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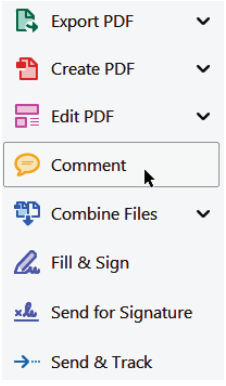

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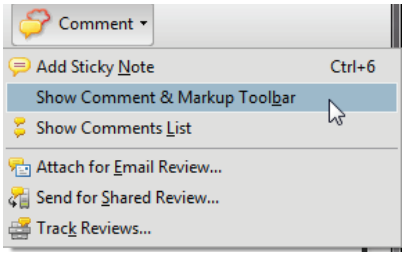

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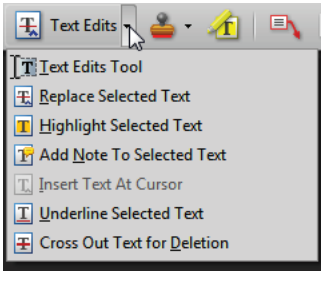

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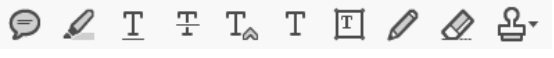

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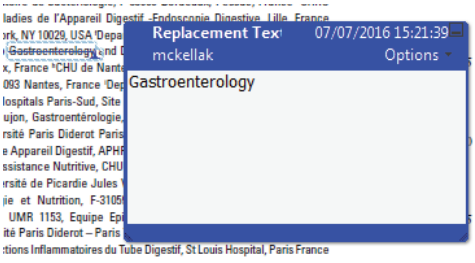

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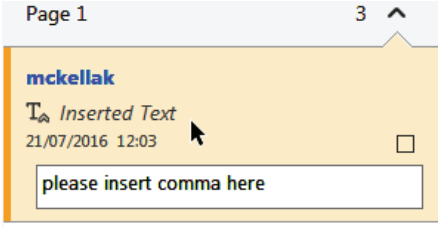

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REVIEW PAPER

ROS and redox balance as multifaceted players of cross-tolerance: epigenetic and retrograde control of gene expression

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Abstract

Retrograde pathways occurring between chloroplasts, mitochondria, and the nucleus involve oxidative and antioxidative signals that, working in a synergistic or antagonistic mode, control the expression of specific patterns of genes following stress perception. Increasing evidence also underlines the relevance of mitochondrion–chloroplast–nucleus crosstalk in modulating the whole cellular redox metabolism by a controlled and integrated flux of information. Plants can maintain the acquired tolerance by a stress memory, also operating at the transgenerational level, via epigenetic and miRNA-based mechanisms controlling gene expression. Data discussed in this review strengthen the idea that ROS, redox signals, and shifts in cellular redox balance permeate the signalling network leading to cross-tolerance. The identification of specific ROS/antioxidative signatures leading a plant to different fates under stress is pivotal for identifying strategies to monitor and increase plant fitness in a changing environment. This review provides an update of the plant redox signalling network implicated in stress responses, in particular in cross-tolerance acquisition. The interplay between reactive oxygen species (ROS), ROS-derived signals, and antioxidative pathways is also discussed in terms of plant acclimation to stress in the short and long term.

Keywords: Acclimation, chloroplast, (cross)-tolerance, epigenetic modifications, mitochondria, nucleus, reactive oxygen species, redox signals, retrograde controls of gene expression.

Introduction

Plants, like all living organisms, are continuously exposed to environmental changes, some of which occur cyclically (day/night, seasons) and some others which are unexpected. The unexpected situations involve the incidence of climatic and biotic/anthropic factors that are disadvantageous for plant growth and reproduction. Therefore, the occurrence of these factors represents a stressful condition (or more simply a stress) for plants, requiring the activation of metabolic responses (stress response), including repair and protective mechanisms, to allow plant survival. The biological concept of 'stress' received different definitions over time. In 1996, Lichtenthaler introduced a definition of stress in plant biology as 'any unfavourable condition or substance that affects or blocks a plant's metabolism, growth or development' (Lichtenthaler, 1996). Indeed, environmental stresses inevitably reduce crop yields, depending on their intensity and duration, but also on the physiological phase and genetic and epigenetic characteristics of the plant receiving the stress

(Ferrer *et al.*, 2018; Formentin *et al.*, 2018). Many studies dealing with plant response to adverse growing conditions have aimed to establish agricultural and/or biotechnological strategies to reduce crop losses. These studies have led to the identification of different molecular players involved in plant tolerance to specific stressful conditions, such as drought, salinity, anoxia, cold, heat, and pathogen attack. However, in the real world, plants are frequently exposed to a combination of these situations, rather than just one. For example, specific climate conditions, such as warmer temperatures and high humidity, make plants more prone to biotic stress (Woods *et al.*, 2016). The interest of the scientific community has thus recently moved toward identifying molecular features that can confer cross-tolerance to plants. Cross-tolerance refers to the capability of a plant that is acclimated to one kind of stress also to tolerate other kinds of adverse conditions (Pastori and Foyer, 2002). This mainly depends on the ability of the plant to rearrange its metabolism and gene expression in response to a certain stimulus. The metabolic rearrangement of the plant cells exposed to a specific stress can confer tolerance to multiple stressful situations (Ramegowda *et al.*, 2013). The control of the plant cell redox state plays a major role since it activates plant responses against various stressful conditions.

This review provides an update of the plant redox signalling network implicated in stress responses, focusing on the possible players involved in the establishment of cross-tolerance. It examines the involvement of reactive oxygen species (ROS) and ROS-derived signals in retrograde pathways that control gene expression re-modulation under adverse environmental conditions. Emerging evidence is discussed that suggests the involvement of redox mechanisms in the epigenetic control of gene expression, which seems to be implicated in the heritable features of plant tolerance.

Tolerance, cross-tolerance, and ROS

Stress acclimation by priming

Plants have evolved a number of strategies to grow and reproduce in environmental contexts showing different physico-chemical parameters. These strategies involve morphological and metabolic adaptive mechanisms, depending on the acquisition of specific genetic traits. Therefore, the adaptation of plants to different environments is part of the evolutionary thrust and source of biodiversity. In this evolutionary framework, plant species differ in terms of sensitivity to specific adverse factors of abiotic and biotic nature. Intraspecific variability is also observed (Formentin *et al.*, 2018). However, both sensitive and tolerant plant species or varieties can acquire or increase their tolerance to a stress by priming.

Priming consists of exposing a plant to a sublethal stressful condition which makes the pre-treated plant more able to cope with a subsequent similar or even more serious adverse situation (Goswami *et al.*, 2013; Wang *et al.*, 2014*a*). Therefore, the effect of priming, inducing protective mechanisms in the pre-treated plants, is mainly referred to acclimation to stress.

A protective effect induced by a priming stimulus against a later stressful event has been described by Wang *et al.* (2014*b*); they subjected wheat plants to a mild drought priming event before anthesis, and then to severe drought during grain filling. Pre-exposure of wheat to drought resulted in alleviating the consequences of this stress during grain filling, thus reducing crop losses. An altered cell structure, expression of genes mainly encoding proteins related to photosynthesis, abscisic acid (ABA)-mediated responses, and redox enzymes, such as ascorbate peroxidase (APX), have been observed in primed plants compared with non-primed plants under drought during grain filling (Wang *et al.*, 2014*b*). The authors hypothesize that the higher APX activity and the increased amount of photosynthetic proteins in primed plants contribute to improve ROS scavenging capacity, to reduce lipid peroxidation and increase the photosynthetic rate in response to a later stress (Wang *et al.*, 2014*b*). In wheat plants, waterlogging priming increases the activity of enzymes of the ascorbate–glutathione (ASC–GSH) cycle and the gene expression for proteins related to ethylene biosynthesis, such as methionine synthase and *S*-adenosine methionine synthase (Wang *et al.*, 2016*a*). In this case, the increased ethylene biosynthesis induced by priming alleviates the negative effects of waterlogging by promoting stomatal opening, although the molecular mechanisms by which gene expression regulation occurs are still not clear (Wang *et al.*, 2016*a*).

A priming stimulus can derive from biotic and abiotic stresses. Plants that have been previously exposed to a sublethal stress can exhibit a more resistant behaviour in the same generation or in the following one. Indeed, cases of transgenerational priming are known (Luna *et al.*, 2012; Espinas *et al.*, 2016; Mauch-Mani *et al.*, 2017). Priming requires a lag phase that separates the priming stimulus from a later stress exposure. During the priming phase, changes occur at physiological, biochemical, genetic, and epigenetic levels, thus allowing plants to remember the previous stress and develop strategies to be better prepared for the subsequent stress episode (Beckers and Conrath, 2007; Hossain *et al.*, 2017). Recurrent exposures to sublethal stresses can result in an improved ability of plants to activate faster and stronger responses to subsequent stress conditions. This can help plants to achieve stress acclimation, also called stress memory (Bruce *et al.*, 2007; Hu *et al.*, 2015; Fleta-Soriano and Munné-Bosh, 2016; Antoniou *et al.*, 2017). The molecular basis of plant stress memory is still largely unknown. A growing number of pieces of evidence underline that the accumulation of signalling compounds, such as reactive species (ROS, reactive carbonyl species, and reactive nitrogen species), hormones, sugars, and transcription factors (TFs), and changes in the chromatin structure are induced by a priming stimulus and may mediate stress memory establishment (Conrath, 2011; Hossain *et al.*, 2017).

A reprogramming of the expression of genes related to drought tolerance, such as *RD29B* and *RD22*, has been observed in coffee plants exposed to recurrent drought episodes (Menezes-Silva *et al.*, 2017). These primed plants develop a differential acclimation that potentiates their protective mechanisms in order to cope with a subsequent stress

better than non-primed plants (Menezes-Silva *et al.*, 2017). Recently, another study further demonstrated that an extensive transcriptional reprogramming process underlies drought tolerance (Guedes *et al.*, 2018). A differential expression analysis conducted on two coffee plant clones, one drought tolerant and one drought sensitive, subjected to one and three drought cycles, has resulted in the identification of drought-responsive genes. Forty-nine drought-responsive genes were up-regulated after one and three drought exposures in a tolerant clone, while only one gene was induced in the drought-sensitive clone, where programmed cell death gene categories were enriched after the third exposure to water scarcity. The identified memory genes in the tolerant clone were mainly linked to ABA metabolism, protein folding, and stress induced by pathogens (Guedes *et al.*, 2018).

Thermo-tolerance is probably the most commonly described plant acclimation response to a stress (Mittler *et al.*, 2012). When the environmental temperature exceeds the optimal growing temperature by at least 10 °C, a heat response is activated in the plant. This mainly consists of an increase in the expression and activity of molecular chaperones and related TFs, named heat shock proteins (HSPs) and heat shock factors (HSFs), respectively. These components of the heat response are ubiquitous in eukaryotes. HSPs are used to preserve the cell proteins from irreversible denaturation or from acquiring wrong conformations that would lead to their removal. HSFs bind to conserved DNA sequences in the HSP gene promoter, named heat shock elements, thus activating their expression (Schöffl *et al.*, 1998).

Chromatin structure is also a determinant for gene expression regulation (Struhl and Segal, 2013; Zentner and Henikoff, 2013), and epigenetic regulation has also been suggested to play a key role in plant acclimation to abiotic stresses although the molecular mechanisms underpinning this regulation are still not clear (Chinnusamy and Zhu, 2009; Struhl and Segal, 2013). In Arabidopsis exposed to heat stress, the accumulation of H3K4 tri- and dimethylation at memory-related loci is required for the maintenance of acquired thermotolerance (Lämke *et al.*, 2016). The increase in H3K4 methylation is dependent on the HSFA2 TF and it correlates with a sustained induction of gene expression (Lämke *et al.*, 2016). In hemp and blue mustard plants primed by cold exposure, epigenetic modifications regulate plant gene expression to cope with various environmental stresses. In these plants, changes in chromatin state and alterations in DNA methylation were found (Mayer *et al.*, 2015; Song *et al.*, 2015). Another example comes from genome-wide DNA methylation analysis of turnip leaves. This analysis shows that cold acclimation induces up- and down-regulation of the methylation levels depending on the genomic region considered. This epigenetic mechanism influences gene expression in primed plants (T. Liu *et al.*, 2017). In the alpine subnival plant *Chorispora bungeana*, up-regulation of ADH1 is associated with a strong tolerance to cold stress. The authors found that ADH1 gene expression is regulated by epigenetic modifications especially H3K9 acetylation and H3K4 trimethylation (L. Liu *et al.*, 2017). In plants, trimethylation of histone H3 lysine 4 (H3K4me3) is highly linked to active transcription (Zhang *et al.*, 2009). Transcriptional memory following drought stress has also been associated with enhanced H3K4me3 levels that are required for efficient elongation of transcription, perhaps through RNA polymerase II stalling (Ding *et al.*, 2012).

The expression of HSFs and HSPs is also induced by other stressful conditions, such as anoxia and salinity, suggesting the role of these proteins in cross-tolerance mechanisms (Banti *et al.*, 2008; Fu *et al.*, 2016). In fact, plants primed to one kind of stress also become more tolerant toward other types of stress, suggesting that plant responses activated by different situations share common molecular players (Hossain *et al.*, 2017).

Exposure of plants to cold and heat priming can result in an increased tolerance to numerous biotic and abiotic stresses (Chou *et al.*, 2012; Zhang *et al.*, 2013; Faralli *et al.*, 2015). Tomato plants pre-treated with mild cold, paraquat, and drought are better prepared to respond to more severe subsequent chilling, photooxidative, and drought stresses, respectively (Zhou *et al.*, 2014). In wheat, HSPs are strongly induced by heat and/or drought priming, with the result of ameliorating plant tolerance to a post-anthesis high-temperature stress (Zhang *et al.*, 2016*a, b*). Consistently, overexpression of specific HSPs confers tolerance to a wide range of abiotic stresses. In Arabidopsis, the constitutive expression of HSP70 from chrysanthemum confers improved tolerance to drought, heat, and salt stresses (Song *et al.*, 2014). Transgenic rice plants overexpressing OsHsp17.0 and OsHsp23.7 display higher tolerance to drought and salt stress compared with control plants, thus suggesting that OsHsp17.0 and OsHsp23.7 play a key role in acclimation to salt and drought stresses (Zou *et al.*, 2012). Moreover, Arabidopsis plants overexpressing HsfA1a showed enhanced tolerance to diverse stresses by up-regulation of HSP gene expression (Qian *et al.*, 2014).

miRNAs also play a key role in the priming-induced responses under various abiotic and biotic stresses (Stief *et al.*, 2014; Zhang, 2015; Shriram *et al.*, 2016). Several studies show that various stresses, such as drought, salinity, heavy metals, and high and low temperature, significantly alter miRNA expression (Jia *et al.*, 2009; Kong and Yang, 2010; Barrera-Figueroa *et al.*, 2011; Li *et al.*, 2011; Wang *et al.*, 2011; Kong *et al.*, 2014; Wu *et al.*, 2017). miRNAs negatively regulate the expression of specific target genes at the post-transcriptional level through base pairing with complementary mRNA targets, in particular those coding for TFs (Jones-Rhoades *et al.*, 2006; Nigam *et al.*, 2015; Zhang, 2015). miRNAs are not always involved in enhancing the acclimation of plants to stress. Their role is still not entirely clear, and numerous studies mainly suggest that they have versatile roles depending on the stress and plant genotype (Zhang, 2015; Shriram *et al.*, 2016). In Arabidopsis, miR408 overexpression determines higher tolerance to salinity, cold, and oxidative stress, but also enhanced sensitivity to drought and osmotic stress (Ma *et al.*, 2015). The expression of miR156, miR159, miR169, miR319, miR393, and miR397 has been reported to be significantly increased in Arabidopsis exposed to salt stress, whereas the expression of miR398 is significantly inhibited (Liu *et al.*,

2008). Salinity stress inhibits the expression of miR156 in maize (Ding *et al.*, 2009) while its expression is induced in Arabidopsis (Liu *et al.*, 2008). In common bean, the participation of miR1514a during drought has been recently revealed by Sosa-Valencia *et al.* (2017). miR1514a shows differential expression levels in response to drought and targets the mRNA coding for NAC TFs in order to mediate its cleavage in roots (Sosa-Valencia *et al.*, 2017). Moreover, a transcriptome analysis of transgenic hairy roots with a higher and lower miR1514a content shows that the expression of several genes related to metabolism, morphogenesis, and stress responses is affected, therefore suggesting that their expression is regulated by the NAC TF (Sosa-Valencia *et al.*, 2017). Transgenic plants overexpressing specific miRNAs have altered ability to cope with a subsequent stress. In creeping bent-grass, the overexpression of rice primary miR528 (pri-miR528) induces an enhanced tolerance to salt stress and N deficiency. In these plants, the improved salt stress tolerance is linked to increased water retention, maintenance of cell membrane integrity, improved capacity to modulate ionic equilibrium, and control of redox homeostasis by regulating catalase (CAT) and ascorbic acid oxidase (AAO) activities (Yuan *et al.*, 2015).

ROS involvement in cross-tolerance

One priming effect is enhancement of antioxidative cellular systems (Li *et al.*, 2014; Wang *et al.*, 2014*a*). It is largely accepted that stressful conditions promote the overproduction of ROS with a subsequent change in cellular redox balance (Halliwell 2006; Foyer and Noctor, 2016). Due to their oxidative nature toward different cell components, ROS were originally considered as toxic compounds causing severe cell injuries ultimately resulting in cell death. Today, it is clear that ROS also have a signalling mode that triggers defence responses, probably because aerobic organisms, which are inevitably involved in ROS production, have evolved the ability to use these unwanted chemical species as useful molecular signals (De Gara *et al.*, 2010). Plants also possess ROS-generating systems, such as the respiratory burst oxidase homologues (RBOHs), which belong to a family of plasma membrane enzymes with NADPH oxidase activity. RBOH activation occurs under abiotic and biotic stress, leading to the production of superoxide anions ($O_2^{\cdot-}$) which are dismutated to hydrogen peroxide (H_2O_2) and oxygen within the apoplastic compartment (Sirichandra *et al.*, 2009; Drerup *et al.*, 2013). RBOH-dependent ROS production is involved in stress acclimation (Zhou *et al.*, 2014). Consistently, Arabidopsis double mutants defective in RBOHD1-RBOHF1 and RBOHD2-RBOHF2, show reduced ROS production, and, in turn, a decreased tolerance to salt stress compared with wild-type plants (Ma *et al.*, 2012). In tomato, the activation of *Sl*RBOH1 under high CO_2 conditions increases the H_2O_2 level in the vascular system and apoplast in the shoot. In turn, H_2O_2 induces the expression of salt-responsive genes, positively related to salt tolerance. Consistently, high CO_2-pre-treated tomato plants were more tolerant to salt stress compared with non-primed plants. The high CO_2-primed plants showed increased photosynthetic efficiency, reduced transpiration, and minor accumulation of Na^+ in the shoot, thus preserving a more physiological Na^+/K^+ rate. On the basis of these results, the authors hypothesized that under increased CO_2 availability, H_2O_2 produced by *Sl*RBOH1 activation could reduce stomatal conductance, also ameliorating the plant water balance. Consistently, *Sl*RBOH1 silencing suppressed the increased salt tolerance induced by high CO_2 (Yi *et al.*, 2015).

Several RBOHs are involved in signalling pathways, activated by abiotic as well as biotic stress (Ben Rejeb *et al.*, 2015; Li *et al.*, 2015; Liu and He, 2016; Wang *et al.*, 2016*b*; Y.J. Wang *et al.*, 2016; He *et al.*, 2017). They are, therefore, good candidates as cross-tolerance players.

Apoplastic H_2O_2, produced as a consequence of RBOH activation, is frequently found to be associated with an increase in cytosolic Ca^{2+} concentration. We will not look deeply into many aspects of Ca^{2+} signalling that have been discussed extensively in numerous recent reviews (Edel and Kudla, 2016; Kmiecik *et al.*, 2016; Ranty *et al.*, 2016; Gaupels *et al.*, 2017). We focus on highlighting a number of particularly important points in the context of the bidirectional interaction between ROS and calcium signalling pathways needed to modulate cellular responses to biotic and abiotic stresses. To date, two Ca^{2+} channels at the plasma membrane have been identified to be peroxide responsive: the Ca^{2+}-permeable Stelar K^+ Outward Rectifier (SKOR) (Gaymard *et al.*, 1998) and the annexins. Annexin 1 (ANN1) has been recently characterized in Arabidopsis roots as a Ca^{2+} transport protein involved in regulating the root epidermal responses to high extracellular H_2O_2, thus placing AtANN1 as a component of the H_2O_2 signalling (Richards *et al.*, 2014). At the level of the whole root, AtANN1 mediates the epidermal Ca^{2+} uptake and K^+ efflux (Laohavisit *et al.*, 2012). Mutants with loss of function of AtANN1 showed altered Ca^{2+} and K^+ fluxes in root epidermis and impaired transcriptional response under exogenous H_2O_2 (Richards *et al.*, 2014).

Under drought conditions, H_2O_2 accumulation in the apoplast activates Ca^{2+} channels, and the consequent cytosolic Ca^{2+} peak further activates RBOH proteins, thus triggering an amplification loop in ROS–Ca^{2+} signalling and promoting ABA-induced stomatal closure (Drerup *et al.*, 2013). Moreover, the rise in Ca^{2+} cytosolic concentration triggers the activation of the vacuolar ion channel TWO PORE CHANNEL (TPC1) that can, directly or indirectly, lead to the release of Ca^{2+} from the vacuole, thereby further amplifying the RBOH activation (Evans *et al.*, 2016; Gilroy *et al.*, 2016).

RBOH proteins are characterized by Ca^{2+}-binding EF-hand motifs in their N-terminal regions (Oda *et al.*, 2010; Kadota *et al.*, 2015). Mutational studies on RBOH proteins showed that Ca^{2+} binding on these EF-hand motifs is required for ROS production (Ogasawara *et al.*, 2008; Kadota *et al.*, 2015). Regulation of RBOH proteins by Ca^{2+} can occur not only by direct binding of Ca^{2+} to EF-hand motifs, but also by post-translational modifications catalysed by different kinases, such as the OPEN STOMATA1 (OST1), Ca^{2+}-dependent protein kinases (CPKs), and calcineurin B-like

(CBL)-interacting protein kinases (CIPKs) (Kurusu *et al.*, 2015). For instance, in Arabidopsis, CPK5 was recently shown to phosphorylate Ser148, Ser163, and Ser347 of RBOHD in a Ca^{2+}-dependent manner and regulate its activity (Dubiella *et al.*, 2013). In rice, the role of OsCPK17 in cold stress tolerance has recently been studied (Almadanim *et al.*, 2017). A precise regulation of OsCPK17 gene expression is critical for proper rice responses to cold stress. An example of this is the lower tolerance to cold stress by both knockout and overexpressing plants compared with the wild type and an RNAi line (Almadanim *et al.*, 2017). Additionally, OsCPK17 activity depends on its structural rearrangement induced by calcium binding and on its phosphorylation state (Almadanim *et al.*, 2018).

Apoplastic H_2O_2, produced as a consequence of RBOH activation, may also be responsible for triggering the mitogen-activated protein kinase (MAPK)-dependent phosphorylation cascade which leads to the expression of ROS-responsive genes under stress (Zhou *et al.*, 2014; Liu and He, 2017; Song *et al.*, 2018). In particular, to give some examples, in *Solanum lycopersicum*, MAPK1 and 2 seem to control the expression of cytosolic APX (cAPX), glutathione reductase 1 (GR1), catalase 1 (CAT1), and Cu/Zn superoxide dismutase (SOD), and consequently acclimation to chilling conditions (Zhou *et al.*, 2014), whereas MAPK5 and 6 control the expression of Cu/Zn-SOD under high light and of FeSOD under salt in Arabidopsis (Liu and He, 2017).

Managing ROS levels by the modulation of producing and scavenging systems can shift the role of these reactive species from toxic molecules to crucial messengers, putatively involved in cross-tolerance. In fact, ROS themselves are reported to induce antioxidant protective mechanisms under stressful conditions. A crosstalk between ROS signalling and heat stress responses has also been found. In particular, HSP expression seems to require H_2O_2. Similarly, genes coding for redox enzymes, such as APX1/2 of Arabidopsis, possess heat shock elements actively bound by HSFs under oxidative conditions (Miller and Mittler, 2006; de Pinto *et al.*, 2015). Therefore, the regulation of gene expression under stress could also be mediated by the activation of specific TFs subjected to redox control.

Stress-dependent and controlled alterations of cell redox balance can be transmitted by thiol–disulphide switch mechanism operated by thioredoxins (Trxs). Trxs are proteins presenting two cysteines in their active site causing the reduction of target proteins. The reduced form of Trxs is then regenerated by NADH- or ferredoxin-dependent Trx reductases. Thus, these proteins participate in the signalling network where redox signals, comprising ROS and redox balance sensors, are perceived and transmitted (Sevilla *et al.*, 2015). In this context, Trxs seem to mediate the transmission of redox signals at different levels. NONEXPRESSOR PATHOGENESIS-RELATED GENE 1 (NPR1) is a classic example of protein regulated by thiol switch under stressful conditions. In particular, NPR1 is considered the master regulator of the expression of defence genes under pathogen challenge identified in Arabidopsis. NPR1 activity is under a complex redox regulation. In the cytosol, NPR1 is present in its inactive oligomeric form built by intermolecular disulphide bonds (Mou *et al.*, 2003). The formation of the oligomeric form of NPR1 seems to be promoted by *S*-nitroso-glutathione (GSNO, cellular NO donor)-dependent *S*-nitrosylation (Tada *et al.*, 2008), whereas, the activation of NPR1 depends on its monomerization that occurs by a thiol–disulphide switch catalysed by Trxs (probably TRX-*5h* and Trx-*3h* in Arabidopsis; Tada *et al.*, 2008). In its monomeric form, NPR1 enters the nucleus where it activates TGACG motif-binding factor 1 (TGA1) which binds DNA, activating the expression of PR proteins involved in the systemic acquired resistance during plant–pathogen incompatible interaction (Mou *et al.*, 2003). TGA1 also seems to be redox regulated by GSNO-dependent *S*-nitrosylation. In particular, NO seems to increase TGA1 DNA binding activity and NPR1–TGA1 interaction (Lindermayr *et al.*, 2010).

Another protein regulated by a thiol–disulphide switch is an Apetala 2-type TF (Rap 2.4a). Rap 2.4a binds DNA when it is in dimeric form, whereas it is released from DNA in oligomeric form. The transition between dimeric and oligomeric forms seems to be mediated by the cellular redox status. Rap 2.4a controls the expression of chloroplast proteins, encoded by nuclear genes. Among these proteins, 2-Cys peroxiredoxin A, thylakoid APX (tAPX), and stromal APX (sAPX) have been identified, thus suggesting a role for Rap 2.4a in sensing and adjusting cell redox balance (Shaikhali *et al.*, 2008).

All the findings reported above strongly suggest that the cross-tolerance molecular network includes redox partners. Direct experimental evidence of ROS involvement in acclimation processes leading to acquired tolerance has been clearly shown by priming plants with H_2O_2 (Hossain *et al.*, 2015). H_2O_2 was the first to be considered as the main ROS involved in signalling pathways, because of its ability to cross biological membranes by diffusion or through aquaporins, and its relative high half-life in the cellular environment (1 ms). However, recently, other ROS have also been shown to be implicated in the signalling pathways activated by plants against stress (Kim and Apel, 2013; Carmody *et al.*, 2016). Therefore, a specific ROS signature can characterize plant responses to different stressful conditions, also determining different fates.

In order to reveal the mechanisms activated by plants in complex environmental situations, several studies have reported the effects of plant exposure to combined stresses (Suzuki *et al.*, 2014). Although not all stress combinations have a positive effect on plant tolerance, experimental evidence has revealed that the simultaneous imposition of multiple stresses on plants triggers the expression of specific patterns of genes compared with those observed when plants are exposed to a single stress (Prasch and Sonnewald, 2013; Rasmussen *et al.*, 2013; Rivero *et al.*, 2014; Suzuki *et al.*, 2014). The redox regulation of the stress-induced metabolic rearrangement could thus play a significant role in reprogramming gene expression by activating different routes depending on the kind, amount, timing, and site of production of ROS and their redox signals. This plasticity of the plant cell redox signalling network could be crucial in establishing protective mechanisms promoting cross-tolerance.

Redox regulation of nuclear gene expression: the role of ROS in the retrograde pathways involved in plant stress responses

Adverse environmental conditions lead to metabolic impairment in the exposed plant cells. Briefly, this impairment is generally characterized by the inhibition of protein synthesis and the subsequent reduction in protein turnover, restriction of the photosynthetic capability, and compromised/deregulated oxidative metabolism. The consequent increase in ROS production mainly occurs in chloroplasts and mitochondria. These organelles share common metabolic features, including pathways involving electron flow chains and a high concentration of oxygen which make mitochondria and chloroplasts prone to ROS release. Both organelles also have a prokaryotic origin, which confers on them specific genetic traits. During evolution, the majority of genes belonging to the genome of ancestral prokaryotes have been transferred to the nuclear genome of the derived plant cell, thus requiring a co-ordinated molecular trafficking between the nucleus, chloroplasts, and mitochondria. This trafficking occurs in an anterograde direction, from nucleus to cytosol, and finally to mitochondria or chloroplasts, providing the required proteins to these latter subcellular compartments. In addition, in the retrograde direction, it controls the expression of nuclear genes by the release of signals from plastids and mitochondria into the cytosol (Woodson and Chory, 2008).

Specific retrograde pathways are activated in response to stress involving the ROS produced in mitochondria or chloroplasts and newly discovered redox sensors. The molecular players in these retrograde pathways seem to be commonly involved in plant responses activated by different stresses, thus suggesting their role in cross-tolerance. This strengthens the theory that these organelles have developed the ability to use oxygen-derived undesired metabolites to send signals, thereby triggering metabolic responses aimed at protecting plant cells against fatal environmental injuries. Chloroplasts and mitochondria have thus moved from being major ROS-producing sites to being the main subcellular compartments involved in redox sensing and gene expression re-organization in response to specific stimuli.

Redox-regulated retrograde pathways in chloroplasts

The phosphorylation state of light-harvesting complex II (LHCII) components as well as of PSI and PSII core proteins is responsible for the functional redistribution of light energy between the two photosystems. Under stressful conditions, this post-translational protein modification appears to lead to a possible modulation of the singlet oxygen ($^1O_2$)/$O_2^{\cdot-}$ (and consequently H_2O_2) ratio, with a regulated effect on the expression of specific gene patterns. As SNT7 kinase is responsible for the maintenance of the steady-state phosphorylation of LHCII proteins, it has been suggested as a new component of chloroplastic retrograde signalling (Tikkanen *et al.*, 2012).

Since metabolic impairment caused by stress can lead to redox-dependent organelle dysfunction, pharmacological and genetic approaches capable of disrupting physiological processes have been used to investigate the involvement of redox signals in the activation of mitochondrial and chloroplastic retrograde pathways (Maruta *et al.*, 2012; Broda and Van Aken, 2018). In fact, as a consequence of chloroplast dysfunction, nuclear genes coding for photosynthesis components were inhibited. In line with this, *gun* (genome uncoupled) mutants have been identified as retrograde defective mutants in which the expression of nuclear genes coding for functional plastidial proteins is independent of the chloroplast functional state (Koussevitzky *et al.*, 2007; Tarahi Tabrizi *et al.*, 2016).

An increasing body of evidence suggests that $^1O_2$ and H_2O_2 produced within the chloroplast under stress control a different subset of nuclear genes. $^1O_2$ is produced by the energy transfer at the PSII level when the energy dissipation systems of chloroplasts are not able to limit the formation of the chlorophyll triplet state. The energy of this excited chlorophyll passed onto molecular oxygen with the subsequent production of this highly reactive ROS (Holt, 2005; Halliwell, 2006). Therefore, excessive light conditions trigger the increased production of $^1O_2$. However, different stresses affecting photosynthetic electron transport can potentially lead to an overproduction of $^1O_2$ within chloroplasts, thus making PSII prone to photo-inactivation (Apel and Hirt, 2004). $^1O_2$ signalling has been implicated in incompatible plant–pathogen interactions as well as heat responses (Grun *et al.*, 2007; Lin *et al.*, 2014; Fig. 1A).

Since $^1O_2$ has a very short life (4 μs in aqueous solution), it is expected that this ROS regulates gene expression under stress by modulating other intermediate signals. Likewise, it has also been proposed that carotenoid oxidative products determined by $^1O_2$ accumulation, such as β-cyclocitral and dihydroactinidiolide, work as the intermediate retrograde signals originating in the chloroplast. Being a volatile compound, the role of β-cyclocitral in systemic acquired acclimation under high light has also been proposed (Carmody *et al.*, 2016). The expression of genes required for systemic acquired acclimation thus seems to be mediated by $^1O_2$ signalling more than by H_2O_2 control (Carmody *et al.*, 2016; Fig.1A).

The investigation of Arabidopsis *flu* mutants, which accumulate the photo-sensitizer protochlorophyllide, an intermediate of the chlorophyll biosynthetic route, also led to the identification of another $^1O_2$-dependent retrograde signalling pathway. $^1O_2$-mediated signals seem to be transmitted to EXECUTOR1 and 2 (EX1 and EX2), two proteins present in the chloroplast envelope. The function of these proteins has not been clearly demonstrated (Kim and Apel, 2013). However, they may be sensors of the $^1O_2$ produced within the chloroplast, which transmits a signal to the nucleus, thus activating the expression of defence genes or activating programmed cell death (de Pinto *et al.*, 2012; Tarahi Tabrizi *et al.*, 2016; Fig. 1A). In line with this, in the double mutants EX1 and EX2, the expression of nuclear defence genes induced by $^1O_2$ is suppressed (Lee *et al.*, 2007).

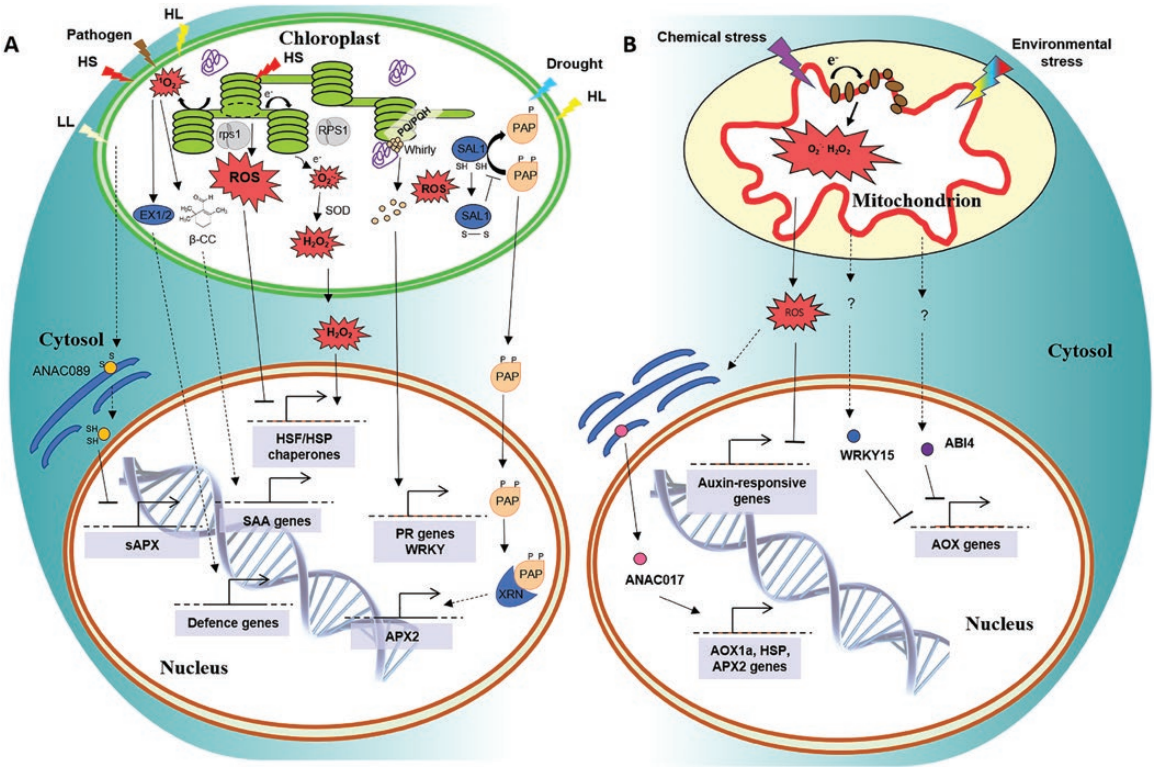

Fig. 1. Redox control of retrograde pathways involved in plant defence responses. (A) Redox-regulated retrograde pathways in chloroplasts. The picture reports the main sites of ROS production in chloroplasts under different stressful conditions. The regulation of nuclear gene expression by ROS and ROS-derived signals involved in retrograde pathways is reported. (B) Redox-regulated retrograde pathways in mitochondria. The picture reports retrograde pathways triggered by mitochondrial ROS. In particular, ROS signals produced in mitochondria under complex environmental situations can also be induced by chemical treatment, which causes mitochondrial dysfunction. ABI4, ABA-INSENSITIVE4; AOX, alternative oxidase; APX, ascorbate peroxidase; APX2, ascorbate peroxidase 2; EX1/2, EXECUTOR1 and 2; HL, high light; HS, heat shock; HSF, heat shock transcription factor; HSP, heat shock protein; LL, low light; PAP, 3'-phosphoadenosine 5'-phosphate; PQ/PQH, plasto-quinone redox state; PR genes, pathogen-related genes; ROS, reactive oxygen species; RPS1, ribosomal proteins S1; SAA, systemic acquired acclimation; sAPX, stromal ascorbate peroxidase; SOD, superoxide dismutase; XRN, 5' to 3' exoribonucleases; β-cc, β-cyclocitral.

Arabidopsis *snt7* knockout mutants also have an altered expression of ROS-related genes. Plasma membrane RBOHD, mitochondrial alternative oxidase (AOX), and cytoplasmic thioredoxin TRX5 are down-regulated, while the chloroplastic antioxidant enzyme monodehydroascorbate reductase 6 is up-regulated (Tikkanen *et al.*, 2012). This thus highlights that chloroplastic retrograde signalling influences the metabolic pathways of the whole cells and not only those related to the photosynthetic organelles. Interestingly, all these genes are regulated in the opposite way in Arabidopsis *flu* knockouts, where the $^1O_2$ signalling is altered. These differences in gene expression may depend on the altered H_2O_2 metabolism occurring in Arabidopsis *snt7* mutants (Tikkanen *et al.*, 2012), thus suggesting that H_2O_2 triggers signalling pathways that are antagonistic to those activated by $^1O_2$ (Laloi *et al.*, 2007).

Within the chloroplast, H_2O_2 derives from the dismutation of $O_2^{\cdot-}$, which is formed by univalent oxygen reduction taking place at the PSI level, where the electrons derived from water photolysis can be diverted to oxygen (Asada, 2006). $O_2^{\cdot-}$ and consequently H_2O_2 production is enhanced by abiotic and biotic stress (Foyer and Noctor, 2003; De Gara *et al.*, 2010).

Mutants defective in sAPX and tAPX led to the identification of genes activated or repressed by chloroplastic H_2O_2 (Miller *et al.*, 2007; Maruta *et al.*, 2012). In tAPX-silenced mutants, ROS-responsive genes were down-regulated under high light, thus suggesting that when ROS overcome a threshold value, their signalling role is impaired. In addition, in normal light conditions, the increased H_2O_2 level due to chloroplastic APX down-regulation acts as a negative regulator of the cold response and as a positive regulator of biotic stress response (Maruta *et al.*, 2012).

These findings strengthen the idea that a specific ROS signature is required for the activation of defence responses depending on the stress experienced by the plant, and that this ROS signalling mode is actuated by a tight and fine control of the cell redox state, at local and global levels, by the co-ordination of different oxidant and antioxidant systems. Curiously, the Arabidopsis TF ANAC089 seems to work in a retrograde pathway activated under low light which leads to the suppression of sAPX gene expression. ANAC089 is located in the endomembrane compartment in its inactive form. Reducing conditions seem to switch the disulphide bridge of inactive ANAC089 to sulphhydryl groups, thus determining the proteolytic release of this TF from the endomembrane system. This has been reported to be promoted under low light, when sAPX is expected to be less required (Klein *et al.*, 2012).

The most known genes activated by H_2O_2 are those coding for HSF/HSP and chaperones (Mittler *et al.*, 2004). Chloroplasts have been considered as the plant cell compartments mainly involved in heat stress sensing. The oxygen-evolving complex associated with PSII is a thermolabile system, the dissociation of which from PSII during heat stress impairs the photosynthetic electron flow (Sun and Guo, 2016).

Yu *et al.* (2012) identified an Arabidopsis chloroplast ribosomal protein S1 (RPS1), which seems to control the expression of thylakoid proteins. *Rps1* mutants show defective chloroplast membrane integrity and increased heat sensitivity. In wild-type plants, heat stress induced the expression of nuclear HSFA2, which is suppressed in *rps1*-defective mutants. Yu *et al.* thus argue that a disruption in the synthesis of thylakoid proteins occurring in *rps1* mutants is responsible for the loss of membrane integrity. This event would perturb ROS production and consequently redox-dependent retrograde signalling which leads to HSFA gene expression in wild-type plants under stress (Yu *et al.*, 2012).

During stress, the plastoquinone (PQ) redox state can be affected. Recently a family of multimeric proteins, named WHIRLYs, were proposed as the putative sensor of the PQ oxidative state. WHIRLYs are multimeric proteins simultaneously associated with thylakoid membranes and the chloroplast nucleoid. Changes in the PQ redox state seem to cause WHIRLY monomerization. In the monomeric form, WHIRLYs act as retrograde signals aimed at promoting the expression of defence genes, such as those coding for pathogenesis-related proteins. WHIRLYs also activate the expression of a complex class of TFs acting as positive and negative regulators of stress tolerance, named WRKY (Foyer *et al.*, 2014). These TFs work in a flexible multimeric form and thus can act as the activator or repressor of gene expression depending on the cluster built (Phukan *et al.*, 2016). Their modular behaviour probably makes these proteins prone to participation in a number of retrograde pathways involving both chloroplasts and mitochondria (Van Aken *et al.*, 2013).

Several putative retrograde signals correlated to oxidative stressful conditions have been identified in chloroplasts. However, the connections between redox impairment/signalling and retrograde pathways are still poorly identified, as the network in which they are involved is complex. Among the chloroplast retrograde signals involved in plant stress responses, the nucleotide 3'-phosphoadenosine 5'-phosphate (PAP) has been identified (Estavillo *et al.*, 2011). PAP accumulates under drought and high light conditions in plant leaves. PAP can restore ABA responsiveness in insensitive ABA mutants, promoting stomatal closure under drought.

PAP accumulation has been shown to be responsible for the up-regulation of ABA biosynthetic genes and ABA/Ca^{2+} signalling components (Pornsiriwong *et al.*, 2017). PAP levels are regulated by the phosphatase SAL1, which localizes in the chloroplasts and mitochondria of Arabidopsis. The *Sal1* mutant has been found to be resistant to drought and up-regulation of 25% of high-light responsive genes (Wilson *et al.*, 2009).

Interestingly, *sal1*-defective mutants have shown the constitutive expression of APX2, an inducible gene coding for a cytosolic H_2O_2 scavenger enzyme (Karpinski *et al.*, 1997). In line with this, under drought conditions, H_2O_2 accumulates less in the mutant tissues than in the wild type. This depends on a higher PAP accumulation in the mutant and suggests that PAP induces the expression of the APX2 gene under stressful conditions. PAP accumulation in *sal1* mutants also modulates the expression of plastid redox-associated nuclear genes. Given that PAP inhibits the activity of the nuclear enzymes 5' to 3' exoribonucleases (XRNs), it has been proposed as a mobile signal controlling gene expression through RNA catabolism.

Recently, SAL1 has been indicated as an oxidative stress sensor. Oxidative conditions caused SAL1 inhibition in the chloroplast of Arabidopsis. AtSAL1 is subject to a fine regulation by oxidative-dependent conformational changes, such as dimerization, disulphide bond formation, and thiol exchanges. It has also been suggested that the redox-buffering capability of the chloroplast, which depends above all on the glutathione redox state (GSH+GSSG/GSH), can also influence AtSAL1 activity by glutathionylation (Chan *et al.*, 2016).

Redox-regulated retrograde pathways in mitochondria

A common consequence of sublethal stressful conditions is the reduction in growth and biomass production. This is a direct consequence of the impairment of both photosynthesis and respiration, although this impairment does not occur to the same extent for the two processes. For example, both photosynthesis and respiration are reduced during drought, although plant cell respiration seems to be less affected (Atkin and Macherel, 2009). This is in line with the hypothesis that mitochondria assist chloroplast functions during drought-dependent photosynthesis inhibition (Flexas *et al.*, 2006). Mitochondria would thus continue to sustain the ATP required for sucrose biosynthesis and also export reducing equivalents, such as NADPH, which accumulate in the chloroplast as a consequence of the decreased photosynthetic efficiency. The decreased regeneration of oxidized pyridine nucleotides, the last electron acceptors of the photosynthetic electron flow, make the chloroplast more prone to ROS release under stress. Thus, due to their ability to drain reducing equivalents, mitochondria also control the chloroplast (and cellular) redox state, by counteracting ROS formation.

The ROS buffering of plant cells also depends on mitochondria for the synthesis of ascorbate (ASC), since it is one of its main soluble antioxidants. The last enzyme in the ASC biosynthetic pathway L-galactono-1,4-lactone dehydrogenase (GLDH) is located in the inner mitochondrial membrane and is responsible for cytochrome *c* reduction in the plant respiratory chain (Bartoli *et al.*, 2000). ASC biosynthesis is affected by respiratory inhibitory conditions, but is also enhanced by high light, suggesting the photoprotective role of this antioxidant (Smirnoff, 2000; Millar *et al.*, 2003; Talla *et al.*, 2011).

Although GLDH does not seem to be the regulatory step in ASC biosynthesis, it has been recently reported that an

allele of GLDH confers drought tolerance in wheat (J. Zhang *et al.*, 2016). Under stress, the rate of electron input exceeds the electron transfer through the respiratory pathway, leading to the over-reduction of the ubiquinone pool and consequently increasing the production of ROS, such as $O_2^{\cdot-}$ and H_2O_2 (Foyer and Noctor, 2003). Mitochondrial ROS suppress auxin-responsive genes, probably contributing to the inhibition of growth under environmental stress (Ivanova *et al.*, 2014), apart from the obvious growth inhibitory effect due to the impairment of ATP production occurring when ROS overproduction hinders the phosphorylation process. Taken together, these data strongly suggest that mitochondrial metabolism plays a key role in controlling the whole-plant cell redox balance. However, information on the involvement of mitochondrial ROS in retrograde signalling is scarce.

It has been suggested that different TFs, such as ABI4 and various components of NAC and WKRY classes, represent intermediate players in redox-mediated retrograde signals derived from mitochondria during different types of stress. Many of these TFs regulate the expression of alternative oxidase (AOX).

AOX up-regulation restricts ROS production in mitochondria. Interestingly, an increase in AOX expression not only maintains the functionality of the cytochrome *c* pathway, but also positively affects the chloroplastic metabolism under severe drought, probably by reducing the oxidative damage of the whole cells (Dahal and Vanlerberghe, 2017). Consistently, AOX activation has been involved in acclimation to high light, a condition possibly leading to an excess of reducing equivalent (Yoshida *et al.*, 2011).

The AOX promoter is under the negative control of the TF ABI4 (Giraud *et al.*, 2009; Fig. 1B). Arabidopsis *abi4* mutants have been identified due to their ABA-insensitive phenotype and are more sensitive to drought-induced oxidative stress (Finkelstein, 1994; Cheng *et al.*, 2011). In these mutants, the down-regulation of ABI4 gene expression makes AOX constitutively expressed, with the loss of its rotenone-inducible character. On the other hand, the absence of AOX1a induces increased sensitivity to high light and drought in Arabidopsis knockout plants. Knockout plants also show great alterations in the expression of genes coding for the components of cellular antioxidant systems, especially those localized in chloroplasts (Giraud *et al.*, 2008), thus further confirming a tight interplay between these two organelles. Given that the ABI4 TF is also involved in chloroplastic retrograde signalling (Sun *et al.*, 2011; León *et al.*, 2013), this further highlights the coordination between the metabolism of these two organelles and nuclear gene expression. The crosstalk between ABA and ROS signalling networks is also involved in plant acquired tolerance against multiple stresses (Suzuki *et al.*, 2016; Zandalinas *et al.*, 2016).

WRKY15 is a negative regulator of AOX expression. In plants that overexpress the TF WRKY15, hypersensitivity to salt stress has been induced (Vanderauwera *et al.*, 2012; Fig. 1B).

Mitochondrial dysfunction induced by antimycin A (inhibitor of complex III) causes the release of the Arabidopsis ANAC017 TF from endoplasmic reticulum membranes, leading to the up-regulation of the nuclear genes coding for AOX1a, HSPs, and APX2 (Van Aken *et al.*, 2016*a, b*; Fig. 1B). *Cis*-regulatory elements, named mitochondrial dysfunction motifs (MDMs), have been found in the promoters of genes regulated by conditions inducing mitochondrial dysfunction (chemical inhibition of the respiratory chain or mutants lacking or with a reduced level of mitochondrial proteins), which trigger mitochondrial retrograde regulation (MRR). ANAC013, another TF presumably located in the endoplasmic reticulum, binds these motifs, thus taking part in MRR. Moreover, the ANAC013 gene also contains an MDM, probably allowing autoamplification of its expression under mitochondrial perturbations. Interestingly, the overexpression of ANAC013 increases the tolerance of Arabidopsis plants to the oxidative stress induced by both methyl viologen, perturbing photosynthetic electron flow, and rotenone, an inhibitor of the respiratory chain (De Clercq *et al.*, 2013).

AOX is also up-regulated under different stressful conditions at the post-transcriptional level. Over-reducing conditions of the mitochondrial electron transfer chain activate AOX by promoting the conversion of its dimeric form into the active monomeric form as a consequence of the reduction of a functional disulphide bond (Day *et al.*, 1995). Experimental evidence suggests that AOX could be activated by a thiol–disulphide switch operated by Trxs (Martí *et al.*, 2009; Yoshida *et al.*, 2013). Interestingly, Daloso *et al.* (2015) demonstrated that in *Arabidopsis thaliana* the mitochondrial Trx system *in vivo* regulates the activity of different enzymes of the tricarboxylic acid (TCA) cycle. In particular, the mitochondrial Trx*o*1 deactivates fumarase and succinate dehydrogenase, and curiously activates the cytosolic citrate lyase involved in fatty acid metabolism. On the basis on these findings, the authors point to a role for mitochondrial Trxs as crucial mediators of mitochondria–cytosol crosstalk controlling carbon fluxes into the cell (Daloso *et al.*, 2015).

In pea, it has been shown that PsTrx*o*1 localizes in mitochondria and the nucleus under physiological conditions (Martí *et al.*, 2009). The overexpression of this Trx in TBY-2 cells increased their tolerance toward oxidative stress and promoted cell proliferation under standard conditions since this Trx interacts with a nuclear factor involved in DNA replication [proliferating cell nuclear antigen (PCNA); Ortiz-Espín *et al.*, 2015; Calderón *et al.*, 2017]. The high proliferative rate of TBY-2-transformed cells also seems to depend on GSH accumulation in their nuclei. This result is consistent with findings that the regulation of the nuclear redox state works in plant growth and stress responses (Locato *et al.*, 2015).

Other mitochondrial proteins possibly involved in regulation of gene expression under stress are AtCOX17-1/2. AtCOX17-1 and ATCOX17-2 are mitochondrial proteins, probably located in the intermembrane space, which are involved in cytochrome *c* oxidase assembly by assisting Cu insertion. The expression of AtCOX17 proteins is induced by abiotic (drought, salt, UV-B, and high light) and biotic (phytophagy and *Pseudomonas*) stresses, suggesting a role in cross-tolerance. Moreover, AtCOX17-overexpressing plants are

more tolerant to salt stress and consistently up-regulate salt-responsive genes, whereas silencing of AtCOX17 reduces the expression of stress-responsive genes, among which are TF genes, such as NAC and WRKY, and redox genes (CAT and AAO). Consistently the amount of ROS increased in these knockout plants under salt stress. This experimental evidence suggests a role for this protein in cross-tolerance.

Among oxidative stress-related genes, those involved in response to chloroplast dysfunction (observed in *flu* mutants and induced by methyl viologen treatment) are also down-regulated. Interestingly, MRR genes induced by chemical inhibition of the respiratory chain (by treatment with antimycin A and rotenone) are also down-regulated in *atcox17*-silenced plants. AtCOX17 expression is induced in *abi-4*-defective mutants, as also occurs for AOX1a, a marker of retrograde signalling induced by mitochondrial dysfunction. Consistently, MRR genes showed a similar expression trend in *aox1a*-defective mutants and *atcox17*-silenced plants. All these findings suggest that the lack of AtCOX17 proteins might reveal an overlapping modulation of genes induced by chloroplast and mitochondrial oxidative stress acting downstream in retrograde pathways (Garcia *et al.*, 2016).

Another player involved in the co-ordination between respiration and photosynthesis under stress is uncoupling protein 1 (UCP1). UCP1 is a mitochondrial protein, which is also involved in mitochondria–nucleus communication during stress. UCP1 is located in the inner mitochondrial membrane, where it works in dissipating the proton gradient between the mitochondrial intermembrane space and the matrix, thus reducing ATP production. The up-regulation of UCP1 has been associated with increased tolerance toward multiple stresses, suggesting a role in cross-tolerance. In particular, UCP1 overexpression increased tolerance to drought and salt in Arabidopsis, salt, drought, hyperosmotic, cold, and oxidative stress in *Nicotiana tabacum*, and heat shock and pathogens in tomato (Chen *et al.*, 2013, Barreto *et al.*, 2014, 2017).

The transcriptome of UCP1-overexpressing tobacco plants mimics that observed under hypoxic conditions in the wild type. Interestingly, among the up-regulated genes, there are those coding for chloroplast proteins. This is probably a mechanism actuated by transgenic plants to respond to the increased energy demand, due to the drop in the mitochondrial ATP production caused by UCP1 up-regulation. In particular, transcripts of chloroplast proteins involved in lipid metabolism are up-regulated, probably in order to re-use the excess acetyl-CoA, accumulated when the TCA cycle is inhibited in mitochondria, as occurs under oxygen deprivation. This would have the effect of releasing alternative energetic substrates (Barreto *et al.*, 2016). Moreover, since UCP1 overexpression resembles hypoxia, stomatal conductance could also be modulated to promote oxygen uptake, consequently increasing the CO_2 level into the plants, and relieving the inconvenience of the photosynthetic block caused by drought (Barreto *et al.*, 2017). Indeed, UCPs and AOX down-regulation reduce photosynthetic efficiency (Dahal *et al.*, 2014, 2015). The overexpression of UCP1 also determines the up-regulation of genes required for mitochondrial biogenesis and antioxidant machinery, consistent with reduced ROS accumulation observed in transgenic plants (Barreto *et al.*, 2014).

A genome-wide analysis revealed the existence of overlapping gene regulation under mitochondrial and chloroplast perturbations, common to the abiotic and biotic stress response. In particular, over a quarter of genes induced by mitochondrial perturbations are also up-regulated under chloroplast dysfunction. Among these genes, redox genes and WRKY have been found. However, despite the overlapping gene regulation, this study also showed that the expression of mitochondrial and plastid proteins encoded by nuclear genes is specifically regulated depending on the applied perturbation, which affects a specific class of organelles (Van Aken and Whelan, 2012).

Interplay between epigenetic mechanisms and redox metabolism in stress responses

Short- and long-term acclimation and adaptation processes are strategies enabling plants to survive in unfavourable environmental conditions. In addition to the retrograde pathways previously described, short-term strategies also include the rapid recovery of physiological cellular homeostasis altered after stress, while long-term strategies include transgenerational changes. Besides the onset of new genetic traits through breeding or genetic mutations leading to new varieties with increased tolerance against stressful conditions, plants can develop stable and heritable tolerance to a new stress without altering DNA sequences. This is possible through stable changes in the chromatin state that are able to regulate gene expression via epigenetic mechanisms. These changes can be correctly defined as epigenetic marks only if they are either meiotically or mitotically hereditable (Chinnusamy and Zhu, 2009). A wide range of epigenetic mechanisms have been described to date. These mechanisms include both post-translational modifications of histone proteins and chemical modifications of DNA. Growing evidence also indicates that RNAi-dependent silencing mechanisms are also involved in transcriptional or post-transcriptional gene expression regulation after plant exposure to stress (Li *et al.*, 2017). Some examples of epigenetic and RNAi mechanisms involved in stress responses have already been described in the section dedicated to stress acclimation by priming.

Many studies have revealed a close link between numerous epigenetic marks and redox metabolism through key intermediates, such as NAD, 2-oxoglutarate, FAD, and acetyl-Co A, which work as linkers between epigenetic processes and stress responses. Fluctuations in the concentration of these intermediates may have an effect on epigenetic signalling, leading to gene expression and phenotypic trait modifications. This aspect has been extensively investigated in animals and yeast, and some evidence also exists for plant systems.

DNA methylation

DNA methylation is an epigenetic mechanism that plays a role in transcriptional regulation in all eukaryotes. Generally,

methylation takes place on the cytosine base producing 5-meC. In addition, the local context of the methylation is crucial and may vary among different organisms (Bender, 2004; Law and Jacobsen, 2010; Cyr and Domann, 2011). In plants, DNA methylation occurs in the symmetric CG and CHG context (where H is A, C, or T) and in the asymmetric CHH context (Law and Jacobsen, 2010) mainly in transposons and other repetitive DNA elements (Zhang *et al.*, 2006). This epigenetic modification also plays an important role in gene expression regulation. In fact, the DNA methylation of promoter regions generally represses transcription initiation, while, at least in Arabidopsis, methylation within the gene body inhibits transcript elongation (Zilberman *et al.*, 2007). Environmental changes can cause the hypermethylation or hypomethylation of DNA (J. Liu *et al.*, 2015). Exposure of Arabidopsis plants to heat stress leads to an enhanced global methylation (Boyko *et al.*, 2010). A similar alteration occurs in cork oak (*Quercus suber* L.) grown at 55 °C (Correia *et al.*, 2013), while in cotton (*Gossypium hirsutum*), high temperature exposure significantly reduces the global methylation state (Min *et al.*, 2014). The DNA methylation pattern is maintained by two types of enzymes: DNA methyltransferases (DNMTs) and DNA demethylases. DNMT enzymes use *S*-adenosyl-methionine (SAM) as a methyl donor (Law and Jacobsen, 2010). Methionine is the precursor of SAM and is produced starting from folate which provides the 5-methyl-tetrahydrofolate moiety. The treatment of Arabidopsis plants with sulphamethazine, an inhibitor of folate biosynthesis, induces a reduction in the folate pool size causing a methionine deficiency with a consequent reduction in DNA methylation (Zhang *et al.*, 2012). The enzyme homologous gene silencing 1 (HOG1), which is involved in the synthesis of the methionine precursor, seems to be subject to redox modulation (Shen *et al.*, 2016; Fig. 2). This protein can in fact be *S*-nitrosylated and is a possible target of Trx and glutaredoxin, thus revealing a link between redox metabolism and epigenetic control (Shen *et al.*, 2016).

DNA demethylation also highlights the existence of a tight connection between the redox status and epigenetic control. The active removal of 5-methylcytosine from DNA is catalysed by four distinct enzymes, REPRESSOR OF SILENCING 1 (ROS1), DEMETER (DME), DME-like 2 (DML2), and

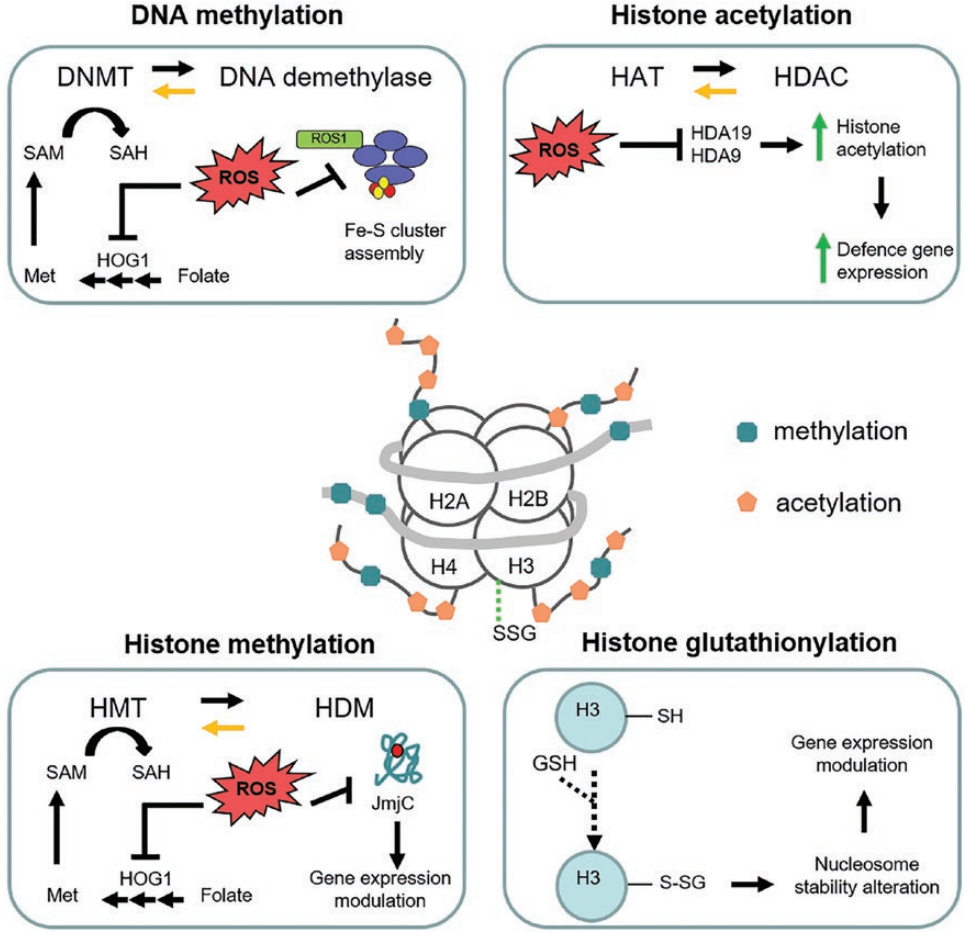

Fig. 2. Redox-regulated epigenetic mechanisms in plant stress responses. A schematic representation of nucleosome structure is reported: DNA is wrapped around each histone octamer protein. Epigenetic modifications are represented: histone acetylation and methylation, DNA methylation, and histone glutathionylation. The picture is focused on the connections between plant epigenetic mechanisms modulating nuclear gene expression and ROS signalling. DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; HOG1, homologous gene silencing 1; Met, methionine; ROS, reactive oxygen species; ROS1, REPRESSOR OF SILENCING 1; SAH, *S*-adenosyl-homocysteine; SAM, *S*-adenosyl-methionine.

DML3 (Zhang and Zhu, 2012; Wang *et al.*, 2016*c*). Recent studies demonstrate that ROS1 and DME require a direct interaction with the Fe–S cluster assembly machinery, which is highly susceptible to oxidation by ROS (Fig. 2). Their demethylase activity can consequently be altered by stress-derived oxidative conditions (Shen *et al.*, 2016).

Histone modifications

There are numerous types of well-characterized histone modifications, such as methylation, acetylation, phosphorylation, ADP-ribosylation SUMOylation, deimination, and ubiquitylation (Kouzarides, 2007).

Histone acetylation is considered as one of the principal epigenetic mechanisms responsible for chromatin regulation in plant cells. This post-translational modification, which occurs above all at lysine residues of the N-terminal tails of histone proteins, is catalysed by histone acetyltransferases (HATs) (which are responsible for the addition of acetyl groups) and histone deacetylases (HDACs) that catalyse their removal. Histone acetylation is generally associated with gene activation, since the HAT enzymes, by the transfer of acetyl groups, neutralize the positive charge of lysine residues, thus reducing the affinity of nucleosomes for DNA, leading to a more relaxed chromatin conformation (Vermaak *et al.*, 2003; Z. Wang *et al.*, 2014; Dhar *et al.*, 2015). In contrast, HDAC enzymes lead to a condensed chromatin state, thus resulting in gene expression repression (Chen and Tian, 2007). HAT isoenzymes use acetyl-CoA to acetylate lysine residues in all eukaryotic cells. HDACs do not generally require a cofactor for deacetylation; however, among these isoenzymes, sirtuin-like proteins are NAD^+-dependent deacetylases. A rearrangement of the histone acetylation status has been reported during plant growth and development, as well as in response to environment changes (Chen and Tian, 2007; Ma *et al.*, 2013; Rodríguez-Sanz *et al.*, 2014; Z. Wang *et al.*, 2014; H. Zhang *et al.*, 2016).

Many examples have been reported of the involvement of HDACs in the regulation of stress-related genes in different conditions, such as cold, salt, drought, and biotic stresses (Yuan *et al.*, 2013; Zheng *et al.*, 2016; Asensi-Fabado *et al.*, 2017; Ueda *et al.*, 2017), thus suggesting the possible involvement of these mechanisms in cross-tolerance. In addition, a connection with redox metabolism has been suggested in animals and yeast, as well as in plant systems (Shen *et al.*, 2016). In rice, only two sirtuin-like genes have been identified (OsSRT1 and OsSRT2). Rice plants overexpressing OsSRT1 have shown an enhanced tolerance to oxidative stress, while OsSRT1 RNAi induces H_2O_2 overproduction, DNA fragmentation, and cell death (Huang *et al.*, 2007).

These observations suggest that OsSRT1 may play a role in the modulation of the cellular redox state, altering the gene expression of redox-related genes probably through epigenetic mechanisms (Huang *et al.*, 2007; Shen *et al.*, 2016). HDA19 and HDA9 are two histone deacetylases described as being involved in biotic and abiotic stress responses (Chen and Wu, 2010; Choi *et al.*, 2012; Zheng *et al.*, 2016). HDA19 and HDA9 are oxidized upon treatment with salicylate and flg22, two elicitors of defence pathways, known to alter cellular redox homeostasis. This oxidation could reduce their activity, thereby enhancing histone acetylation and the expression of stress-responsive genes (P. Liu *et al.*, 2015; Fig. 2).

Histone methylation mostly occurs at lysine and arginine residues at the N-terminal tails. The location of methylated residues as well as the number of methyl groups for each residue can differ, thus causing a specific and differential functional effect. The context-dependent property of histone methylation is clearly evident in the case of the trimethylation of Lys4 of histone H3 (H3K4me3) which is strongly linked with active transcription when localized in the promoter region, while it is associated with transcriptional silencing when localized in gene bodies (Liang *et al.*, 2004; Tariq and Paszkowski, 2004; Liu *et al.*, 2010). Histone methyltransferase (HMT) and demethylase (HDM) are the enzymes that specifically methylate or demethylate histone residues, respectively (Liu *et al.*, 2010; Xiao *et al.*, 2016). HMTs are able to catalyse histone methylation using SAM as a methyl group donor, to form *N*-methyl protein adducts and *S*-adenosyl-homocysteine (SAH) as by-products (Thorstensen *et al.*, 2011).

Histone demethylation is catalysed by two different classes of enzymes: the jumonji C (JmjC) demethylases, which are Fe(II)- and 2-oxoglutarate-dependent dioxygenases, and FAD-dependent amino oxidase, including lysine-specific demethylase 1 (LSD1) (Chen *et al.*, 2011). There is a clear connection between histone methylation, energy metabolism, and cell redox balance in animals and yeast cells (Sundar *et al.*, 2013; Niu *et al.*, 2015; Guillaumet-Adkins *et al.*, 2017) and is also emerging in plants. The enzymes responsible for histone methylation in plants are sensitive to ROS produced in the cells under adverse conditions (Fig. 2). The activity of Fe(II)- and 2-oxoglutarate-dependent dioxygenase is assisted by ASC which maintains the ferrous iron state required for enzymatic catalysis and is inhibited by H_2O_2 (Farrow and Facchini, 2014).

In plants 2-oxoglutarate is produced by isocitrate dehydrogenase (ICDH). Different isoforms of ICDH have been described depending on their specific cofactor and subcellular localization. In Arabidopsis, double knockout mutants (*cat2*, cytosolic-*icdh*) show perturbation in redox homeostasis, the accumulation of oxidized glutathione, and induction of stress-related genes. These effects are enhanced in double *cat2* cytosolic-*icdh* mutants compared with *cat2* mutants, which suggests that cytosolic-ICDH could be involved in redox signalling linked to stressful conditions (Mhamdi *et al.*, 2010).

Many JmjC proteins have been reported to be responsive to plant exposure to stress by modulating the expression of stress-related genes, probably acting together with ROS which, generated during stressful conditions, lead to the establishment of a complex network of defence responses (Shen *et al.*, 2016). However, it is not clear whether the activity of JmjC proteins is directly altered by ROS.

Glutathione and epigenetic modifications

Glutathione (GSH) seems to be not only a powerful reductant and second messenger, but also a new post-translational

modifier of the histone code, capable of modulating the chromatin structure (García-Giménez *et al.*, 2013*b*). This reveals a new connection between epigenetic control and cellular redox homeostasis. Histone H3 can be *S*-glutathionylated in mammalian cells at Cys110, a highly conserved residue in mammals and plants, which alters the stability of nucleosomes and modulates the chromatin structure by decreasing the proportion of α-helices (García-Giménez and Pallardó, 2014; Fig. 2).

Protein glutationylation may also be involved in the regulation of cell cycle progression under stressful conditions in which GSH acts as a redox-sensitive epigenetic modulator (Diaz Vivancos *et al.*, 2010*a*; Locato *et al.*, 2015). The treatment of plant cells with the fungal toxin ophiobolin A leads to cell cycle arrest and alters GSH partitioning between the nucleus and cytosol. This treatment also determines a modified pattern of glutathionylated proteins, thus suggesting that the fungal toxin may affect GSH functions in the progression of the cell cycle, altering both the nuclear levels of these redox molecules and the GSH-dependent post-translational modifications (Locato *et al.*, 2015). In mammalian cells, the glutathionylation of H3 histone and of c-Jun, a subunit of the transcription factor AP-1, are two important post-translational modifications with an impact on cell proliferation (Klatt *et al.*, 1999; García-Giménez *et al.*, 2013*a*).

Finally, GHS can influence epigenetic processes, inhibiting the activity of the enzymes involved in the synthesis of SAM, which is used by DNA methyltransferases (DNMTs) and HMTs as a substrate for DNA and histone methylation, respectively (García-Giménez and Pallardó, 2014; García-Giménez *et al.*, 2017). Therefore, the modulation of GSH metabolism may control oxidative stress and epigenetic mechanisms (García-Giménez *et al.*, 2017). However, this still needs to be extensively investigated in plants.

Conclusions and new perspectives

In order to combat complex environmental conditions, plants have evolved the ability to actuate metabolic and morphological adaptive modifications. This involves the acquisition of a number of molecular pathways within plant cells, including an intricate network of primary signals, intermediates, and executors working at promoting defence responses synergistically or competitively. In this network, the fine control of the cell redox balance has a central role, as ROS themselves or their derived signals are involved in nearly all pathways activated by plants in response to stress.

ROS production and oxidative modifications of cell components during adverse conditions have been re-evaluated in terms of their signalling mode. Different redox signals (oxidants and antioxidants) and redox-dependent regulatory mechanisms, such as post-translational modifications (i.e. thiol switch, glutathionylation, and *S*-nitrosylation), as well as those controlling gene expression, have been implicated in plant responses to stress. However, the importance of the redox control on the various pathways activated by plants to protect themselves against stress still needs extensive investigation.

The aim of this review was to provide an update of the redox signalling mechanisms putatively implicated in cross-tolerance acquisition. The involvement of specific redox players is crucial in retrograde pathways controlling gene expression under various stressful conditions. In particular, stress-induced ROS with their derived signals are required in the activation of plant defensive strategies involving gene expression reorganization. In fact, the production of different ROS at specific cell sites activates the expression of specific patterns of genes under different adverse conditions. This strengthens the idea that plant cell redox control is crucial in plant tolerance acquisition, since ROS-dependent redox alterations permeate the signalling network, at different levels and with different mechanisms, leading to cross-tolerance.

The involvement of redox mechanisms in epigenetic modifications which confer transgenerational tolerance features may also provide an area for investigation related to cross-tolerance mechanisms. However, epigenetic control can also be considered as part of the genome-wide mechanisms which have also recently been correlated to complex phenotypes. For example, specific patterns of single nucleotide polymorphisms (SNPs), normally involving non-coding DNA sequences, have been correlated positively and negatively to plant tolerance to stress (Tian *et al.*, 2011). Likewise, stress priming can affect DNA methylation or the histone acetylation/methylation state, thus modifying gene expression. Whether these mechanisms are under redox control still needs to be demonstrated. However, experimental evidence highlights the effects of stress-derived oxidative conditions on epigenetic control in plants.

GSH, the main cell redox sensor, may also be involved in epigenetic mechanisms. Stress-dependent alterations in GSH subcellular partitioning seem to cause perturbation of the cell redox state responsible for cell cycle arrest (Locato *et al.*, 2015). Thus, glutathionylation of nuclear proteins, including histones, might affect the expression of genes coding for cell cycle regulators. A redox clock controlling cell cycle progression has been hypothesized in animals and plant systems (Diaz Vivancos *et al.*, 2010*b*; Chiu and Dawes, 2012).

The experimental evidence reported in this review also shows that the ROS network activated by stress also modulates the hormone signalling pathways controlling plant growth and development (Ivanova *et al.*, 2014). All these new findings place ROS and cell redox balance at the crossroads of the mechanisms controlling growth and survival in complex environmental situations.

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