 and O_2^- is reached, it acts as a signal which determines the differentiation of root hair cells [224]. The fact that PFT1/MED25 is involved in different signaling pathways and mechanisms such as flowering time and light signaling [212-216], JA signaling [217], JA-mediated pathogen defense [223], abiotic stress [213] and root hair development [224] prompted the authors to suggest that PFT1 probably control these processes by regulating redox homeostasis [224]. Involvement of the mediator complex in redox signaling and regulation has been also proposed through the interaction of MED18 and YIN YANG1 (YY1), a zinc finger transcription factor, which associates with the promoter regions of genes encoding proteins known for long to be involved in redox regulation and signaling i.e. GRXS13/ROXY18, GRXC9/ROXY19 and TRXh5. Moreover, the deregulated expression of GRXS13/ROXY18, GRXC9/ROXY19 and TRXh5 in yy1 and med18 mutants suggested a synergistic role for GRXs and TRXs in plant immunity [227]. More recently we reported that representative members of the head, middle and tail modules of the mediator complex, MED28, MED10a and MED32 are targets of redox-regulation [228]. These proteins form intermolecular disulfide bonds, which are reduced by at least one representative member of GRXs and TRXs families, although with different efficiencies [228]. In particular, MED28 oligomer formation involved both covalent and non-covalent interactions [229]. Moreover, med32 and med28

mutants display phenotypes (altered root development and senescence) associated with redox changes [230].

6. The power of Mass Spectrometry and Proteomics in developing the study of redox regulated transcription

Recent studies acknowledged proteomic as a powerful technique to characterize induced protein modifications involved in the regulation of several redox-regulated signaling pathways involved in cellular physiological processes [235,236]. Identification of the general basis the polypeptide targets of redox activity and how these modifications may control protein function and the cellular pathways of which they are a part of is the intention of redox proteomics. Nowadays, a quantitative evaluation of protein oxidation under different cellular conditions is provided by the field of redox proteomics that is increasing. Moreover, nowadays combined nano-liquid chromatography, electrophoretic protein/peptide separation techniques, mass spectrometry, and affinity based methodologies have provided a better understanding of the protein oxidative modifications present in various biological systems under different physiological conditions.

Carbonyl formation, oxidation of side chains of amino acids, products of glycation reactions, reactive alkenal product of lipid peroxidation are common oxidative post-translational modifications (oxPTMs) to proteins [237]. To this end, the sensitive Cys residue to e.g. nitrosylation and oxidation states of the sulfur atom of the Cys thiol may be is the prime target of redox modification [238]. Furthermore, the involvement of the oxidation of Cys residues leading to oligomerization of subunits of the Mediator complex may play an important regulatory role [228]. However, the methods that analyze redox regulation of plant transcription have only partly reached the necessary sensitivity to address the level of complexity in vivo. Thus, there is an urgent need to improve proteome sensitivity to characterize low abundant proteins with various oxPTMs [137].

One possibility to characterize low abundant TFs proteins with mass spectrometry is to use nucleus fractionation to enhance the sensitivity in the mass spectrometry analysis [239-241]. Examples from nucleus extraction procedures and using nucleus recombinant proteins in Arabidopsis have identified S-nitrosylations of different of proteins [187,242,243]. A nuclear overexpressed Thioredoxin (Trxo 1) was identified to interact with the proliferating cell nuclear antigen (PCNA) and thus to be a potential target [245]. Chaki et al. treated Arabidopsis suspension cell cultures with pathogens before nuclear proteins were extracted and treated with the S-nitrosylating agent GSNO [244]. A biotin switch assay was performed and biotin-labelled proteins were purified by neutravidin affinity chromatography and identified by mass spectrometry. Most of the S-nitrosylated candidates were involved in protein and RNA metabolism, stress response, and cell organization and division. In addition, plant-specific histone deacetylases were identified suggesting that nitric oxide regulated epigenetic processes in plants [244].

Although much work has been carried out using untargeted or discovery mass spectrometry approaches, identification of oxPTMs has supported from the development of targeted or semi-targeted scanning routines, combined with chemical labeling and enrichment approaches [245]. However, many pitfalls exist and both advantages and limitations in redox analysis by mass spectrometry has been discussed in several review articles [235,236,245,247]. Limitations and pitfalls can be summarized as follows: the lack of standard proteomics methodology (lack of well-established validation protocols for oxPTM) when oxPTMs analysis is performed. Adding to this the wide variety of methodologies, and the complex data analysis. The lack of competence of the

invistigator, as well as the poor bioinformatic background can be other factors. Finding solutions to these limitations and pitfalls in the future will certainly advance our way in studying nuclear proteins and hence redox-regulated transcription.

7. Conclusions

The redox-signaling pathway involves several players (receptors/acceptors, transmitters/transducers, responders) and the redox network involves inputs from various redox cues. In this review, a special attention has been given to redox-regulation of transcription that is an evolutionary conserved mechanism in which changes in the ROS and/or the redox state of the cell leads to changes or alterations in the gene expression. We discussed several examples of the redox regulated TFs from different organisms and their response to stress/environmental conditions. Moreover, PTMs of TFs such as covalent interaction (disulfide bond formation) are important for their regulation to help the plants to cope with external stresses. The recent findings, as highlighted in this review, have made it clear that proteomics and mass spectroscopic have to be improved to identify the low abundant nuclear proteins and to increase the sensitivity to identify PTMs such as Cys residues involved in covalent interactions.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Bryant DA, Frigaard N-U (2006) Prokaryotic photosynthesis and phototrophy illuminated. *Trends Microbiol* 14: 488-496.
2. Allen JF, Martin W (2007) Out of thin air. *Nature* 445: 612-614.
3. Hohmann-Mariott MF, Blankenship RE (2012) The photosynthetic world, In: Eaton-Rye JJ, Trypathy BC, Sharkey TD, et al., Photosynthesis: Plastid Biology, Energy Conversion and Carbon Assimilation, Springer.
4. Horton P, Ruban AV, Walters RG (1996) Regulation of light harvesting in green plants. *Annu Rev Plant Physiol Plant Mol Biol* 47: 655-684.
5. Aro EM, McCaffery S, Anderson JM (1993) Photoinhibition and D1 protein degradation in peas acclimated to different growth irradiance. *Plant Physiol* 103: 835-843.
6. Aro EM, Virgin I, Anderson JM (1993) Photoinhibition of photosystem II: inactivation, protein damage and turnover. *Biochem Biophys Acta* 1143: 113-134.
7. Gollan PJ, Tikkanen M, Aro EM (2015) Photosynthetic light reactions: integral to chloroplast retrograde signalling. *Curr Opin Plant Biol* 27: 180-191.
8. Hossain MS, Dietz KJ (2016) Tuning of redox regulatory mechanisms, reactive oxygen species and redox homeostasis under salinity stress. *Front Plant Sci* 7: 548.
9. Foyer CH, Noctor G (2005) Redox homeostasis and antioxidant signalling: a metabolic interface

between stress perception and physiological responses. *Plant Cell* 17: 1866-1875.
10. Apel K, Hirt H (2004) Reactive oxygen species: metabolism, oxidative stress, and signal transduction. *Annu Rev Plant Biol* 55: 373-399.
11. Foyer CH, Ruban AV, Noctor G (2017) Viewing oxidative stress through the lens of oxidative signalling rather than damage. *Biochemical J* 474: 877-883.
12. Sheibe R, Dietz KJ (2012) Reduction–oxidation network for flexible adjustment of cellular metabolism in photoautotrophic cells. *Plant Cell Envi* 155: 1477-1485.
13. Dietz KJ, Pfannschmidt T (2011) Novel regulators in photosynthetic redox control of plant metabolism and gene expression. *Plant Physiol* 155: 1477-1485.
14. Dietz KJ, Turkan I, Krieger-Liszkay A (2016) Redox- and reactive oxygen species-dependent signalling in and from the photosynthesizing chloroplast. *Plant Physiol* 171: 1541-1550.
15. Kleine T, Leister D (2013) retrograde signal galore. *Front Plant Sci* 4: 45.
16. Nakayama T, Archibald JM (2012) Evolving a photosynthetic organelle. *BMC Biol* 10: 35.
17. Giege P, Sweetlove LJ, Cognat V, et al. (2005) Coordination of nuclear and mitochondrial genome expression during mitochondrial biogenesis in Arabidopsis. *Plant Cell* 17: 1497-1512.
18. Woodson JD, Chory J (2008) Coordination of gene expression between organellar and nuclear genomes. *Nat Rev Genet* 9: 383-395.
19. Bradbeer JW, Atkinson YE, Borner T, et al. (1979) Cytoplasmic synthesis of plastid polypeptides may be controlled by plastid-synthesized RNA. *Nature* 279: 816-817.
20. Oelmuller R, Levitan I, Bergfeld R, et al. (1986). Expression of nuclear genes as affected by treatments acting on the plastids. *Planta* 168: 482-492.
21. Susek RE, Ausubel FM, Chory J (1993) Signal transduction mutants of Arabidopsis uncouple nuclear CAB and RBCS gene expression from chloroplast development. *Cell* 74: 787-799.
22. Yoshida R, Sato T, Kanno A, et al. (1998) Streptomycin mimics the cool temperature response in rice plants. *J Exp Bot* 49: 221-227.
23. Sullivan JA, Gray JC (1999). Plastid translation is required for the expression of nuclear photosynthesis genes in the dark and in roots of the pea lip1 mutant. *Plant Cell* 11: 901-910.
24. Pogson BJ, Woo NS, Förster B, et al. (2008) Plastid signalling to the nucleus and beyond. *Trends Plant Sci* 13: 602-609.
25. Chi W, Feng P, Ma J, et al. (2015) Metabolites and chloroplast retrograde signaling. *Curr Opin Plant Biol* 25: 32-38.
26. Chan KX, Phua SY, Crisp P, et al. (2015) Learning the languages of the chloroplast: retrograde signaling and beyond. *Annu Rev Plant Biol* 67: 25-53.
27. Estavillo GM, Chan KX, Phua SY, et al. (2013) Reconsidering the nature and mode of action of metabolite retrograde signals from the chloroplast. *Front Plant Sci* 3: 300.
28. Xiao Y, Savchenko T, Baidoo EE, et al. (2012) Retrograde signaling by the plastidial metabolite MEcPP regulates expression of nuclear stress-response genes. *Cell* 149: 1525-1535.
29. Estavillo GM, Crisp PA, Pornsiriwong W, et al. (2011) Evidence for a SAL1-PAP chloroplast retrograde pathway that functions in drought and high light signaling in Arabidopsis. *Plant Cell* 23: 3992-4012.
30. Ramel F, Birtic S, Ginies C, et al. (2012) Carotenoid oxidation products are stress signals that mediate gene responses to singlet oxygen in plants. *Proc Natl Acad Sci USA* 109: 5535-5540.
31. Woodson JD, Perez-Ruiz JM, Chory J (2011). Heme synthesis by plastid ferrochelatase I regulates nuclear gene expression in plants. *Curr Biol* 21: 897-903.

32. Kropat J, Oster U, Rüdiger W, et al. (1997) Chlorophyll precursors are signals of chloroplast origin involved in light induction of nuclear heat-shock genes. *Proc Natl Acad Sci USA* 94: 14168-14172.
33. Kropat J, Oster U, Rudiger W, et al. (2000) Chloroplast signaling in the light induction of nuclear HSP70 genes requires the accumulation of chlorophyll precursors and their accessibility to cytoplasm/nucleus. *Plant J* 24: 523-531.
34. Strand A, Asami T, Alonso J, et al. (2003) Chloroplast to nucleus communication triggered by accumulation of Mg-protoporphyrinIX. *Nature* 421: 79-83.
35. Zhang ZW, Yuan S, Feng H, et al. (2011) Transient accumulation of Mg-protoporphyrinIX regulates expression of PhANGs: new evidence for the signaling role of tetrapyrroles in mature Arabidopsis plants. *J Plant Physiol* 168: 714-721.
36. Susek RE, Ausubel FM, Chory J (1993) Signal transduction mutants of Arabidopsis uncouple nuclear CAB and RBCS gene expression from chloroplast development. *Cell* 74: 787-799.
37. Mochizuki N, Brusslan JA, Larkin R, et al. (2001) Arabidopsis genomes uncoupled 5 (GUN5) mutant reveals the involvement of Mg-chelatase H subunit in plastid-to-nucleus signal transduction. *Proc Natl Acad Sci USA* 98: 2053-2058.
38. Larkin RM, Alonso JM, Ecker JR, et al. (2003) GUN4, a regulator of chlorophyll synthesis and intracellular signaling. *Science* 299: 902-906.
39. Koussevitzky S, Nott A, Mockler TC, et al. (2007) Signals from chloroplasts converge to regulate nuclear gene expression. *Science* 316: 715-719.
40. Ankele E, Kindgren P, Pesquet E, et al. (2007) In vivo visualization of Mg-protoporphyrinIX, a coordinator of photosynthetic gene expression in the nucleus and the chloroplast. *Plant Cell* 19: 1964-1979.
41. Mochizuki N, Tanaka R, Tanaka A, et al. (2008). The steady-state level of Mg-protoporphyrin IX is not a determinant of plastid-to-nucleus signaling in Arabidopsis. *Proc Natl Acad Sci USA* 105: 15184-15189.
42. Moulin M, McCormac AC, Terry MJ, et al. (2008). Tetrapyrrole profiling in Arabidopsis seedlings reveals that retrograde plastid nuclear signaling is not due to Mg-protoporphyrin IX accumulation. *Proc Natl Acad Sci USA* 105: 15178-15183.
43. Kindgren P, Noren L, Barajas Lopez J, et al. (2011) Interplay between HEAT SHOCK PROTEIN 90 and HY5 controls PhANG expression in response to the GUN5 plastid signal. *Mol Plant* 5: 901-913.
44. Kindgren P, Eriksson MJ, Benedict C, et al. (2011) A novel proteomic approach reveals a role for Mg-protoporphyrinIX in response to oxidative stress. *Physiol Plant* 141: 310-320.
45. Lee HC, Hon T, Zhang L (2002) The molecular chaperone Hsp90 mediates heme activation of the yeast transcriptional activator Hap1. *J Biol Chem* 277: 7430-7437.
46. Cordoba E, Salmi M, Leon P (2009). Unravelling the regulatory mechanisms that modulate the MEP pathway in higher plants. *J Exp Bot* 60: 2933-2943.
47. Rodríguez-Concepción M (2006) Early steps in isoprenoid biosynthesis: multilevel regulation of the supply of common precursors in plant cells. *Phytochem Rev* 5: 1-15.
48. Rossel JB, Walter PB, Hendrickson L, et al. (2006) A mutation affecting ASCORBATE PEROXIDASE 2 gene expression reveals a link between responses to high light and drought tolerance. *Plant Cell Environ* 29: 269-281.
49. Wilson PB, Estavillo GM, Field KJ, et al. (2009) The nucleotidase/phosphatase SAL1 is a

negative regulator of drought tolerance in Arabidopsis. *Plant J* 58: 299-317.
50. Estavillo GM, Crisp PA, Pornsiriwong W, et al. (2011) Evidence for a SAL1-PAP chloroplast retrograde pathway that functions in drought and high light signaling in Arabidopsis. *Plant Cell* 23: 3992-4012.
51. Gigolashvili T, Geier M, Ashykhmina N, et al. (2012) The Arabidopsis thylakoid ADP/ATP carrier TAAC has an additional role in supplying plastidic phosphoadenosine 5′-phosphosulfate to the cytosol. *Plant Cell* 24: 4187-4204.
52. Gy I, Gasciolli V, Lauressergues D, et al. (2007) Arabidopsis FIERY1, XRN2, and XRN3 are endogenous RNA silencing suppressors. *Plant Cell* 19: 3451-3461.
53. Kim C, Apel K (2013) Singlet oxygen-mediated signaling in plants: moving from flu to wild type reveals an increasing complexity. *Photosynth Res* 116: 455-464.
54. Op den Camp RGL, Przybyla D, Ochsenbein C, et al. (2003) Rapid induction of distinct stress responses after the release of singlet oxygen in Arabidopsis. *Plant Cell* 15: 2320-2332.
55. Von Gromoff ED, Alawady A, Meinecke L, et al. (2008) Heme, a plastid-derived regulator of nuclear gene expression in chlamydomonas. *Plant Cell* 20: 552-567.
56. Voss B, Meinecke L, Kurz T, et al. (2011) Hemin and magnesium-protoporphyrinIX induce global changes in gene expression in Chlamydomonas reinhardtii. *Plant Physiol* 155: 892-905.
57. Espinas NA, Kobayashi K, Takahashi S, et al. (2012). Evaluation of unbound free heme in plant cells by differential acetone extraction. *Plant Cell Physiol* 53: 1344-1354.
58. Zhang L, Hach A (1999) Molecular mechanism of heme signaling in yeast: the transcriptional activator Hap1 serves as the key mediator. *Cell Mo Life Sci*. 56: 415-426.
59. Baier M, Dietz K-J (2005) Chloroplasts as source and target of cellular redox regulation: a discussion on chloroplast redox signals in the context of plant physiology. *J Exp Bot* 56: 1449-1462.
60. Gollan PJ, Tikkanen M, Aro EM (2017) Photosynthetic light reactions: integral to chloroplast retrograde signalling. *Curr Opin Plant Biol* 27: 180-191.
61. Barajas-Lopez JD, Blanco NE, Strand A(2013) Plastid-to-nucleus communication, signals controlling the running of the plant cell. *Biochem Biophys Acta* 1833: 425-437.
62. Pfalz J, Liebers M, Hirth M, et al. (2012) Environmental control of plant nuclear gene expression by chloroplast redox signals. *Front Plant Sci* 3: 257.
63. Jung HS, Mockler TC (2014) A new alternative in plant retrograde signaling. *Genome Biol* 15: 117.
64. Escoubas J-M, Lomas M, LaRoche S, et al. (1995) Light intensity regulation of cab gene transcription is signalled by the redox state of the plastoquinone pool. *Proc Natl Acad Sci USA* 92: 10237-10241.
65. Maxwell DP, Laudenbach DE, Huner NPA (1995) Redox regulation of light-harvesting complex II and cab mRNA abundance in Dunaliella salina. *Plant Physiol* 109: 787-795.
66. Maxwell DP, Falk S, Trick GC, et al. (1994) Growth at low temperature mimics high-light acclimation in Chlorella vulgaris. *Plant Physiol* 105: 535-543.
67. Maxwell DP, Laudenbach DE, Huner N (1995) Redox regulation of light-harvesting complex II and cab mRNA abundance in Dunaliella salina. *Plant Physiol* 109: 787-795.
68. Pfannschmidt T, Nilsson A, Tullberg A, et al. (1999) Direct transcriptional control of the chloroplast genes psbA and psaAB adjusts photosynthesis to light energy distribution in plants IUBMB Life 48: 271-276.

69. Pfannschmidt T, Schütze K, Brost M, et al. (2001) A novel mechanism of nuclear photosynthesis gene regulation by redox signals from the chloroplast during photosystem stoichiometry adjustment. *J Biol Chem* 276: 36125-36130.
70. Oswald O, Martin T, Dominy PJ, et al. (2001) Plastid redox state and sugars: interactive regulators of nuclear-encoded photosynthetic gene expression. *Proc Natl Acad Sci USA* 98: 2047-2052.
71. Hihara Y, Sonoike K, Kanehisa M, et al. (2003) DNA microarray analysis of redox-responsive genes in the genome of the cyanobacterium Synechocystis sp. strain PCC 6803. *J Bacteriol* 185: 1719-1725.
72. Fey V, Wagner R, Brautigam K, et al. (2005) Retrograde plastid redox signals in the expression of nuclear genes for chloroplast proteins of Arabidopsis thaliana. *J Biol Chem* 280: 5318-5328.
73. Piippo M, Allahverdiyeva Y, Paakkarinen V, et al. (2006) Chloroplast-mediated regulation of nuclear genes in Arabidopsis thalianain the absence of light stress. *Physiol Genomics* 25: 142-152.
74. Bräutigam K, Dietzel L, Kleine T, et al. (2009). Dynamic plastid redox signals integrate gene expression and metabolism to induce distinct metabolic states in photosynthetic acclimation in Arabidopsis. *Plant Cell* 21: 2715-2732.
75. Shao N, Vallon O, Dent R, et al. (2006) Defects in the cytochrome b6/f complex prevent light-induced expression of nuclear genes involved in chlorophyll biosynthesis. *Plant Physiol* 141: 1128-1137.
76. Bellaflore S, Barneche F, Peltier G, et al. (2005) State transitions and light adaptation require chloroplast thylakoid protein kinase STN7. *Nature* 433: 892-895.
77. Tikkanen M, Gollan PJ, Mekala NR, et al. (2014) Light-harvesting mutants show differential gene expression upon shift to high light as a consequence of photosynthetic redox and reactive oxygen species metabolism. *Philos Trans R Soc London Ser B: Biol Sci* 369.
78. Gläßer C, Haberer G, Finkemeierm I, et al. (2014) Meta-analysis of retrograde signaling in Arabidopsis thaliana reveals a core module of genes embedded in complex cellular signaling networks. *Mol Plan* 20: 1167-1190
79. Jacquot JP, Eklund H, Rouhier N, et al. (2009) Structural and evolutionary aspects of thioredoxin reductases in photosynthetic organisms. *Trends Plant Sci* 14: 336-343.
80. Schürmann P, Buchanan BB (2008) The ferredoxin/thioredoxin system of oxygenic photosynthesis. *Antioxid Redox Signal* 10: 1235-1274.
81. Serrato AJ, Fernández-Trijueque J, Barajas-López JD, et al. (2013) Plastid thioredoxins: A "one-for-all" redox-signaling system in plants. *Front Plant Sci* 4: 463.
82. Meyer Y, Siala W, Bashandy T, et al. (2008) Glutaredoxins and thioredoxins in plants. *Biochem Biophys Acta* 1783: 589-600.
83. Romano PGN, Horton P, Gray JE (2004) The Arabidopsis cyclophilins gene family. *Plant Physiol* 134: 1268-1282.
84. Kumari S, Roy S, Singh P, et al. (2013) Cyclophilins: Proteins in search of function. *Plant Signal Behav* 8.
85. Chueca A, Sahrawy M, Pagano EA, et al. (2002) Chloroplast fructose-1,6-bisphosphatase: structure and function. *Photosynth Res* 74: 235-249.
86. Thormählen I, Zupok A, Rescher J, et al. (2017) Thioredoxins Play a Crucial Role in Dynamic Acclimation of Photosynthesis in Fluctuating Light. *Mol Plant* 10: 168-182.
87. Dietz KJ (2011) Peroxiredoxins in plants and cyanobacteria. *Antioxid Redox Signal* 15: 1129-1159.

88. Tripathi BN, Bhatt I, Dietz KJ (2009) Peroxiredoxins: a less studied component of hydrogen peroxide detoxification in photosynthetic organisms. *Protoplasma* 235: 3-15.
89. Cerveau D, Ouahrani D, Marok MA (2015) Physiological relevance of plant 2-Cys peroxiredoxin overoxidation level and oligomerization status. *Plant Cell Environ* 39: 103-119.
90. Serrato AJ, Perez-Ruiz JM, Spinola MC, et al. (2004) A novel NADPH thioredoxin reductase, localized in the chloroplast, which deficiency causes hypersensitivity to abiotic stress in Arabidopsis thaliana. *J Biol Chem* 279: 43821-43827.
91. Lepisto A, Pakula E, Toivola J, et al. (2013) Deletion of chloroplast NADPH-dependent thioredoxin reductase results in inability to regulate starch synthesis and causes stunted growth under short-day photoperiods. *J Exp Bot* 64: 3843-3854.
92. Perez-Ruiz JM, Spinola MC, Kirchsteiger K, et al. (2006) Rice NTRC is a high-efficiency redox system for chloroplast protection against oxidative damage. *Plant Cell* 18: 2356-2368.
93. Perez-Ruiz JM, Guinea M, Puerto-Galan L, et al. (2014) NADPH thioredoxin reductase C is involved in redox regulation of the Mg-chelatase I subunit in Arabidopsis thaliana chloroplasts. *Mol Plant* 7: 1252-1255.
94. Thormählen I, Meitzel T, Groysman J, et al. (2015) Thioredoxin f1 and NADPH-dependent thioredoxin reductase C have overlapping functions in regulating photosynthetic metabolism and plant growth in response to varying light conditions. *Plant Physiol* 169: 1766-1786.
95. Nikkanen L, Toivola J, Rintamäki E (2016) Crosstalk between chloroplast thioredoxin systems in regulation of photosynthesis. *Plant Cell Environ* 39: 1691-1705.
96. Yoshida K, Hisabori T (2016) Two distinct redox cascades cooperatively regulate chloroplast functions and sustain plant viability. 113: E3967-3976.
97. Baier M, Stroher E, Dietz KJ (2004) The acceptor availability at photosystem I and ABA control nuclear expression of 2-Cys peroxiredoxin-A in Arabidopsis thaliana. *Plant Cell Physiol* 45: 997-1006.
98. Baier M, Stroher E, Dietz K-J (2004) The acceptor availability at photosystem I and ABA control nuclear expression of 2-Cys peroxiredoxin-A in Arabidopsis thaliana. *Plant Cell Physiol* 45: 997-1006.
99. Shaikhali J, Heiber I, Seidel T, et al. (2008). The redox-sensitive transcription factor Rap2.4a controls nuclear expression of 2-Cys peroxiredoxin A and other chloroplast antioxidant enzymes. *BMC Plant Biol* 8: 48.
100. Shaikhali J, Baier M (2010). Ascorbate regulation of 2-Cys peroxiredoxin-A promoter activity is light-dependent. *J Plant Physiol* 167: 461-467.
101. Heiber I, Stroher E, Raatz B, et al. (2007) The redox imbalanced mutants of Arabidopsis differentiate signaling pathways for redox regulation of chloroplast antioxidant enzymes. *Plant Physiol* 143: 774-1788.
102. Hiltscher H, Rudnik R, Shaikhali J, et al. (2014) The radical induced cell death protein 1 (RCD1) supports transcriptional activation of genes for chloroplast antioxidant enzymes. *Front Plant Sci* 5: 475.
103. Kimura M, Yamamoto YY, Seki M, et al. (2003) Identification of Arabidopsis genes regulated by high light-stress using cDNA microarray. *Photochem Photobiol* 77: 226-233.
104. Rossel JB, Wilson IW, Pogson BJ (2002) Global changes in gene expression in response to high light in Arabidopsis. Plant Physiol 130: 1109-1120.
105. Vandenabeele S, Van der Kelen K, Dat J, et al. (2003) A comprehensive analysis of hydrogen

peroxide-induced gene expression in tobacco. *Proc Natl Acad Sci USA* 100: 16113-16118.
106. Laloi C, Stachowiak M, Pers-Kamczyc E, et al. (2007) Cross-talk between singlet oxygen-and hydrogen peroxide-dependent signalling of stress responses in Arabidopsis thaliana. *Proc Natl Acad Sci USA* 104: 672-677.
107. Desikan R, Mackerness S, Hancock JT, et al. (2001) Regulation of the Arabidopsis transcriptome by oxidative stress. *Plant Physiol* 127: 159-172.
108. Fahnenstich H, Scarpeci TE, Valle EM, et al. (2008) Generation of hydrogen peroxide in chloroplasts of Arabidopsis overexpressing glycolate oxidase as an inducible system to study oxidative stress. *Plant Physiol* 148: 719-729.
109. Li Z, Wakao S, Fischer BB, et al. (2009) Sensing and responding to excess light. *Annu Rev Plant Biol* 60: 239-260.
110. Bechtold U, Richard O, Zamboni A, et al. (2008) Impact of chloroplastic- and extracellular-sourced ROS on high light-responsive gene expression in Arabidopsis. *J Exp Bot* 59: 121-133.
111. Gadjev I, Vanderauwera S, Gechev TS, et al. (2006) Transcriptomic footprints disclose specificity of reactive oxygen species signalling in Arabidopsis. *Plant Physiol* 141: 436-445.
112. Van Breusegem F, Bailey-Serres J, Mittler R (2008) Unraveling the tapestry of networks involving reactive oxygen species in plants. *Plant Physiol* 147: 978-984.
113. Li T, Li H, Zhang YX, et al. (2011) Identification and analysis of seven H_2O_2-responsive miRNAs and 32 new miRNAs in the seedlings of rice (Oryza sativa L. ssp. indica). *Nucleic Acids Res* 39: 2821-2833.
114. Vandenabeele S, Vanderauwera S, Vuylsteke M, et al. (2004) Catalase deficiency drastically affects gene expression induced by high light in Arabidopsis thaliana. *Plant J* 39: 45-58.
115. Queval G, Hager J, Gakiere B, et al. (2008) Why are literature data for H_2O_2 contents so variable? A discussion of potential difficulties in the quantitative assay of leaf extracts. *J Exp Bot* 59: 135-146.
116. Bienert GP, Møller AL, Kristiansen KA, et al. (2007) Specific aquaporins facilitate the diffusion of hydrogen peroxide across membranes. *J Biol Chem* 282: 1183-1192.
117. Henzler T, Steudle E (2000) Transport and metabolic degradation of hydrogen peroxide in Chara corallina: model calculations and measurements with the pressure probe suggest transport of H2O2 across water channels. *J Exp Bot* 51: 2053-2066.
118. Mubarakshina MM, Ivanov BN, Naydov IA, et al. (2010) Production and diffusion of chloroplastic H2O2 and its implication to signalling. *J Exp Bot* 61: 3577-3587.
119. Sierla M, Rahikainen M, Salojärvi J, et al. (2012) Apoplastic and chloroplastic redox signaling networks in plant stress responses. *Antioxid Redox Signal* 18: 2220-2239 .
120. Møller IM, Sweetlove LJ (2010) ROS signalling-specificity is required. *Trends Plant Sci* 15: 370-374.
121. Caplan JL, Kumar AS, Park E, et al. (2015) Chloroplast stromules function during innate immunity. *Dev Cell* 34: 45-57.
122. Meskauskiene R, Nater M, Goslings D, et al. (2001) FLU: a negative regulator of chlorophyll biosynthesis in Arabidopsis thaliana. *Proc Natl Acad Sci USA* 98: 12826-12831.
123. Wagner D, Przybyla D, Op den Camp R, et al. (2004) The genetic basis of singlet oxygen-induced stress responses of Arabidopsis thaliana. *Science* 306: 1183-1185.
124. Lee KP, Kim C, Landgraf F, Apel K (2007) EXECUTER1 - and EXECUTER2 - dependent

transfer of stress‐related signals from the plastid to the nucleus of Arabidopsis thaliana. *Proc Natl Acad Sci USA* 104: 10270-10275.

125. Coll NS, Danon A, Meurer J, et al. (2009) Characterization of soldat8, a suppressor of singlet oxygen-induced cell death in Arabidopsis seedlings. *Plant Cell Physiol* 50: 707-718.
126. Meskauskiene R, Wursch M, Laloi C, et al. (2009) A mutation in the Arabidopsis mTERF-related plastid protein SOLDAT10 activates retrograde signaling and suppresses 1O2-induced cell death. *Plant J* 60: 399-410.
127. Gauthier A, Idänheimo N, Brosché M, et al. (2011) Characterization of RLSs in Arabidopsis thaliana Proceedings of the 10th International Conference on Reactive Oxygen and Nitrogen Species in Plants. P5.
128. Joo JH, Wang S, Chen JG, et al. (2005) Different signaling and cell death roles of heterotrimeric G protein alpha and beta subunits in the Arabidopsis oxidative stress response to ozone. *Plant Cell* 17: 957-970.
129. Suharsono U, Fujisawa Y, Kawasaki T, et al. (2002) The heterotrimeric G protein alpha subunit acts upstream of the small GTPase Rac in disease resistance of rice. *Proc Natl Acad Sci USA* 99: 13307-13312.
130. Torres MA, Morales J, Sánchez-Rodríguez C, et al. (2013) Functional interplay between Arabidopsis NADPH oxidases and heterotrimeric G protein. *Mol Plant Microbe Interact* 26: 686-694.
131. Petrov VD, Van Breusegem F. (2012) Hydrogen peroxide a central hub for information flow in plant cells. *AoB Plants* 2012: pls014.
132. Noctor G, Foyer F (2016) Intracellular redox compartmentation and ROS-related communication in regulation and signaling. *Plant Physiol* 171: 1581-1592.
133. König J, Muthuramalingam M, Dietz KJ (2012) Mechanisms and dynamics in the thiol/disulfide redox regulatory network: transmitters, sensors and targets. *Curr Opin Plant Biol* 15: 261-268.
134. Chen YI, Wei PC, Hsu JL, et al. (2016) NPGPx (GPx7): a novel oxidative stress sensor/transmitter with multiple roles in redox homeostasis. *Am J Transl Res* 8: 1626-1640.
135. Miller G, Schlauch K, Tam R, et al. (2009) The plant NADPH oxidase RBOHD mediates rapid systemic signaling in response to diverse stimuli. *Science Signal* 2: ra45.
136. Rizhsky L, Davletova S, Liang H, et al. (2004) The zinc finger protein Zat12 is required for cytosolic ascorbate peroxidase 1 expression during oxidative stress in Arabidopsis. *J Biol Chem* 279: 11736-11743.
137. Dietz KJ (2013) Redox regulation of transcription factors in plant stress acclimation and development. *Antioxid Redox Signal* 2: 1356-1372.
138. Marinho SH, Real C, Cyrne L, et al. (2014) Hydrogen peroxide sensing, signaling and regulation of transcription factors. *Redox Biol* 2: 535-562.
139. Christman MF, Storz G, Ames BN (1989) OxyR, a positive regulator of hydrogen peroxide-inducible genes in Escherichia coli and Salmonella typhimurium, is homologous to a family of bacterial regulatory proteins. *Proc Natl Acad Sci USA* 86: 3484-3488.
140. Imlay JA (2008) Cellular defenses against superoxide and hydrogen peroxide. *Annu Rev Biochem* 77: 755-776.
141. Zheng M, Aslund F, Storz G (1998) Activation of the OxyR transcription factor by reversible bond formation. *Science* 279: 1718-1721.
142. Lee C, Lee SM, Mukhopadhyay P, et al. (2004) Redox regulation of OxyR requires specific

disulfide bond formation involving a rapid kinetic reaction path. *Nat Struct Mol Biol* 11: 1179-1185.
143. Kim SO, Merchant K, Nudelman R, et al. (2002) OxyR: a molecular code for redox-related signaling. *Cell* 109: 383-396.
144. Mizoi J, Shinozaki K, Yamaguchi-Shinozaki K (2015) AP2/ERF family transcription factors in plant abiotic stress responses. *Biochim Biophys Acta* 1819: 86-96.
145. Vogel MO, Moore M, König K, et al. (2014) Fast retrograde signaling in response to high light involves metabolite export, MITOGEN-ACTIVATED PROTEIN KINASE6, and AP2/ERF transcription factors in Arabidopsis. *Plant Cell* 26: 1151-1165.
146. Alsharafa K, Vogel MO, Oelze ML, et al. (2014) Kinetics of retrograde signalling initiation in the high light response of Arabidopsis thaliana. *Philos Trans R Soc Lond B Biol Sci* 369.
147. Wu J, Weiss B (1992) Two-stage induction of the soxRS (superoxide response) regulon of Escherichia coli. *J Bacteriol* 174: 3915-3920.
148. Gu M, Imlay JA (2011) The SoxRS response of Escherichia coli is directly activated by redox-cycling drugs rather than by superoxide. *Mol Microbiol* 79: 1136-1150.
149. Lin ECC (2009) Metabolism is associated with formation of harmful oxygen species (oygen stress), In: J W Lengeler, G D H G Schlegel, Biology of the Prokaryotes, 1 Ed., John Wiley & Sons, 535-536.
150. Yamasaki K, Kigawa T, Inoue M, et al. (2005) Solution structure of an Arabidopsis WRKY DNA binding domain. *Plant Cell* 17: 944-956.
151. Yamasaki K, Kigawa T, Inoue M, (2004) A novel zinc-binding motif revealed by solution structures of DNA-binding domains of Arabidopsis SBP-family transcription factors. *J Mol Biol* 337: 49-63.
152. Chen L, Zhang L, Yu D (2010) Wounding-induced WRKY8 is involved in basal defense in arabidopsis. *Mol Plant Microbe Interact* 23: 558-565.
153. Banerjee A and Roychoudhury A (2015) WRKY proteins: signaling and regulation of expression during abiotic stress responses. *Scientific World J* 2015: 807560.
154. Yoo KS, Ok SH, Jeong BC, et al. (2011) Single cystathionine β-synthase domain–containing proteins modulate development by regulating the thioredoxin system in Arabidopsis. *Plant Cell* 23: 3577-3594.
155. Zinta G, Khan A, Abdelgawad H, et al. (2016) Unveiling the redox control of plant reproductive development during abiotic stress. *Front Plant Sci* 7: 700.
156. Moye-Rowley WS (2003) Regulation of the transcriptional response to oxidative stress in fungi: similarities and differences. *Eukaryot Cell* 2: 381-389.
156. Kuge S, Arita M, Murayama A, et al. (2001) Regulation of the yeast Yap1 nuclear export signal is mediated by redox signal-induced reversible disulfide bond formation. *Mol Cell Biol* 21: 6139-6150.
157. Miller G, Mittler R (2006) Could heat shock transcription factors function as hydrogen peroxide sensors in plants? *Ann Bot* 98: 279-288.
158. Hübel A, Schöffl F (1994) Arabidopsis heat shock factor: isolation and characterization of the gene and the recombinant protein. *Plant Mol Biol* 26: 353-362.
159. Jung HS, Crisp PA, Estavillo GM, et al. (2013) Subset of heat-shock transcription factors required for the early response of Arabidopsis to excess light. *Proc Natl Acad Sci USA* 110: 14474-14479.

160. Giesguth M, Sahm A, Simon S, et al. (2015) Redox-dependent translocation of the heat shock transcription factor AtHSFA8 from the cytosol to the nucleus in Arabidopsis thaliana. *FEBS Lett* 589: 718-725.
161. Eferl R, Wagner EF (2003) AP-1: a double-edged sword in tumorigenesis. *Nat Rev Cancer* 3: 859-868.
162. Karin M, Takahashi T, Kapahi P, et al. (2001) Oxidative stress and gene expression: the AP-1 and NF-kappaB connections. *Biofactors* 15: 87-89.
163. Klatt P, Molina EP, De Lacoba MG, et al. (1999) Redox regulation of c-Jun DNA binding by reversible S-glutathiolation. *FASEB J* 13: 1481-1490.
164. Ariel FD, Manavella PA, Dezar CA, et al. (2007) The true story of the HD-Zip family. *Trends Plant Sci* 12: 419-426.
165. Tron AE, Bertoncini CW, Chan RL, et al. (2002) Redox regulation of plant homeodomain transcription factors. *J Biol Chem* 277: 34800-34807.
166. Comelli RN, Gonzalez DH (2007) Conserved homeodomain cysteines confer redox sensitivity and influence the DNA binding properties of plant class III HD-Zip proteins. *Arch Biochem Biophys* 467: 41-47.
167. Kobayashi M, Yamamoto M (2006) Nrf2-Keap1 regulation of cellular defense mechanisms against electrophiles and reactive oxygen species. *Adv Enzyme Regul* 46: 113-140.
168. Huang HC, Nguyen T, Pickett CB (2002) Phosphorylation of Nrf2 at Ser-40 by protein kinase C regulates antioxidant response element-mediated transcription. *J Biol Chem* 277: 42769-42774.
169. Li P, Wind JJ, Shi X, et al. (2011). Fructose sensitivity is suppressed in Arabidopsis by the transcription factor ANAC089 lacking the membrane-bound domain. *Proc Natl Acad Sci USA* 108: 3436-3441.
170. Klein P, Seidel T, Stöcker B, et al. (2012) The membrane-tethered transcription factor ANAC089 serves as redox-dependent suppressor of stromal ascorbate peroxidase gene expression. *Front Plant Sci* 3: 247.
171. Yang Z-T, WangMJ, Sun L (2014) The membrane-associated transcription factor NAC089 controls ER-stress-induced programmed cell death in plants. *PLoS Genet* 10: e1004243.
172. Mohora M, Greabu M, Alexandra T, et al. (2009) Redox-sensitive signaling factors and antioxidants. *Farmacia* 57: 399-411.
173. Hayden MS, Ghosh S (2004) Signaling to NF-kappaB. *Genes Dev* 18: 2195-2204.
174. Kabe Y., Ando K, Hirao S, et al. (2005) Redox regulation of NFkappaB activation: distinctredox regulation between the cytoplasm and the nucleus. *Antioxid.Redox Signal* 7: 395-403.
175. Sah SK, Reddy KR, Li J (2016). Abscisic acid and abiotic stress tolerance in crop plants. *Front Plant Sci* 7: 571.
176. Stone SL, Williams LA, Farmer LM, et al. (2006) KEEP ON GOING, a RING E3 ligase essential for Arabidopsis growth and development, is involved in abscisic acid signaling. *Plant Cell* 18: 3415-3428.
177. Lyzenga WJ, Liu H, Schofield A, et al. (2013) Arabidopsis CIPK26 interacts with KEG, components of the ABA signalling network and is degraded by the ubiquitin-proteasome system. *J Exp Bot* 64: 2779-2791.
178. Dai M, Xue Q, Mccray T, et al. (2013) The PP6 phosphatase regulates ABI5 phosphorylation and abscisic acid signaling in Arabidopsis. *Plant Cell* 25: 517-534.
179. Miura K, Lee J, Jin JB, et al. (2009) Sumoylation of ABI5 by the Arabidopsis SUMO E3 ligase

SIZ1 negatively regulates abscisic acid signaling. *Proc Natl Acad Sci USA* 106: 5418-5423.
180. Xanthoudakis S, Curran T (1992) Identification and characterization of Ref-1, a nuclear protein that facilitates AP-1 DNA-binding activity. *EMBO J* 11: 653-665.
181. Hirota K, Matsui M, Iwata S, et al. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. *Proc Natl Acad Sci USA* 94: 3633-3538.
182. Després C, DeLong C, Glaze S, et al. (2000) The Arabidopsis NPR1/NIM1 protein enhances the DNA binding activity of a subgroup of the TGA family of bZIP transcription factors. *Plant Cell* 12: 279-290.
183. Zhang Y, Fan W, Kinkema M, et al. (1999) Interaction of NPR1 with basic leucine zipper transcription factors that bind sequences required for salicylic acid induction of the PR-1 gene. *Proc Natl Acad Sci USA* 96: 6523-6528.
184. Després C, Chubak C, Rochon A, et al. (2003) The Arabidopsis NPR1 disease resistance protein is a novel cofactor that confers redox regulation of DNA binding activity to the basic domain/leucine zipper transcription factor TGA1. *Plant Cell* 15: 2181-2191.
185. Mou Z, Fan W, Dong X (2003) Inducers of plant systemic acquired resistance regulate NPR1 function through redox changes. *Cell* 113: 935-944.
186. Tada Y, Spoel SH, Pajerowska-Mukhtar K, et al. (2008) Plant immunity requires conformational charges of NPR1 via S-nitrosylation and thioredoxins. *Science* 321: 952-956.
187. Lindermayr C, Sell S, Müller B, et al. (2010) Redox regulation of the NPR1-TGA1 system of Arabidopsis thaliana by nitric oxide. *Plant Cell* 22: 2894-2907.
188. Xing S, Zachgo S (2008) ROXY1 and ROXY2, two Arabidopsis glutaredoxin genes, are required for anther development. *Plant J* 53: 790-801.
189. Li S, Gusche N, Zachgo S (2011) The ROXY1 C-terminal L**LL motif is essential for the interaction with TGA transcription factors. *Plant Physiol* 157: 2056-2068.
190. Heine FG, Hernandez JM, Grotewold E (2004) Two cysteines in plant R2R3 MYB domains participate in REDOX-dependent DNA binding. *J Biol Chem* 279: 37878-37885.
191. Guehmann S, Vorbrueggen G, Kalkbrenner F, et al. (1992) Reduction of a conserved Cys is essential for Myb DNA-binding. *Nucleic Acids Res* 20: 2279-2286.
192. Li S (2015) The Arabidopsis thaliana TCP transcription factors: A broadening horizon beyond development. *Plant Signal Behav* 10: e1044192.
193. Viola IL, Güttlein LN , Gonzalez DH (2013) Redox modulation of plant developmental regulators from the class I TCP transcription factor family. *Plant Physiol* 162: 1434-1447.
194. Shaikhali J, Noren L, Barajas-Lopez JD, et al. (2012) Redox-mediated mechanisms regulate DNA-binding activity of the G-group of bZIP transcription factors in Arabidopsis. *J Biol Chem* 287: 27510-27525.
195. Jakoby M., Weisshaar B., Dröge-Laser W., et al. (2002) bZIP transcription factors in Arabidopsis. *Trends Plant Sci* 7: 106-111.
196. Schindler U, Terzaghi W, Beckmann H, et al. (1992) DNA binding site preferences and transcriptional activation properties of the Arabidopsis transcription factor GBF1. *EMBO J* 11: 1275-1289.
197. Shen H, Cao K, Wang X (2008) AtbZIP16 and AtbZIP68, two new members of GBFs, can interact with other G group bZIPs in Arabidopsis thaliana. *BMB Rep* 41: 132-138.
198. Kleine T, Kindgren P, Benedict C, et al. (2007) Genome-wide gene expression analysis reveals a critical role for CRYPTOCHROME1 in the response of Arabidopsis to high irradiance. *Plant*

Physiol 144: 1391-1406.
199. Hsieh WP, Hsieh HL, Wu SH (2012) Arabidopsis bZIP16 transcription factor integrates light and hormone signaling pathways to regulate early seedling development. *Plant Cell* 24: 3997-4011.
200. Shaikhali J (2015) GIP1 protein is a novel cofactor that regulates DNA-binding affinity of redox-regulated members of bZIP transcription factors involved in the early stages of Arabidopsis development. *Protoplasma* 252: 867-883.
201. Lee HW, Park JH, Park MY, et al. (2014) GIP1 may act as a coactivator that enhances transcriptional activity of LBD18 in Arabidopsis. *J Plant Physiol* 171: 14-18.
202. Kelleher III RJ, Flanagan PM, Kornberg RD (1990) A novel mediator between activator proteins and the RNA polymerase II transcription apparatus. *Cell* 61: 1209-1215.
203. Backstrom S, Elfving N, Nilsson R, et al. (2007) Purification of a plant mediator from Arabidopsis thaliana identifies PFT1 as the MED25 subunit. *Mol Cell* 26: 717-729.
204. Mathur S, Vyas S, Kapoor S, et al. (2011) The Mediator complex in plants: structure, phylogeny, and expression profiling of representative genes in a dicot (Arabidopsis) and a monocot (rice) during reproduction and abiotic stress. *Plant Physiol* 157: 1609-1627.
205. Cantin GT, Stevens JL, Berk AJ (2003) Activation domain-Mediator interactions promote transcription preinitiation complex assembly on promoter DNA. *Proc Natl Acad Sci USA* 100: 12003-12008.
206. Wang G, Balamotis MA, Stevens JL, et al. (2005). Mediator requirement for both recruitment and postrecruitment steps in transcription initiation. *Mol Cell* 17: 683-694.
207. Malik S, Barrero MJ, Jones T (2007) Identification of a regulator of transcription elongation as an accessory factor for the human Mediator coactivator. *Proc Natl Acad Sci USA* 104: 6182-6187.
208. Takahashi H, Parmely TJ, Sato S, et al. (2011) Human Mediator subunit MED26 functions as a docking site for transcription elongation factors. *Cell* 146: 92-104.
209. Mukundan B, Ansari A (2011) Novel role for Mediator complex subunit Srb5/Med18 in termination of transcription. *J Biol Chem* 286: 37053-37057.
210. Kim YJ, Zheng B, Yu Y, et al. (2011) The role of Mediator in small and long noncoding RNA production in Arabidopsis thaliana. *EMBO J* 30: 814-822.
211. Lai F, Orom UA, Cesaroni M, et al. (2013) Activating RNAs associate with Mediator to enhance chromatin architecture and transcription. *Nature* 494: 497-501.
212. Cerdan PD, Chory J (2003) Regulation of flowering time by light quality. *Nature* 423: 881-885.
213. Elfving N, Davoine C, Benlloch R, et al. (2011) The Arabidopsis thaliana Med25 mediator subunit integrates environmental cues to control plant development. *Proc Natl Acad Sci USA* 108: 8245-8250.
214. Zhang X, Yao J, Zhang Y, et al. (2013) The Arabidopsis mediator complex subunits MED14/SWP and MED16/SFR6/IEN1 differentially regulate defense gene expression in plant immune responses. *Plant J* 75: 484-497.
215. Zheng Z, Guan H, Leal F, et al. (2013) Mediator subunit18 controls flowering time and floral organ identity in Arabidopsis. *PLoS One* 8: e53924.
216. Klose C, Buche C, Fernandez AP, et al. (2012) The Mediator complex subunit PFT1 interferes with COP1 and HY5 in the regulation of Arabidopsis light-signaling. *Plant Physiol* 160: 289-307.
217. Cevik C, Kidd BN, Zhang P, et al. (2012) Mediator 25 acts as an integrative hub for the

regulation of jasmonate-responsive gene expression in Arabidopsis. *Plant Physiol* 160: 541-555.
218. Dhawan R, Luo H, Foerster AM, et al. (2009) HISTONE MONOUBIQUITINATION1 interacts with a subunit of the Mediator complex and regulates defense against necrotrophic fungal pathogens in Arabidopsis. *Plant Cell* 21: 1000-1019.
219. Wang C, Du X2, Mou Z (2016) The mediator complex subunits MED14, MED15, and MED16 are involved in defense signaling crosstalk in Arabidopsis. *Front Plant Sci* 7: 1947.
220. Fallath T, Kidd BN, Stiller J, et al. (2017) MEDIATOR18 and MEDIATOR20 confer susceptibility to Fusarium oxysporum in Arabidopsis thaliana. *PLoS One* 12: e0176022.
221. Gillmor CS, Park MY, Smith MR, et al. (2010) The MED12-MED13 module of Mediator regulates the timing of embryo patterning in Arabidopsis. *Development* 137: 113-122.
222. Autran D, Jonak C, Belcram K, et al. (2002) Cell numbers and leaf development in Arabidopsis: a functional analysis of the STRUWWELPETER gene. *EMBO J* 21: 6036-6049.
223. Kidd BN, Edgar CI, Kumar KK, et al. (2009) The mediator complex subunit PFT1 is a key regulator of jasmonate-dependent defense in Arabidopsis. *Plant Cell* 21: 2237-2252.
224. Sundaravelpandian K, Chandrika NN, Schmidt W (2013) PFT1, a transcriptional Mediator complex subunit, controls root hair differentiation through reactive oxygen species (ROS) distribution in Arabidopsis. *New Phytol* 197: 151-161.
225. Zhang X, Wang C, Zhang Y, et al. (2012) The Arabidopsis mediator complex subunit16 positively regulates salicylate-mediated systemic acquired resistance and jasmonate/ethylene-induced defense pathways. *Plant Cell* 24: 4294-309.
226. Fu ZQ, Dong X (2013) Systemic acquired resistance: turning local infection into global defense. *Annu Rev Plant Biol* 64: 839-863.
227. Lai Z, Schluttenhofer CM, Bhide K, et al. (2014) MED18 interaction with distinct transcription factors regulates multiple plant functions. *Nat Commun* 5: 3064.
228. Shaikhali J, Davoine C, Brännström K, et al. (2015) Biochemical and redox characterization of the mediator complex and its associated transcription factor GeBPL, a GLABROUS1 enhancer binding protein. *Biochem J* 468: 385-400.
229. Shaikhali J, Davoine C, Björklund B, et al. (2016) Redox regulation of the MED28 and MED32 mediator subunits is important for development and senescence. *Protoplasma* 253: 957-963.
230. Shaikhali J, Rouhier N, Hecker A, et al. (2017) Covalent and non-covalent associations mediate MED28 homo-oligomerization. *J Plant Biochem Physiol* 5: 1-5.
231. Cao H, Bowling SA, Gordon AS, et al. (1994) Characterization of an Arabidopsis mutant that is nonresponsive to inducers of systemic acquired resistance. *Plant Cell* 6: 1583-1592.
232. Zhang Y, Tessaro MJ, Lassner M, et al. (2003) Knock-out analysis of Arabidopsis transcription factors TGA2, TGA5, and TGA6 reveals their redundant and essential roles in systemic acquired resistance. *Plant Cell* 15: 2647-2653.
234. Zhang X, Wang C, Zhang Y (2012) The Arabidopsis mediator complex subunit16 positively regulates salicylate-mediated systemic acquired resistance and jasmonate/ethylene-induced defense pathways. *Plant Cell* 24: 4294-4309.
235. Bachi A, Dalle-Donne I, Scaloni A (2013) Redox proteomics: chemical principles, methodological approaches and biological/biomedical promises. *Chem Rev* 113: 596-698.
236. Mock HP, Dietz KJ (2016) Redox proteomics for the assessment of redox-related posttranslational regulation in plants. *Biochim Biophys Acta* 1864: 967-73.
237. Butterfield DA, Perluigi M (2017) Redox Proteomics: A Key Tool for New Insights into Protein

Modification with Relevance to Disease. *Antioxid Redox Signal* 26: 277-279.
238. Butterfield DA, Gu L, Di Domenico F, et al. (2014) Mass spectrometry and redox proteomics: applications in disease. *Mass Spectrom Rev* 33: 277-301.
239. Erhardt M, Adamska I, Franco OL (2010) Plant nuclear proteomics--inside the cell maestro. *FEBS J* 277: 3295-3307.
240. Narula K, Datta A, Chakraborty N, et al. (2013) Comparative analyses of nuclear proteome: extending its function. *Front Plant Sci* 4: 100.
241. Petrovská B, Šebela M, Doležel J (2015) Inside a plant nucleus: discovering the proteins. *J Exp Bot* 66: 1627-1640.
242. Holtgrefe S, Gohlke J, Starmann J, et al. (2008) Regulation of plant cytosolic glyceraldehyde 3 phosphate dehydrogenase isoforms by thiol modifications. *Physiol Plant* 133: 211-228.
243. Tavares CP, Vernal J, Delena RA, et al. (2014) S-nitrosylation influences the structure and DNA binding activity of AtMYB30 transcription factor from Arabidopsis thaliana. *BBA Proteins Proteomics* 1844: 810-817.
244. Chaki M, Shekariesfahlan A, Ageeva A, et al. (2015) Identification of nuclear target proteins for S-nitrosylation in pathogen-treated Arabidopsis thaliana cell cultures. *Plant Sci* 238: 115-126.
245. Calderóna A, Ortiz-Espína A, Iglesias-Fernándezb R, et al. (2017) Thioredoxin (Trxo1) interacts with proliferating cell nuclear antigen (PCNA) and its overexpression affects the growth of tobacco cell culture. *Redox Biol* 11: 688-700.
246. Verrastro I, Pasha S, Jensen KT, et al. (2015) Mass spectrometry-based methods for identifying oxidized proteins in disease: advances and challenges. *Biomolecules* 5: 378-411.
247. Boronat S, Domènech A, Hidalgo E (2017) Proteomic characterization of reversible thiol oxidations in proteomes and proteins. *Antioxid Redox Signal* 26: 329-344.

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