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Review

Acquiring control: The evolution of ROS-Induced oxidative stress and redox signaling pathways in plant stress responses



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ABSTRACT

Reactive oxygen species (ROS) – the byproducts of aerobic metabolism – influence numerous aspects of the plant life cycle and environmental response mechanisms. In plants, ROS act like a double-edged sword; they play multiple beneficial roles at low concentrations, whereas at high concentrations ROS and related redox-active compounds cause cellular damage through oxidative stress. To examine the dual role of ROS as harmful oxidants and/or crucial cellular signals, this review elaborates that (i) how plants sense and respond to ROS in various subcellular organelles and (ii) the dynamics of subsequent ROS-induced signaling processes. The recent understanding of crosstalk between various cellular compartments in mediating their redox state spatially and temporally is discussed. Emphasis on the beneficial effects of ROS in maintaining cellular energy homeostasis, regulating diverse cellular functions, and activating acclimation responses in plants exposed to abiotic and biotic stresses are described. The comprehensive view of cellular ROS dynamics covering the breadth and versatility of ROS will contribute to understanding the complexity of apparently contradictory ROS roles in plant physiological responses in less than optimum environments.

1. Introduction

During the evolution of oxygenic photosynthesis about 2.4 billion years ago, reactive oxygen species (ROS) most likely appeared as unintended companions of aerobic life (Anbar, 2008). According to an estimate, about 1–2% of O₂ consumption in plants leads to ROS formation in various subcellular organelles such as chloroplasts (Asada, 2006), mitochondria (Sweetlove et al., 2002), peroxisomes (Corpas et al., 2017), and possibly other compartments. The most commonly produced ROS are superoxide (O₂^{•-}), hydrogen peroxide (H₂O₂), hydroxyl radical (•OH) and singlet oxygen (¹O₂) (Gill and Tuteja, 2010). Under physiological steady-state conditions, ROS are detoxified by various antioxidative defense mechanisms; nevertheless, excessive ROS generation may overwhelm the defense system, leading to oxidative stress, cell damage and eventually cell death (Halliwell, 2006).

The concept of ROS as merely damaging molecules has changed

recently to the current view that they act as universal signaling metabolites (Foyer et al., 2017). Recent studies suggest that ROS are produced purposefully to induce redox signals, which regulate a diverse array of cellular responses essential for life (Finkel, 2011). For instance, ROS-induced redox signaling in plants triggers a program of gene expression that helps maintain cellular redox homeostasis and progression of numerous basic biological processes related to cellular proliferation and differentiation. In addition, cell death—previously considered to be the consequence of ROS-induced oxidative stress—is now reported to be caused by ROS activating a programmed cell death (PCD) pathway (Dangl and Jones, 2001). Taken together, these reports indicate that ROS-induced redox signaling acts as an important regulator of various physiological responses.

The roles of ROS as oxidants and/or redox signaling components largely depends on a subtle balance between the production and detoxification of ROS in different subcellular organelles (Mittler, 2017).

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Abbreviations used

ABI	ABA insensitive 4	Met	methionine
AOX1	alternative oxidase 1	MetSO	methionine sulphoxide
APX	ascorbate peroxidase	MFA	monofluoroacetate
Arg	arginine	Mg-ProtoIX	Mg-Protoporphyrin IX
ASC	ascorbate	NADPH	nicotinamide adenine dinucleotide phosphate
At	<i>Arabidopsis thaliana</i>	NDPK2	nucleotide diphosphate kinase 2
ATP	adenosine triphosphate	NO	nitric oxide
CAT	catalase	OXI1	oxidative signal-induced kinase 1
³ Chl	chlorophyll triplet	O ₂	molecular oxygen
Cys	cysteine	O ₂ ⁻	superoxide radical
DCMU	3-(3,4-dichlorophenyl)-1,1-dimethylurea	¹ O ₂	singlet oxygen
DHA	dehydroascorbate	·OH	hydroxyl radical
DHAR	dehydroascorbate reductase	PCD	programmed cell death
DNA	deoxyribonucleic acid	PhANG	photosynthesis-associated nuclear genes
EX1/EX2	executer 1/2	PPR	pentatricopeptide-repeat
flu	fluorescent	PQ	plastoquinone
Gpx	glutathione peroxidase	PQH ₂	plastohydroquinone
GR	glutathione reductase	PQ ⁻	plastosemiquinone
GRX	glutaredoxin	PR	pathogenesis-related
GSH/GSSG	reduced/oxidized glutathione	PRX	peroxiredoxin
GSNO	S-nitrosoglutathione	PSI/II	photosystem I/II
GST	glutathione-S-transferase	PTP	protein tyrosine phosphatase
GUN1	genome-uncoupled 1	PUFA	polyunsaturated fatty acids
His	histidine	RNS	reactive nitrogen species
H ₂ O ₂	hydrogen peroxide	ROS	reactive oxygen species
Lys	lysine	RuBisCO	ribulose-1,5-bisphosphate carboxylase oxygenase
MAPK	mitogen-activated protein kinase	SOD	superoxide dismutase
MDA	malondialdehyde	STN7/8	chloroplast protein kinases involved in state transitions
MDHA	monodehydroascorbate	tAPX	thylakoid ascorbate peroxidase
MDHAR	monodehydroascorbate reductase	TCA	trichloroacetic acid
MDM	mitochondrial dysfunction motif	Thr	threonine
ME	methyl ester	Trp	tryptophan
		TRX	thioredoxin
		Tyr	tyrosine

This is firmly controlled by the entire redox-sensing and signaling networks that regulate the cellular ROS levels spatially and temporally by modifying the ROS production and detoxification mechanisms (Noctor et al., 2017). In this regard, inter-organellar crosstalk via retrograde (organelle-to-nucleus) or anterograde (nucleus-to-organelle) signaling pathways is very important. This crosstalk employs oxidants and antioxidants as flexible integrators of redox signals that are translated into acclimation responses (Chan et al., 2016).

Most reviews on ROS focused either on plant oxidative stress responses (Das and Roychoudhury, 2014; Gill and Tuteja, 2010), or ROS as universal signaling metabolites (Dietz et al., 2016; Mignolet-Spruyt et al., 2016; Noctor et al., 2017; Waszczak et al., 2018), and their role in plant stress tolerance (Choudhury et al., 2016; Kmiecik et al., 2016; Sharma et al., 2012; Sierla et al., 2013). However, a comprehensive appraisal of the available knowledge on cellular ROS dynamics covering the versatility of ROS is lacking. Therefore, this review provides a comprehensive overview of ROS chemistry, production sites and its cellular processing systems. This also discusses the ROS-induced redox regulatory networks, with particular emphasis on chloroplastic and mitochondrial retrograde signaling processes and their connections with the systemic signaling pathways in plants exposed to abiotic and biotic stresses. This review will help understanding the emerging complexity of apparently contradictory ROS roles in plant physiological responses in stress environments. This is also expected to promote the future research on ROS and redox regulation of stress acclimation in model plants and its subsequent translation to crop species.

2. The fundamentals of ROS generation in plants

Plants – like other aerobic organisms – benefit from oxygen, but at the same time face the challenge of maintaining an appropriate redox balance for their optimal growth and development in oxidizing environments (Sies et al., 2017). The molecular ground-state oxygen (O₂) is the most stable state and therefore harmless molecule. However, O₂ can oxidize various non-radicals by removing an electron, provided they have the same spin quantum number, that occupies the empty space in the π^* orbital (Fig. 1A) (Halliwell, 2006). Due to spin restriction (opposite spin; +1/2 and -1/2) caused by the same spin quantum, the unpaired electrons are sometimes transferred as a single electron at a time, and hence, are unlikely to facilitate a rapid reaction with non-radicals (Halliwell, 2006). Alternatively, the reactivity of O₂ with radicals may be very fast, generating different types of ROS (Elstner, 1982).

In higher plants, aerobic metabolism causes the production of ROS as byproducts, either by transfer of sufficient free energy capable of reversing the spin on any unpaired electron and thus producing ¹O₂, or during a sequential single electron reduction pathway of molecular O₂ to produce O₂⁻, H₂O₂ or ·OH (Fig. 1B) (Halliwell, 2006). Among these, ¹O₂ can exist in the sigma state (¹Σg O₂), and the delta state (¹Δg O₂) (Fig. 1A). The ¹Σg O₂ state, i.e. free radical, contains two unpaired electrons, which rapidly decays to the ¹Δg O₂ state (non-radical) - the most frequently encountered form (Fig. 1A) (Halliwell, 2006). Generally, ¹O₂ is a short-lived molecule (about 1–4 μs half-life) with a small

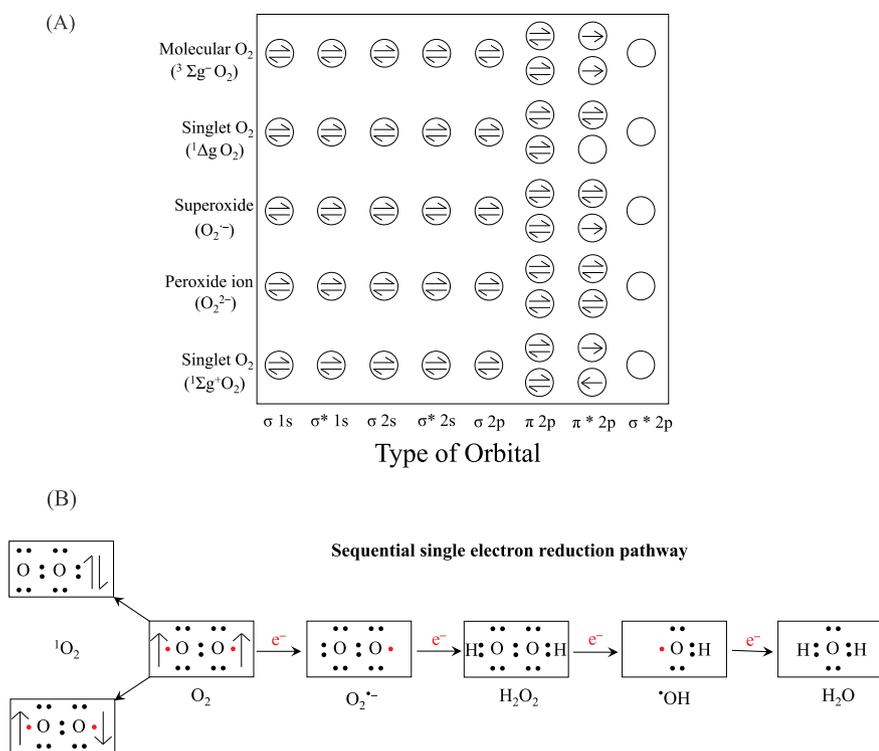


Fig. 1. The atomic properties of molecular oxygen (O_2) and its principal chemical species. **(A)** The molecular bonds in diatomic oxygen molecule and its derivatives. The molecular oxygen contains 16 electrons, with two unpaired electrons having the same spin quantum number that allows the molecular oxygen to accept one electron at a time (modified after Halliwell, 2006). **(B)** Lewis structures for O_2 and its excitation to form singlet oxygen (1O_2). Sequential single electron reduction of O_2 produces ROS such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\cdot OH$).

diffusion range of 30 nm (Table 1) (Egorov et al., 1989; Skovsen et al., 2005), but it can still cause damage to wide-ranging cellular targets (e.g., lipids, proteins) and trigger cell death (Davies, 2004; Triantaphylides et al., 2008).

The inability of molecular O_2 to accept more than one electron at a time, due to its spin restriction, results in the formation of stable intermediates in the sequential single-electron reduction pathway (Fig. 1B) (Elstner, 1982; Halliwell, 2006). The transfer of a single electron to O_2 (into the π^* orbital) leads to the formation of O_2^- that can further yield a non-radical (peroxide ion, O_2^{2-}) upon addition of another electron (Fig. 1A and B) (Mehler, 1951; Sawyer et al., 1980). Due to its moderate reactivity and short half-life (1–4 μs), O_2^- does not result in severe oxidative damage (Table 1) (Fee and Valentine, 1977); rather, it is transformed into moderately reactive H_2O_2 via monovalent reduction or dismutation by superoxide dismutases (SODs) (Fig. 1B) (Sawyer et al., 1980). Compared to other ROS members, H_2O_2 has

significantly longer half-life (1000 μs or more) (Table 1) (Henzler and Steudle, 2000), and contains no unpaired electrons; therefore, a fraction of H_2O_2 has been shown to rapidly transverse biological membranes via aquaporins (Bienert et al., 2006, 2007), and consequently cause extensive oxidative damage distant from its site of production (Fig. 1B). In plants, H_2O_2 is reported to act as a double-edged sword; it plays multiple beneficial roles at low concentration, regulating several essential physiological processes, whereas at high concentration, it causes severe cellular damage via oxidative modification of DNA and proteins (Table 1) (Mittler and Berkowitz, 2001). However, due to its moderate reactivity, H_2O_2 causes cellular damage after conversion to more reactive species such as $\cdot OH$, which has a single unpaired electron (Haber and Weiss, 1934; Kehrer, 2000). Despite shortest half-life (1 μs), the absence of effective $\cdot OH$ detoxification in plants can result in maximum cellular damages (Table 1) (Bors et al., 1979; Willson, 1979).

Although increased production of ROS can damage cells by

Table 1

The basic characteristics of ROS such as diffusion range, half-life, and reactivity with DNA, lipids and proteins. An increase in reactivity of various ROS is denoted by the increasing number of asterisks.

Name	Symbol	Diffusion range (nm)	Half life (μs)	Reactive specificity	References
Singlet oxygen***	1O_2	30	1–4	lipids and proteins oxidation (Cys, His, Trp, Tyr residues)	Davies, 2004; Egorov et al., 1989; Fischer et al., 2007; Skovsen et al., 2005; Triantaphylides et al., 2008
Superoxide**	O_2^-	30	1–4	reacts with Fe-S proteins, dismutates to H_2O_2	Elstner, 1982; Fee and Valentine, 1977; Mehler, 1951; Sawyer et al., 1980
Hydrogen peroxide*	H_2O_2	> 1000	> 1000	reacts with DNA, proteins (Cys, Met residues)	Bienert et al., 2006, 2007; Henzler and Steudle, 2000; Mittler and Berkowitz, 2001
Hydroxyl radical****	$\cdot OH$	1	1	DNA, RNA, lipids, proteins	Bors et al., 1979; Elstner, 1982; Haber and Weiss, 1934; Kehrer, 2000; Willson, 1979

oxidizing proteins, DNA and lipids directly, various ROS have a different degree of reactivity toward these cellular components (Table 1) (Elstner, 1982). Generally, proteins such as structural proteins, ion channels/transporters, signal transduction components, transcription factors, enzymes etc., are the most likely to be damaged due to increased cellular oxidation (Jacques et al., 2013). However, the vulnerability of amino acid residues to oxidative modification vary considerably, the most susceptible including cysteine (Cys), histidine (His), methionine (Met), tyrosine (Tyr) and tryptophan (Trp). Among these, the chemical properties of sulfur atom in amino acids Cys and Met make them major oxidation sites within the peptide chains. Targeted modification of proteins, e.g., by ROS at specific amino acids, is of particular importance because it causes local protein conformational changes that might initiate specific (oxidative) signaling pathways. For instance, under elevated ROS concentrations, Met is readily oxidized to sulphoxide (MetSO) in various signaling proteins, thus altering their functions (Jacques et al., 2013; and references therein). In a proteome-wide screening for Met oxidation sites in Arabidopsis plants subjected to oxidative stress, Jacques et al. (2015) identified 500 oxidation sites of this amino acid in approximately 400 proteins that undergo reversible posttranslational modifications and influence ROS-induced redox signaling pathways.

2.1. Sites of ROS generation

The conversion of light energy into biological energy by photosynthesis is crucial for life on Earth. However, photosynthesizing organisms are prone to oxidative damages due to their bioenergetics processes, abundance of polyunsaturated fatty acids (PUFA) and other photosensitive compounds (Asada, 2006). As ROS species diffuse over very small distances, before reacting with biological molecules, therefore, the production sites of highly reactive ROS are of particular importance. Under optimal conditions, ROS are continuously produced at a basal level, primarily in the peroxisomes and chloroplasts in the light-dependent processes, and also in mitochondria in light-independent fashion (Table 2). Several studies have described apoplast and any other cellular compartments containing proteins and/or molecules with an adequately high redox potential as ROS formation sites (Daudi et al., 2012; Qi et al., 2017). However, this review focuses on the role of chloroplasts, mitochondria and peroxisomes as the main ROS-producing sites.

2.1.1. Chloroplasts

Under light, chloroplasts are the main source of ROS production in green plants and algae (Asada, 2006). The oxygen produced during photosynthesis accepts electrons, which pass through the photosystems, creating O_2^- and H_2O_2 in the photosystem I (PSI) (Asada et al., 1974), and 1O_2 in the photosystem II (PSII) (Table 2) (Telfer et al., 1994). Formation of ROS in the electron transport chain in plants is increased under stress conditions (drought, salinity, high light, temperature extremes, etc.) that limit CO_2 fixation (Sharma et al., 2012). Under such conditions, overloading of electron transport chain causes electron leakage from ferredoxin to molecular O_2 leading to the formation of O_2^- via Mehler reaction and can damage the Fe-S cluster [4Fe-4S] in the PSI, the process commonly known as PSI photo-inhibition (Mehler, 1951). Due to light absorption in excess of the photosynthetic electron transport capacity, plastoquinone (PQH₂) in the cytochrome *b6/f* complex is reduced [converting plastoquinone (PQ) to plastoquinone (PQ⁻)], with the probability of increased O_2^- production (Vetoshkina et al., 2017). However, production of O_2^- as a primary product of O_2 reduction in thylakoids is a rate-limiting step in the production of other more reactive ROS. The spontaneous disproportionation, or superoxide dismutase (SOD) catalyzed dismutation of O_2^- , produces H_2O_2 that mainly reacts with thiolate proteins (Ogawa et al., 1995); however, H_2O_2 is readily converted to $\cdot OH$ radical in the presence of Fe^{2+} and Cu^+ , commonly known as Fenton reaction (Haber

and Weiss, 1934).

In addition to O_2^- and H_2O_2 formation by the photosynthetic electron transport chain, energy transfer within the photosystems leads to 1O_2 production, a type of ROS resulting from an excitation energy shift from chlorophyll triplet (3Chl) to the molecular oxygen (3O_2) under low light conditions (Telfer et al., 1994). Despite the fact that amount of chlorophyll is higher in the light-harvesting complexes than in the reaction center of PSII, chlorophyll is less prone to oxidative damage by 1O_2 due to efficient quenching of 3Chl by adjacent carotenoids and xanthophylls (Mozzo et al., 2008). Furthermore, 1O_2 might be detoxified by ascorbate (Bisby et al., 1999), tocopherol (Kruk et al., 2005) and plastoquinone (Kurk and Trebst, 2008), that safeguard the photosystems under light.

Chloroplasts produce diverse pools of ROS when photon intensity exceeds than that is required for assimilation of CO_2 (Asada, 2006). Consequently, the number of oxidized proteins in the chloroplasts, including the large RuBisCO (ribulose-1,5-bisphosphate carboxylase oxygenase) subunit, is generally higher under less than optimum conditions (Liu et al., 2008). Therefore, instant and efficient detoxification of thylakoid-generated ROS before their diffusion from the production site is crucial to protect the biological molecules in the stroma and thylakoids (Dietz et al., 2016).

2.1.2. Mitochondria

Plant mitochondria – the energy factories – are the key ROS production sites during the oxidative phosphorylation processes (the final phase of aerobic respiration pathway), contributing to the oxidative stress in plants (Sweetlove et al., 2002). The known sites of mitochondrial ROS generation in the electron transport chain are the complexes I (NADH dehydrogenase) and III (cytochrome *b/c1* complex) that harbor electrons with sufficient energy to reduce molecular O_2 to O_2^- (Table 2) (Bouché et al., 2003; Møller et al., 2001; Turrens et al., 1985). During this process, several proton-pumping enzymes in the complexes I, III and IV transport protons across the proton-impermeable inner membrane of mitochondria and establish an electrochemical proton gradient that is subsequently used for ATP synthesis (Sazanov et al., 1994). The O_2^- produced during the respiratory electron transport chain in the mitochondrial matrix is kept at low concentration due to its fast rate of dismutation to H_2O_2 via MnSOD (manganese superoxide dismutase) (Morgan et al., 2008; Purvis et al., 1995). Approximately 1–5% of O_2 consumed in mitochondria leads to the formation of H_2O_2 that might be subsequently converted to highly reactive $\cdot OH$ in the Fenton reaction (Haber and Weiss, 1934; Popov et al., 1997).

In principle, the amount of ROS produced by mitochondria in comparison to peroxisomes and chloroplasts is low in the light due to photorespiration and photosynthetic processes (Rhoads et al., 2006). Conversely, mitochondrial respiration acts as the main source of ROS formation in the non-green tissues or in the dark (Tiwari et al., 2002). Although the fraction of total ROS produced in the mitochondria is difficult to determine, reduced ubiquinone (a small lipid-soluble proton and electron carrier) localized in the inner membrane of mitochondria serves as the principal electron donor to O_2 and is the primary determinant of the mitochondrial ROS output (Millenaar et al., 1998; Popov et al., 1997). An increase in the rate of electron input, due to intensive respiratory and photorespiratory metabolism, leads to an over-reduced ubiquinone pool and a concomitant increase in mitochondrial ROS production and protein oxidation. Hence, the concentration of oxidized proteins in mitochondria was the highest of all organelles as reported in several studies that used proteomic approaches (Sweetlove and Møller, 2009; Taylor et al., 2005).

Production of mitochondrial ROS increases due to biotic and abiotic stresses that influence the plant cellular responses (Sharma et al., 2012). Protein damage by excess ROS is selectively caused by (i) preferential oxidation of some amino acid residues (e.g., Cys) to form disulfide bonds, (ii) oxidation of arginine (Arg), lysine (Lys) and threonine (Thr) residues leading to irreversible carbonylation in the

side chains, and (iii) Met residue oxidation to form MetSO (Kristensen et al., 2004). The oxidized proteins have been identified in plant mitochondria in the electron transport complexes I and III, including the ATP synthase subunits, pyruvate decarboxylase complex subunits, and tricarboxylic acid (TCA) cycle enzymes (Heazlewood et al., 2004; Kristensen et al., 2004). The thiol-modulated 'Calvin cycle' enzymes are highly sensitive to ROS. The plant mitochondrial proteins (particularly those harboring lipoic acid) are extremely sensitive to lipid peroxidation. Oxidation of mitochondrial membrane polyunsaturated fatty acids (PUFA) is caused by $\cdot\text{OH}$, with the formation of alkenals, hydroxy-alkenals such as malondialdehyde (MDA), and lipid aldehydes that inhibit the TCA cycle activity, thereby leading to the carbon and nitrogen metabolism impairments (Ito et al., 2009). ROS accumulation, particularly highly-reactive $\cdot\text{OH}$, can also damage mitochondrial DNA (Doudican et al., 2005). In summary, upsurges in mitochondrial ROS level are likely to cause various types of cellular damage; hence, as discussed below, mitochondria must be capable of restricting oxidative damage by (i) controlling ROS production and accumulation and (ii) removing excess ROS to allow for appropriate redox conditions required for plant physiology and development.

2.1.3. Peroxisomes

Peroxisomes are ubiquitous subcellular organelles surrounded by a lipid bilayer membrane and lacking DNA, however, these perform essential roles in almost all eukaryotes. In plant cells, peroxisomes are highly dynamic compartments, with subcellular movement and distribution that generally depends upon the actin cytoskeleton rather than the microtubules (Baker and Graham, 2002). These subcellular organelles have an oxidative type of metabolism and are considered the major ROS formation sites in plant cells (Corpas et al., 2017). Similar to the chloroplasts and mitochondria, normal metabolic activities in peroxisomes also produce O_2^- in the organelle matrix and the peroxisomal membranes caused by re-oxidation of NADH (nicotinamide adenine

dinucleotide) in the peroxisomal electron transport chain that yields NAD^+ to be utilized in the peroxisomal metabolic processes (del Río et al., 1989). However, H_2O_2 concentration in peroxisomes is about 2-fold higher than in chloroplasts and up to 50-fold higher than in mitochondria (Foyer et al., 2009). In the photorespiratory pathway in peroxisomes, H_2O_2 is primarily produced by glycolate oxidase that catalyzes the glycolate oxidation to glyoxylate in green tissues (del Río et al., 1996; Xu et al., 2009). Other metabolic processes involved in the peroxisomal H_2O_2 production include fatty acid β -oxidation (Foerster et al., 1981), flavin-oxidase-catalyzed enzymatic reactions (Baker and Graham, 2002), xanthine oxidase (Corpas et al., 2008; Lacy et al., 1998), and the dismutation of O_2^- radicals (Bueno et al., 1995) (Table 2).

Peroxisome-generated ROS are involved in diverse cellular and physiological functions. For instance, overproduction of O_2^- and H_2O_2 in the peroxisomes in response to metabolic or environmental changes was reported to be involved in stress-induced oxidative damage in plants (reviewed by Sandalio and Romero-Puertas, 2015). Moreover, proteomic studies of ROS metabolism in plant cells have indicated the role of peroxisomes as an oxidant signaling source (involving ROS) that can participate in plant cell metabolism under both physiological and stress conditions (Reuman et al., 2009). The peroxisome-generated ROS-based redox signal can be subsequently transmitted into the cytosol, thus participating in the integrated communication system among the cell compartments.

3. Plant antioxidative systems

Under aerobic conditions, life is intimately linked to ROS metabolism. Even though plant cells produce ample amounts of ROS even under physiological conditions, about 99% of ROS produced are metabolized by antioxidative enzymes localized in various subcellular compartments (Table 2; Fig. 2). The balance between the ROS

Table 2

Production sites and types of ROS produced in different subcellular organelles that are subsequently detoxified by various components of the plant antioxidant network through a well-coordinated pathway (Brehelin et al., 2003; Corpas, 2015; Faize et al., 2011; Kaminaka et al., 1998; Laloi et al., 2004; Leterrier et al., 2005; Marty et al., 2009; Miyake and Asada, 1994; Obara et al., 2001; Rodriguez-Serrano et al., 2007; Siendones et al., 1999; Wingsle and Karpinski, 1996).

ROS production sites	ROS produced	ROS scavengers	References
<i>Chloroplasts</i> – Photosynthesis ET – Photosystem I – Photosystem II – Excited chlorophyll	– Superoxide – Hydrogen peroxide – Singlet oxygen	– Cu/Zn-SOD, Fe-SOD – ASC-GSH – APX, Prx – Carotenoids – α -tocopherols	Asada, 2006; Foyer and Halliwell, 1976, 1977; Gorden and Beck, 1979; Horling et al., 2003; Hossain et al., 1984; Kelly and Latzko, 1979; Kruk et al., 2005; Lamkemeyer et al., 2006; Mehler, 1951; Meyer et al., 2012; Mozzo et al., 2008; Miyake et al., 1994; Nakano and Asada, 1981; Ogawa et al., 1995; Pulido et al., 2010; Telfer et al., 1994; Van Camp et al., 1990
<i>Mitochondria</i> – Respiration ET – Complex I – Complex III	– Superoxide – Hydrogen peroxide	– Cu/Zn-SOD, Mn-SOD – ASC-GSH – APX, PrxII	Bouché et al., 2003; Bowler et al., 1991; Finkemeier et al., 2005; Haber and Weiss, 1934; Heazlewood et al., 2004; Jimenez et al., 1997; Meyer et al., 2012; Möller, 2001; Morgan et al., 2008; Obara et al., 2001; Popov et al., 1997; Purvis et al., 1995; Sevilla et al., 1982; Siendones et al., 1999; Tiwari et al., 2002; Turrens et al., 1985
<i>Peroxisomes</i> – Glycolate oxidase – Fatty acid β -oxidation – Flavin oxidase – Xanthine oxidase	– Superoxide – Hydrogen peroxide	– Cu/Zn-SOD, Fe-SOD – ASC-GSH – APX, CAT	Baker and Graham, 2002; Bueno et al., 1995; Corpas et al., 2008; Corpas, 2015; del Río et al., 1989, 1996; Foerster et al., 1981; Jimenez et al., 1997; Lacy et al., 1998; Leterrier et al., 2005; Mhamdi et al., 2012; Reuman et al., 2009; Rodriguez-Serrano et al., 2007; Tuzet et al., 2019; Van Camp et al., 1990; Yamaguchi et al., 1995; Xu et al., 2009
<i>Cytosol</i> – Plasma membrane-associated quinone oxidase	– Superoxide – Hydrogen peroxide	– Cu/Zn-SOD – ASC-GSH – APX, PrxII	Bréhélin et al., 2003; Davletova et al., 2005; Edward et al., 1990; Faize et al., 2011; Hérouart et al., 1993; Horling et al., 2002; Kaminaka et al., 1998; Laloi et al., 2004; Marty et al., 2009; Meyer et al., 2012; Mittler and Zilinskas, 1991; Rahantiana et al., 2017; Wingsle and Karpinski, 1996

[APX (ascorbate peroxidase), ASC (ascorbate), CAT (catalase), DHAR (dehydroascorbate reductase), GR (glutathione reductase), Grx (glutaredoxin), GSH (glutathione), MDAR (monodehydroascorbate reductase), NTR (NADPH-thioredoxin reductase), Prx (peroxiredoxins), SOD (superoxide dismutase), Trx (thioredoxin)].

production and detoxification may be disturbed by various abiotic and biotic stresses (Sharma et al., 2012), and must be kept at a basal level to avoid critical damage to the cell structures. Various classes of compounds found in plants serve as cell antioxidants: (i) antioxidative enzymes such as SOD (superoxide dismutase), ascorbate peroxidase (APX), CAT (catalase), dehydroascorbate reductase (DHAR), monodehydroascorbate reductase (MDAR), glutathione reductase (GR), as well as peroxiredoxins (Prxs), and (ii) non-enzymatic antioxidants such as ascorbate (ASC), glutathione (GSH), α -tocopherol, and carotenoids (Table 2). The enzymes involved in the antioxidative processes and related redox responses can be characterized as follows: (a) proteins using O_2^- and H_2O_2 as substrates and acting as primary antioxidative enzymes; and (b) enzymes involved in regeneration of the reduced-form reductants and in helping maintain a redox state of cells (Table 2) (Mittler et al., 2004).

The most studied antioxidative enzymes in plants are SOD, CAT and APX. Among them, SODs belong to the family of metalloenzymes and represent the primary line of resistance against ROS, dismutating O_2^- to H_2O_2 (Fig. 2) (del Río et al., 2018). In view of their metal cofactors, SODs are categorized into three forms: Cu/Zn-SODs (localized in mitochondria, chloroplasts, peroxisomes and cytosol) (Bueno et al., 1995; Hérouart et al., 1993; Ogawa et al., 1995), Fe-SODs (found in peroxisomes and chloroplasts) (Van Camp et al., 1990), and Mn-SODs (confined to mitochondria) (Bowler et al., 1991; Sevilla et al., 1982). Among them, Mn- and Fe-SODs share considerable structural similarities and are found in both prokaryotes and eukaryotes, whereas Cu/Zn-SODs are unique to eukaryotic organisms (del Río et al., 2018). The occurrence of all three types of SODs in plants suggests their significance in plant physiology. For instance, the metabolic reactions catalyzed by SODs are known to modulate O_2^- radicals, and their enzymatic reactions produce H_2O_2 that acts as a key metabolite and universal signaling molecule under multiple biotic and abiotic stresses (del Río et al., 2018). However, plants contain various enzymes, such as CAT, APX and peroxiredoxins (Prxs), that prevent over-accumulation of H_2O_2 and damages associated with oxidative stress (Fig. 2).

Among different ROS processing enzymes, CAT enzymes contain tetrameric heme and play a distinctive role in metabolizing peroxisomal H_2O_2 produced by a variety of oxidases utilizing different substrates as discussed in the previous section (Table 2). Generally, CAT enzymes are classified into mono-functional (dismutating) and bi-functional (dismutating and peroxidative) enzymes, the latter identified in lower eukaryotes and prokaryotes (Mhamdi et al., 2012). In this context, only three mono-functional type CAT genes are identified in plants species so far, including Arabidopsis (Frugoli et al., 1996), maize (Guan and Scandalios, 1996), pumpkin (Esaka et al., 1997) and rice (Iwamoto et al., 2000). Although CAT enzymes are reported to have highest capacity to transform rapidly H_2O_2 to water and O_2 in peroxisomes without requiring any reducing equivalents (Mhamdi et al., 2012). However, plant CAT enzymes appear simpler, with little or no CAT found in the redox-active chloroplasts and mitochondria compartments (Table 2). However, plants abound in peroxidases and the reductant-requiring peroxidation pathways that operate in different subcellular compartments to remove H_2O_2 (Table 2; Fig. 2). As well as CAT enzymes, these H_2O_2 -metabolizing compounds are also found in peroxisomes (Tutez et al., 2019). Among them, ASC and GSH are the major low-molecular-weight non-enzymatic antioxidant compounds that engage APXs (Gorden and Beck, 1979; Nakano and Asada, 1981) to reduce H_2O_2 to water in the cellular redox cycle, and together with SODs, CAT and Prxs represent the key ROS scavenging antioxidants (Table 2) (Mittler, 2004).

An absence of CAT in photosynthesizing chloroplasts led to the discovery of ASC and GSH metabolites in plant cells (Foyer and Halliwell, 1976), with the subsequent identification of thylakoid-bound ascorbate peroxidase (tAPX) (Gorden and Beck, 1979) and soluble stromal ascorbate peroxidase (sAPX) (Kelly and Latzko, 1979). Later studies identified several genes encoding APX isoforms specifically targeted to chloroplasts (Ishikawa et al., 1997), mitochondria (Leonardis et al., 2000), peroxisomes (Yamaguchi et al., 1995) and cytosol (Mittler and Zilinskas, 1991; Davletova et al., 2005). In parallel, several high-capacity reductases involved in ascorbate regeneration

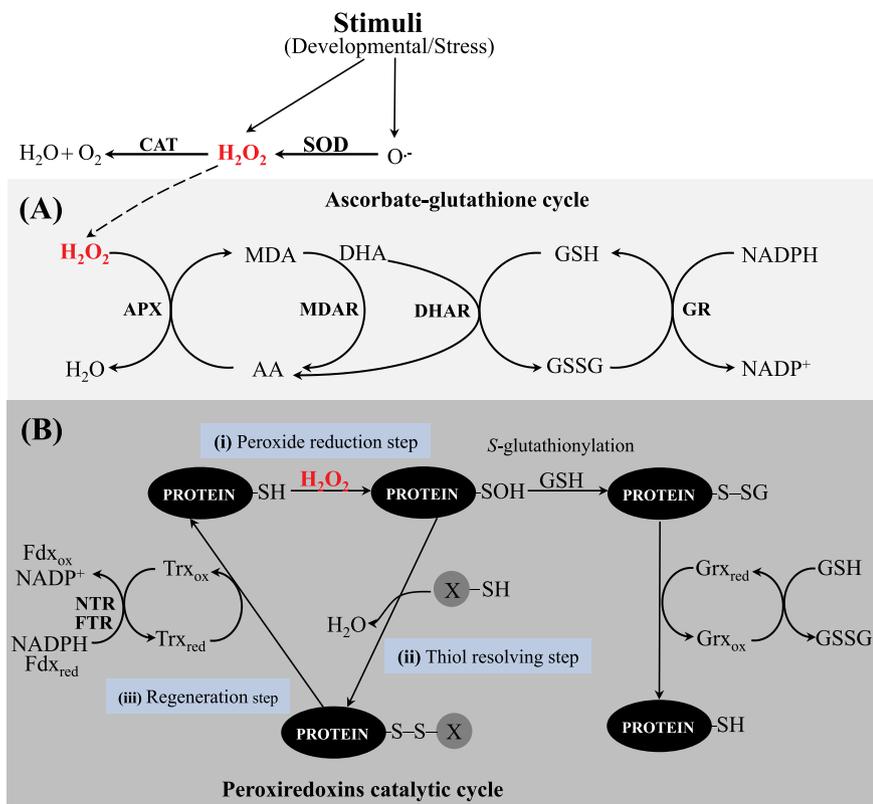


Fig. 2. Major components of plant antioxidant network that work together to detoxify ROS in different subcellular compartments (see text for further details). [AA (ascorbic acid; reduced form); APX (ascorbate peroxidase); CAT (catalase); DHA (dehydroascorbate; oxidized form); DHAR (dehydroascorbate reductase); Fdx (Ferredoxin); FTR (ferredoxin-dependent thioredoxin reductase); GR (glutathione reductase); Grx (glutaredoxin); GSH (glutathione; reduced form); GSSG (glutathione; oxidized form); O_2^- (superoxide); H_2O_2 (hydrogen peroxide); MDA (monodehydroascorbate); MDAR (monodehydroascorbate reductase); NADPH (nicotinamide dinucleotide phosphate); NTR (NADPH-dependent thioredoxin reductase); Prx (peroxiredoxins); SOD (superoxide dismutase); Trx (thioredoxin)].

such as dehydroascorbate reductase (DHAR) (Foyer and Halliwell, 1977), monodehydroascorbate reductase (MDAR) (Hossain et al., 1984), and also other reductants in the form of reduced ferredoxin or NADPH (Asada, 1999) were identified. The resulting reaction scheme now known as ASC-GSH cycle or Foyer-Halliwell-Asada pathway is reported as the best described route for H_2O_2 metabolism in both plants and animals (Fig. 2A) (Asada, 1999). In this pathway, APX enzymes (belonging to heme peroxidases) reduces H_2O_2 with ascorbate as an electron donor and produces monodehydroascorbate (MDA) radicals that subsequently disproportionate to reduced ascorbic acid (AA) and its oxidized form (DHA; dehydroascorbate) by MDAR using reduced ferredoxin or NADPH (Fig. 1A). Dehydroascorbate is also quickly recycled to AA in the presence of DHAR together with the conversion of reduced glutathione (GSH) to its oxidized form (GSSG; glutathione disulfide) (Fig. 2A) (Foyer and Noctor, 2011).

At physiological pH, GSH is fully protonated due to its high pK_a value (~ 8.9), therefore its reactivity towards ROS and disulfides is rather limited (Van Laer et al., 2013). However, maintenance of glutathione in its reduced form (high GSH/GSSG ratio) is critical for a cellular redox balance due to its involvement in the regeneration of reduced ascorbate pool during the ASC-GSH cycle. Therefore, reduced GSH is quickly regenerated from GSSG by the activity of GR (glutathione reductase) using NADPH as an electron donor (Fig. 2A). During ASC-GSH cycle, it is crucial to maintain high level of endogenous ascorbate because APX isoenzymes are highly labile in the absence of reduced ascorbate. Further, ascorbate also plays a key role in the direct chemical removal of ROS, regeneration of tocopherols, as well as production of xanthophylls involved in the excitation energy quenching (Arrigoni and Tullio, 2002). Taken together, ASC and GSH efficiently utilize different high-capacity reductases that enable them to effectively regulate the cellular redox status, distinguishing them from the sacrificial antioxidants (Fig. 2A). Components of this pathway have been found in several subcellular compartments including chloroplasts (Asada, 1999), peroxisomes and mitochondria (Jimenez et al., 1997), and the cytosol (Edwards et al., 1990; Mittler and Zilinskas, 1991; Davletova et al., 2005) (Table 2).

Plants contain other thiol-based peroxidases that function alongside APXs in H_2O_2 removal (Dietz, 2016). Thiol peroxidases belong to a group of heme-free enzymes that principally utilize a cysteinyl thiolate to attack peroxide substrates. Among different thiol peroxidases, Prxs have now been recognized as a central component of antioxidant defense system that efficiently reduces H_2O_2 in various subcellular compartments such as chloroplasts (Horling et al., 2003; Lamkemeyer et al., 2006), mitochondria (Finkemeier et al., 2005) and cytosol (Horling et al., 2002) (Table 2; Fig. 2B). Based on the structure and sequence similarities and positions of the conserved Cys residues, there are at least six groups of the Prx family (Prx type A to F) identified in plants and cyanobacteria (Dietz, 2011). Among them, group E Prx corresponds to the bacterial peroxidases and group F to the Prx homologs in archaea. Groups A to D Prx are common and conserved in higher plants, e.g., the genomes of *Arabidopsis thaliana*, *Oryza sativa* and *Populus trichocarpa* encode genes for all the four types of Prx (Dietz, 2011).

According to the nomenclature commonly used for the classification of Prx family; group A Prxs corresponds to the typical 2-Cys peroxidase (2-CysPrx), group B Prxs to the typical 1-Cys peroxidase (1-CysPrx), group C Prxs to peroxidase Q (PrxQ), and the group D Prxs to type II peroxidase (PrxII) – the latter two also called atypical 2-CysPrx (Liebthal et al., 2018). In all cases, Prx enzymes employ a three step thiol-based catalytic cycle to maintain appropriate level of H_2O_2 (Fig. 2B): (i) Peroxide reduction step, whereby H_2O_2 reacts with the active thiol (R-SH) group and form sulfenic acid derivative (R-SOH), (ii) thiol resolving step, when R-SOH reacts with another resolving thiol (R-SH) to release H_2O and form an inter- or intramolecular disulfide bond. Alternatively, R-SOH can also be modified by glutathione causing Cys S-glutathionylation – a protective mechanism to prevent over-oxidation of the active-site Cys residues, thus minimizing

permanent protein damage, and (iii) regeneration step that corresponds to reduction of disulfide bonds and/or deglutathionylation using different electron donors such as thioredoxins (Trx) and glutaredoxins (Grx) (Fig. 2B) (Dietz, 2011; Liebthal et al., 2018). Plant genomes are reported to contain multiple Trx and Grx genes (Meyer et al., 2012) that employ diverse reducing equivalents in the reduction of inter- or intramolecular disulfide bonds in different subcellular compartments. For instance, oxidized 2-CysPrx can be reduced back by NADPH, a reaction that is catalyzed by NADPH-dependent thioredoxin reductase (NTR) type C or via ferredoxin (Fdx)-dependent thioredoxin reductase (FTR) linked to Fdx in chloroplasts (Fig. 2B) (Lamkemeyer et al., 2006; Pulido et al., 2010). The Grx regeneration involves a two-step reduction pathway utilizing NADPH-dependent glutathione reductases and GSH (Fig. 2B).

In summary, the rich tapestry of antioxidant molecules (both enzymatic and non-enzymatic) found in plants play key roles in removing excess ROS. However, a balance between removal of ROS and the role of ROS in regulating redox-dependent signaling is crucial. Oxidative signaling shifts this balance toward ROS accumulation, via either a reduction in antioxidant capacity or increase in ROS production. The components and the pathways of the ROS signaling network are discussed below.

4. Cellular retrograde signaling: ROS-induced redox signaling

Organelle-to-nucleus communication, typically labeled retrograde signaling, elicits changes in the expression of nuclear genes that encode organelle proteins with the structural and metabolic functions (Fig. 3). Some organelles, such as chloroplasts, peroxisomes and mitochondria produce ROS through photosynthesis, photorespiration and/or respiration (Foyer and Noctor, 2003). Enhanced ROS production, although historically viewed only as a precursor of oxidative stress (a harmful process), has recently been recognized as a source of oxidant signals impacting various proteins through the redox-based, post-translational changes that control the molecular master-switches

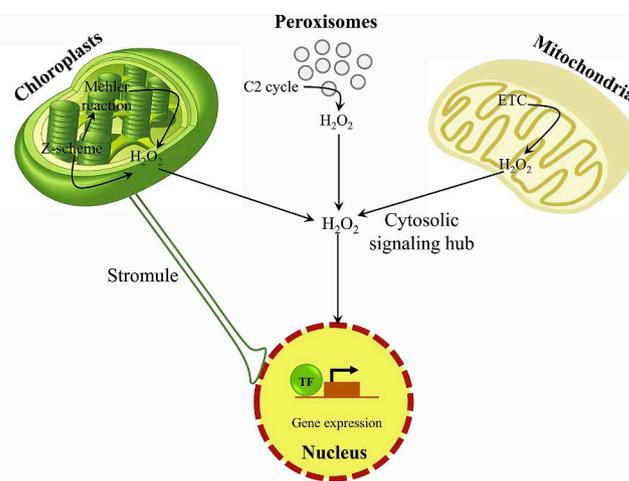


Fig. 3. Retrograde signaling pathways – relaying oxidant signals from organelles (chloroplasts, mitochondria and peroxisomes) to the nucleus. Transporters linked to the activation of retrograde signaling pathways allow H_2O_2 produced by the electron transport chain (ETC) in mitochondria, C2 cycle in peroxisomes, and Mehler reaction in chloroplasts to be transferred via aquaporins to the cytosol and act as a signaling molecule for triggering gene expression in the nucleus. The chloroplast organellar extensions (stromules) may also feed redox information directly to the nucleus for subsequent responses. [The “Z-scheme” in chloroplasts describes the redox changes during the light-dependent reactions of photosynthesis. The Z-scheme of electron transport links the PSII with PSI in a way that resembles the letter Z. While the “C2 cycle” also known as oxidative photosynthetic carbon cycle refers to participation of peroxisomes in photorespiration in plant photosynthetic tissues.].

(Mittler, 2017). Coordination of gene expression among the three genomes of plant cells underpins the integration of signaling pathways and places retrograde signaling in the core of cellular reactions to a specific stimulus (Chan et al., 2016; Pogson et al., 2008).

Among different types of ROS produced, only H₂O₂ can cross plasma membrane and is relatively stable; therefore, it may have an important role in the cell-to-cell signaling to optimize the functioning of various cells (Fig. 3) (Bienert et al., 2006, 2007; Mubarakshina et al., 2010). It should be noted that ROS-damaged molecules could be early participants in a signaling pathway. In this scenario, any effort to disrupt ROS production or detoxification in plants may result in an effect on ROS-mediated redox signaling, rather than causing oxidative stress-induced cell death (Mittler, 2017).

4.1. Transmission of redox signals from chloroplasts to the nucleus

The coordination between chloroplasts and the nucleus is essential and requires a continual stream of communication between the organelles, commonly known as the chloroplast-to-nucleus retrograde signaling (Barajas-López et al., 2013; Baruah et al., 2009; Dietz et al., 2016). The chloroplasts are the major ROS production site under stress and/or during plastid development, eliciting global changes in nuclear gene expression through the redox-dependent retrograde signaling (Pesaresi et al., 2006; Woodson and Chory, 2008). The chloroplast-to-nucleus retrograde signaling pathways may be activated by three different cues: (1) tetrapyrrole biosynthesis intermediates, (2) impairment of organellar transcriptional and translational processes (i.e. plastid gene expression) and (3) changes in the redox conditions in chloroplasts and accumulation of various ROS, such as ¹O₂ and H₂O₂ (Galvez-Valdivieso and Mullineaux, 2010); these potential pathways are discussed below.

Studies on the use of herbicide norflurazon (a carotenoid biosynthesis inhibitor) showed enhanced accumulation of the chlorophyll biosynthesis intermediate Mg-Protoporphyrin IX (Mg-ProtoIX) and its methyl ester (Mg-ProtoIX-ME) that induced a chloroplast-derived signal altering the nuclear gene expression (Strand et al., 2003). This norflurazon effect was found to depend largely on the presence of chloroplast-located *GUN1* [*GENOME-UNCOUPLED 1* that encodes pentatricopeptide-repeat (PPR) containing protein] and nuclear *ABI4* (*ABA INSENSITIVE 4*) (Koussevitzky et al., 2007; Ruckle and Larkin, 2009). The coordination of these two genes was further reported to influence the high-light stress response in Arabidopsis through changed expression of stress-induced zinc-finger proteins (*Zat10* and *Zat12*) in the *gun1* and *abi4* mutant seedlings exposed to high light, also exacerbating their sensitivity to high temperature stress (Koussevitzky et al., 2007; Maruta et al., 2012; Mittler et al., 2006). Among the Mg-ProtoIX binding proteins, the largest category (35%) of proteins was related to various stress responses, including the members of glutathione S-transferase (*AtGSTT1*, *AtGST10*, *AtGSTF3*) and peroxidase (*APX1*, *ATP3*, *ATP15*, *PER22*) families, with peroxidases suggested to play a main role in the degradation of Mg-ProtoIX (Kindgren et al., 2010). Furthermore, Ankele et al. (2007) reported Mg-ProtoIX export from the chloroplasts to the cytosol and suggested its role as a plastid signal during the chloroplast-to-nucleus retrograde signaling under stress. However, Mg-ProtoIX accumulation and its role in retrograde signaling has been questioned in two complementary studies that suggested the rapid flux modifications via the tetrapyrrole pathway (the biosynthesis of heme, siroheme, phytychromobilin, and chlorophyll – the four major tetrapyrrole molecules) exerting significant changes in the expression of photosynthesis-associated nuclear genes (*PhANGs*) in higher plants, with no increase in concentration of Mg-ProtoIX in norflurazon-treated plants (Mochizuki et al., 2008; Moulin et al., 2008). For example, the *gun* mutants (with impaired flux through the tetrapyrrole pathway) express *PhANGs* under oxidative stress, but their expression is strongly inhibited in wild-type plants grown under similar conditions. These findings represent strong evidence for involvement of tetrapyrroles in

the chloroplast-to-nucleus retrograde signaling. On the other hand, seedlings treated with the plastid protein synthesis inhibitors (lincomycin and chloramphenicol) reduced the nuclear plastid gene expression, possibly at the protein translation stage, arbitrated by the *GUN1/ABI4* pathway (Koussevitzky et al., 2007; Nott et al., 2006). The seedling treatment with lincomycin in the presence of light induced generation of ¹O₂ in the PSII, thereby increasing the sensitivity of reaction centers to photo-oxidative stress, and triggering the stimulation of nuclear gene expression in the *GUN1/ABI4*-dependent signaling pathway (Hideg et al., 2007). However, in contrast to the Mg-ProtoIX export, the nature of a signal that originated in the chloroplasts and was transmitted to the nucleus remains unknown.

The chloroplast-to-nucleus retrograde signaling can also be transduced by a change in the photosynthetic electron transport chain redox state, even though the actual components of such a system remain mostly unclear (Koussevitzky et al., 2007; Woodson and Chory, 2008). Nevertheless, the ROS-dependent retrograde signaling, in contrast to plastid gene expression, is suggested to be mainly involved in stress signaling rather than genome coordination under changing environmental conditions (Woodson and Chory, 2008). Although different ROS produced in chloroplasts (¹O₂ and H₂O₂) have been associated with retrograde signaling, the ¹O₂ pathway in higher plants is independent of the above-mentioned *GUN1-ABI4* signaling (op den Camp et al., 2003; Lee et al., 2007; Ochsenbein et al., 2006; Wagner et al., 2004).

To identify the components of the ¹O₂-dependent retrograde signaling pathways, several studies have used Arabidopsis fluorescent (*flu*) mutant seedlings that accumulate the chlorophyll precursor protochlorophyllide when grown under dim light and rapidly accumulate ¹O₂ when transferred from dim to full light (op den Camp et al., 2003). A microarray-based genome-wide transcriptome profiling of *flu* mutants identified a distinct set of genes specifically stimulated by ¹O₂ (indicating the biological activity of ¹O₂ as a signal as opposed to a toxin), causing profound reprogramming of nuclear gene expression (op den Camp et al., 2003; Gadjev et al., 2006). However, because of short half-life and high reactivity, ¹O₂ has exceptionally restricted dispersion *in vivo* and is unlikely to be a signaling molecule (Egorov et al., 1989; Fischer et al., 2007; Skovsen et al., 2005). Possibly, the products of ¹O₂-mediated lipid peroxidation reactions, such as cyclic oxylipins (isoprostanes), may act as secondary messengers and alter the nuclear gene expression in the ¹O₂-dependent retrograde signaling pathways (Thoma et al., 2003). Similarly, two nuclear-encoded chloroplast proteins i.e. EXECUTER1 (EX1, *executer1/flu* double mutant) and EX2 are reported to participate in the ¹O₂-dependent retrograde signaling (Carmody et al., 2016; Kim and Apel, 2013; Lee et al., 2007; Wagner et al., 2004).

Interestingly ¹O₂ may communicate with other components of the redox signaling network. For example, upon exposure to stress conditions, chloroplasts produce H₂O₂ (due to photo-reduction of O₂ at the PSI) that is relatively stable and less reactive than ¹O₂. H₂O₂ may also inhibit the ¹O₂-mediated stress responses as has been observed in the *flu* mutant (Gadjev et al., 2006; Laloi et al., 2007). Therefore, H₂O₂ could serve as a signal in the chloroplasts or diffuse out of the organelle to transduce the signal in the cytosol for the subsequent signal integration with other cellular components (Mullineaux et al., 2006). In this regard, Laloi et al. (2007) reported that the crosstalk between the ¹O₂ and H₂O₂-dependent signaling pathways induce retrograde signals that activate multiple stress responses. For example, reduction of the chloroplast H₂O₂ pool by the thylakoid-bound ascorbate peroxidase (tAPX) overexpression in the *flu* mutants was shown to strongly suppress the ¹O₂-specific nuclear gene expression. In addition, a comparative transcriptomic study in response to specific ROS found that the key set of genes or regulons triggered by ¹O₂ differed markedly to those associated with the H₂O₂ response (Gadjev et al., 2006). The exogenous use of H₂O₂ appeared to improve the oxidation of Q_A, an essential PQ electron acceptor, and to accelerate the electron streaming through the photosystems, thereby decreasing the stress-induced accumulation of ¹O₂, providing a possible physiological explanation for this

phenomenon (Karpinska et al., 2000; Laloi et al., 2007).

4.2. Transmission of redox signals from mitochondria to the nucleus

The respiratory metabolism in mitochondria produces ROS during the respiratory electron transport chain. A control of these mitochondrial processes is fundamental to cell homeostasis that involves sensing and transducing the signal-specific information to the nucleus and reprogramming the transcriptional machinery for the tailored acclimatory responses (Schwarzländer and Finkemeier, 2013; Welchen et al., 2014). Such control of nuclear gene expression during mitochondria-to-nucleus retrograde signaling has been a field of exceptionally dynamic research in recent years. Many factors involved in these transcription regulation processes have been identified in yeast, cultures of animal cells, and plants (Schwarzländer and Finkemeier, 2013).

In plants, the mitochondria-to-nucleus retrograde signaling results in the elevated expression of a specific set of nuclear genes (Ng et al., 2014; Niazi et al., unpublished data). Among these genes, enhanced expression of nuclear-encoded *alternative oxidase 1* (*AOX1*) is identified as a hallmark responder of the mitochondria-to-nucleus retrograde signaling. *AOX1* is strongly expressed in reaction to biotic and abiotic stresses, specifically in response to plants being treated with the inhibitors of mitochondrial electron transport chain such as rotenone (complex I – NADPH dehydrogenase), antimycin A (complex III), and monofluoroacetate (MFA; TCA cycle) (Popov et al., 1997; Vanlerberghe, 2013). The ROS-inducible transcription factor *ABI4* regulated the expression of *AOX1* by binding to the repressor B cis-acting element in the promoter region (Giraud et al., 2009). This notion is further supported by rotenone stimulating the *AOX1* expression in wild-type plants, but not in the *abi4* mutants, demonstrating the importance of *ABI4* in redox reactions and the mitochondria-to-nucleus retrograde signaling (Giraud et al., 2009). On the other hand, the transcription factor *WRKY15* was found as an important repressor of *AOX1*, rendering plants sensitive to osmotic/salt and oxidative stresses (Vanderauwera et al., 2012).

The functional analysis of the mitochondrial stress-responsive genes identified a typical motif in their promoter, called mitochondrial dysfunction motif (MDM), which is perceived by transcription factors belonging to the *NAC*, *NAM*, *ATAF1/2*, and *WRKY* families (De Clercq et al., 2013). Interestingly, among those, the *ARABIDOPSIS NAC DOMAIN CONTAINING PROTEIN-13* and *-17* (*AtNAC013* and *AtNAC017*) are bound to the endoplasmic reticulum (De Clercq et al., 2013; Ng et al., 2013), and are proteolytically released in the presence of ROS and translocated to the nucleus to mediate the mitochondria-to-nucleus communication (Ng et al., 2013).

Identification of *ABI4* at the crossroads of the chloroplast- and mitochondrial-retrograde signaling pathways is of significant interest, and is potentially an emerging point of plastid-mitochondria-nucleus coordination. This is because of linkage of chloroplast and mitochondria through metabolism, energy and the redox state, and information transmission to nucleus about their functional and developmental state (Bailleul et al., 2015; Noguchi and Yoshida, 2008; Pesaresi et al., 2006; Woodson and Chory, 2008). Thus, overexpression of *ABI4* reduced oxidative damage in the thylakoid membranes by neutralizing the excess photosynthetic reducing power and preventing over-reduction of the respiratory electron transport components, thereby releasing excessive energy as heat (Dinakar et al., 2010; Giraud et al., 2009). Nevertheless, the mitochondrial retrograde signaling is not well understood as compared to the chloroplast-to-nucleus retrograde signaling and needs further investigation.

4.3. Transmission of redox signals to the cytosol – the key site of signal integration

The present paradigm of organelle-to-nucleus signaling considers the individual signals and pathways to be separate from each other.

However, our current understanding of the organelle ROS and redox regulatory network demonstrates that the signals are, to some extent, connected spatially, temporally, physiologically, and metabolically. ROS produced in various subcellular organelles are proposed to travel around as a signal that triggers reactions outside organelles. The transmission of redox signal from various organelles into the cytosol (a hub for crosstalk/integration of divergent redox signals, with the cytosolic redox state directly influencing that of the nucleus) involves multiple transduction pathways, e.g., possibly by diffusion, leakage or active transport of ROS (Dietz et al., 2016). Signal transmission within seconds can also be achieved by cytosolic streaming (Tominaga and Ito, 2015) that is active in virtually all plant cells. A possible role of stromules in that signal transduction has also been suggested (Hanson and Hines, 2018).

The cytosol is critical for the upkeep of the cellular metabolic capability, posttranslational modification and control of protein synthesis (Moore et al., 2016). However, in the cytosol, as compared to other compartments such as chloroplasts, few sources of ROS are characterized because cytosol is less affected by light directly and consequently has greater redox stability. Furthermore, the cytosol contains some enzymes, compounds and pathways (such as ASC-GSH) that could play antioxidative roles (Das and Roychoudhury, 2014; Noctor et al., 2017). The redox signals originated in various subcellular compartments act as specific signals upon transmission to the cytosol (Dietz et al., 2016; Noctor and Foyer, 2016). Although the mechanisms of redox signal transmission from these organelles to the cytosol are not clearly understood, they may involve ROS, oxidation products, metabolites, and some unknown transcription products (Dietz et al., 2016; Kopczewski and Kuźniak, 2013; Moore et al., 2016).

Chloroplast-generated ROS, such as $^1\text{O}_2$ and H_2O_2 , have distinct signal transduction pathways to stimulate responses outside of the organelle. Given that $^1\text{O}_2$ is highly reactive and unstable, it should be perceived via specific sensors in the thylakoids or by $^1\text{O}_2$ reaction by-products in the stroma (Kopczewski and Kuźniak, 2013; op den Camp et al., 2003). Such sensors can stimulate a signal transduction pathway directed to the nucleus through the cytosol. For instance, the genetic basis of $^1\text{O}_2$ signaling has been linked to the chloroplast-localized PSBP2 protein in *C. reinhardtii* (Brzezowski et al., 2012), and the two nuclear genes encoding the plastid proteins EX1 and EX2 in *A. thaliana* (Kim et al., 2012) that are necessary for the $^1\text{O}_2$ -induced changes in gene expression. Moreover, the $^1\text{O}_2$ -induced oxidation products of lipids (e.g. 13-keto-octadecatrienoic acid and/or oxylipins 13-hydroxy octadecadienoic acid) (López et al., 2011) and carotenoids (e.g. β -cyclocitral) (Ramel et al., 2012) in the chloroplast are reported to act as signaling compounds. Previous studies suggested that some of $^1\text{O}_2$ produced by chloroplasts may also diffuse to the cytosol and directly react with cytosolic compounds (Fischer et al., 2007), but it mostly remains in the chloroplast due to its high reaction capacity.

H_2O_2 is generated in organelles such as chloroplasts, peroxisomes, mitochondria, and to some extent in the nucleus and endoplasmic reticulum. H_2O_2 is the most abundant and stable ROS molecule in plant cells. It accumulates when O_2^- generated by these organelles is transformed into H_2O_2 and H_2O_2 is reduced to water by antioxidative enzymes such as APX and CAT (Gill and Tuteja, 2010). Nevertheless, a considerable amount of excess H_2O_2 produced by chloroplasts may diffuse across the organelle membranes into the cytosol (Bienert et al., 2006, 2007). This is also demonstrated by the observation that in mutant plants deficient in producing CAT (as the predominantly peroxisome-localized enzyme), the expression of genes coding for the cytosolic antioxidative system was strongly induced (Queval et al., 2011; Rahantaniaina et al., 2013).

Some studies have proposed that specific aquaporin-like proteins may be involved in the facilitated H_2O_2 efflux across the membranes, thus controlling H_2O_2 permeability and signaling in living organisms (Bienert et al., 2006, 2007). Extracellular H_2O_2 is taken up by cells via plasma membrane aquaporins. Similarly, H_2O_2 produced in

chloroplasts and mitochondria is transmitted to the cytosol via aquaporins. Furthermore, vacuolar aquaporins are highly permeable to H_2O_2 and are speculated to function in detoxification processes. Hence, both plasma membrane and tonoplast aquaporins may have roles to play in H_2O_2 signaling and/or regulation (Bienert et al., 2006, 2007).

Subcellular metabolites and antioxidative enzymes also play key roles in the transport of H_2O_2 from organelles to the cytosol and in the resultant signaling (Bienert and Chaumont, 2014). Precise quantification of subcellular metabolite concentrations is difficult due to possible transporter activities or organelles interruption that affect the distribution of metabolites during sample preparation (Noctor and Foyer, 2016). Some shuttle translocators, such as dicarboxylate (malate and oxaloacetate) and phosphate (triose phosphate and phosphate) ones in the chloroplast envelope have long been known to play the key roles in the cytosolic redox signal transduction to the nucleus as part of the chloroplast-to-nucleus signaling (Dietz et al., 2016). Furthermore, antioxidants act not only to keep low ROS concentration, but also to regulate the ROS-dependent signaling through various pathways (Mittler, 2017; Noctor et al., 2017). For instance, the ROS-dependent signaling may be regulated by carotenoid degradation products and by cytosolic GR and DHARs mediating glutathione status and thus linking H_2O_2 -induced oxidative stress to phytohormone signaling (Rahantianiana et al., 2017). The effects of this glutathione-dependent signaling are enhanced by interactions with nitric oxide (NO) through the S-nitrosoglutathione (GSNO) and GSNO reductase system. Moreover, stress-induced perturbations in the glutathione redox potential mediate numerous cell responses by involving other associated components such as NO, glutaredoxins and thioredoxins (Noctor and Foyer, 2016; Tarrago et al., 2009). These components mediate plant development regulation, especially under stress through interactions with various transcription effectors in the cytoplasmic ROS transduction. Similar to antioxidant compounds, antioxidative enzymes may also enable cells to sense and alter the ROS and redox alarms, acting as ROS processors and ROS reducers (Noctor et al., 2017).

In summary, the cytosol, representing a redox-signaling hub, may act as a key integrator of retrograde signals arising from various organelles, enabling communication among different cellular compartments and the nucleus. Importantly, H_2O_2 is the most stable ROS that can be transferred from the organelles to the cytosol and nucleus, thereby leading to changes in the cytosolic and nucleus redox states and triggering signaling networks. These networks may involve redox alterations of protein-protein interactions, secondary messengers and/or gene expression underpinning subsequent plant responses.

5. ROS and redox biology under stress conditions

Plants are frequently exposed to stress conditions (such as salinity, water deficit, heavy metal toxicity, temperature extremes, and insect

and pathogen attack) that may limit vigor and crop yields. Most, if not all, abiotic and biotic stresses prompt changes in the cell redox homeostasis, with increased ROS generation and accumulation, potentially damaging cell constituents, but also transferring information about the state of the cell parts (Noctor et al., 2017). In contrast, low cellular ROS concentrations (below a threshold) hamper normal cellular functions, and also interfere with differentiation and plant immune responses. This indicates that cellular ROS concentrations that are either too high or too low negatively affect plant growth and development (Fig. 4). Importantly, within a defined window of concentrations, ROS act as biological messengers in signaling networks; thus, maintenance of a basal ROS concentration is indispensable for proper redox reactions that impact on nearly every aspect of plant biology, i.e. cell proliferation, metabolism, plant growth and development regulation, defense responses, and cell death (Fig. 4) (Mittler, 2017; and references therein). To initiate specific responses to developmental and environmental stimuli, the ROS signals work up- or downstream from many other secondary messengers [e.g., reactive nitrogen species (RNS), Ca^{2+} , hormones (abscisic acid, jasmonic acid, and salicylic acid), and mitogen-activated protein kinases (MAPKs)] in addition to numerous feed-forward and feed-back regulations in an interwoven way (Fig. 5). For comprehensive description of the ROS signals integration with an array of other signaling pathways, we suggest the following reviews: Baxter et al. (2014), Dietz (2008), and Sewelam et al. (2016). Here, we comprehensively discuss ROS as the vital signals in living cells, particularly under different abiotic and biotic stress conditions.

5.1. ROS-induced retrograde signaling in response to abiotic stresses

Distinct abiotic stresses or their specific combinations are likely to result in the development of various ROS signals in plant cells; decoding these signals by means of various ROS sensors can represent a stress-specific signal that tailors the acclimation reaction to the specific kind of stress. Detecting ROS by plant cells is done either by different ROS sensors (e.g. ROS-sensitive factors such as heat-shock proteins), NPR1 (Non-expressor of Pathogenesis-Related gene 1) or by ROS-related inhibition of phosphatases (Jayakannan et al., 2015; Miller and Mittler, 2006; Mou et al., 2003). Once ROS are detected, they turn on the signal transduction pathway causing differential gene expression, metabolism and development control between the organelles and the nucleus (retrograde signaling), which may subsequently influence nucleus to organelle control i.e. anterograde signaling (Woodson and Chory, 2008). The retrograde signaling is generally divided into two main categories: (i) developmental control of organelle biogenesis and (ii) operational control to modulate stress responses and acclimation (Pogson et al., 2008). ROS metabolism and the organellar redox state in chloroplasts and mitochondria are crucial for retrograde signals that play a key part in the acclimation of plants to fluctuating environmental conditions

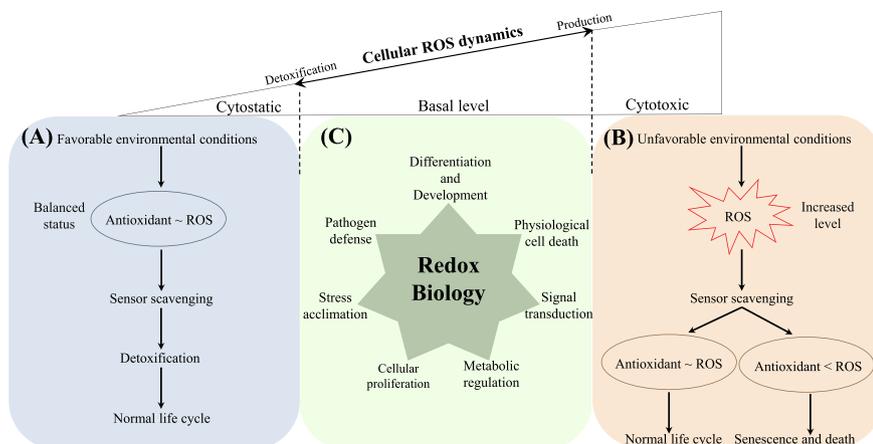


Fig. 4. A schematic representation of cellular ROS dynamics and the consequent plant physiological responses. The figure demonstrates three states of ROS/redox perturbations. (A) In favorable environmental conditions, ROS produced as byproducts of various metabolic pathways are efficiently kept at low concentrations by the presence of the dedicated antioxidative enzymes network. Unfavorable environmental conditions (e.g. abiotic and biotic stresses) (B) cause increased ROS production or decreased antioxidant activity, and the subsequent imbalance leads to senescence and death due to cytotoxic ROS concentrations. (C) ROS-induced redox signaling, that control numerous key cellular processes, occurs at basal ROS concentrations where the balance between ROS production and scavenging is maintained, and the maximum plant growth and development potential is achieved.

(Foyer et al., 2017). Thus, changes in the chloroplastic and mitochondrial redox homeostasis are either communicated to the nucleus via the retrograde pathway or through metabolic coupling into the cytoplasm.

The involvement of chloroplast redox state or cellular ROS signaling is important for understanding redox-regulated gene expression under abiotic stresses, particularly under high-light stress that alter ROS homeostasis and prompt cell death. In chloroplasts, ROS signaling is modulated by the PQ pool redox state and plays a crucial role in plant acclimation to fluctuating light condition, including altered expression of antioxidant and defense-related genes and changed phosphorylation of thylakoid proteins (Li et al., 2009; Mittler et al., 2011). The chloroplast kinases and phosphatases maintain high photosynthetic activity and redox state under diverse abiotic stresses, such as high light (Schliebner et al., 2008). Acclimation to fluctuations in light intensity requires adjusting energy dissemination inside the photosynthetic apparatus to both ensure efficient photosynthesis and protect thylakoids from damage. During a short-term response, stimulation of the state transition to maintain and balance photosynthetic energy dissemination between photosystem II and I is regulated by the PQ pool redox state. During a long-term response (hours or days), cellular energy homeostasis involves readjustment of photosystem stoichiometry and also changes in abundance of reaction center proteins (Suzuki et al., 2012; and references therein). In Arabidopsis, protein kinase STN7 is reported to govern the redox state of PQ via phosphorylation of thylakoid-bound phosphoprotein TSP9 during the state transition; however, the long-term response is indispensable for the low-light stress acclimatory responses, with no described role under high-light stress (Fristedt et al., 2009; Pesaresi et al., 2009). Similarly, STN8 is the STN7-like protein kinase essential for the quantitative phosphorylation of D1 and D2 proteins in the PSII (Vainonen et al., 2005). This protein kinase is also required for high-light-mediated phosphorylation of a 40 kDa protein in the thylakoid layer, suggesting its role in the high-light stress response (Bonardi et al., 2005; Vainonen et al., 2005).

Like chloroplasts, the mitochondrial redox state is important for maintaining cellular energy balance and preventing oxidative damage (Sweetlove and Møller, 2009). The significant research efforts have identified the important roles of AOX, type II NAD(P)H dehydrogenase and uncoupling proteins localized in the inner mitochondrial membrane as the mitochondrial redox state regulators that prevent over-reduction of the mitochondrial electron transport chain and production of excess ROS in different cellular compartments (Noctor et al., 2007; Rasmusson and Wallström, 2010; Sweetlove and Møller, 2009). For instance, during high-light stress, the excess photosynthetic reducing power is dissipated to the mitochondria via a malate-oxaloacetate shuttle involving AOX and type II NAD(P)H dehydrogenase, thus preventing oxidative damage of thylakoid membranes (Noguchi and Yoshida, 2008; Nunes-Nesi et al., 2008; Scheibe et al., 2005). Further, the proteomic-based studies identified several plant-specific phosphoproteins and phosphorylated proteins associated with the mitochondrial electron transport chain, ATP biosynthesis and TCA cycle, thus indicating a major role of mitochondrial protein phosphorylation in regulating the mitochondrial redox state (Ito et al., 2009). However, information about these mitochondrial kinases and phosphatases regarding their interaction partners and the involvement of reversible phosphorylation in the redox regulation and mitochondrial signaling is not yet fully understood. Furthermore, the relative contribution of plant mitochondria to ROS production is quite low due to the presence of AOX that catalyzes the reduction of O₂ by ubiquinone and competes for electrons (Rhoads et al., 2006).

The processes of redox regulation and ROS metabolism in different cellular compartments are interlinked and involved in optimizing cellular functions via various pathways. Although each subcellular compartment (chloroplast, mitochondria, peroxisomes, cytosol, apoplast, and possibly others) has the capacity to establish and control its own ROS homeostasis, the gradients in redox state in different subcellular compartments generate a stimulus-specific ROS signature (Choudhury

et al., 2016). This ROS signature or signal is then transmitted into the cytosol via aquaporins and modifies the redox state of important regulatory proteins (such as transcription factors affecting nuclear gene expression) and ultimately activates acclimation responses (Choudhury et al., 2016; Mignolet-Spruyt et al., 2016). However, to initiate specific responses to developmental and environmental signals, the ROS signals also integrate with other components of the cell signaling pathways such as RNS, hormones and intracellular Ca²⁺ fluxes (Fig. 5) (reviewed in Baxter et al., 2014; Dietz, 2008; Sewelam et al., 2016).

In recent years, significant progress has been made to identify the individual players and functional hierarchy in the ROS sensing and signaling under stress environments, with emphasis on inter-organellar signaling. In this aspect, the cellular energization and ROS metabolism processes are known to be linked to the MAPK (mitogen-activated protein kinase) signaling pathway that regulates ROS and redox homeostasis (Liu and He, 2017; Pitzschke et al., 2006). Given that H₂O₂ is a mild oxidant with the longest half-life that may be transported across the plasma membrane via aquaporins (Bienert et al., 2006, 2007); therefore, H₂O₂ may directly activate MAPK cascades inside the cell via different MAPKKs, or by inactivating MAPK repressors such as dual-specificity protein tyrosine phosphatase 1 (AtDsPTP1) (Liu and He, 2017; and references therein). Studies on transgenic Arabidopsis have revealed that exogenous H₂O₂ application can activate components of the MAPK cascades (AtMPK3 and AtMPK6) and participate in the oxidative stress signaling pathways (Kovtun et al., 2000). Experiments using transient expression assays in protoplasts showed that AtMPK3 and AtMPK6 activation requires ANP1 (a MAPKKK) that itself can be stimulated by H₂O₂ and can initiate the MAPK cascade for subsequent stress-responsive gene expression, thereby mediating enhanced tolerance against heat shock, freezing and salt stress (Kovtun et al., 2000). Similarly, the Arabidopsis nucleotide diphosphate kinase 2 (AtNDPK2) was reported to be associated with the H₂O₂-mediated MAPK signaling (Moon et al., 2003). H₂O₂ stress strongly induced the expression of AtNDPK2 that interacted with AtMPK3 and AtMPK6, consequently decreasing ROS accumulation and increasing tolerance of transgenic Arabidopsis against salt, cold and oxidative stress (Moon et al., 2003). In another study, it was shown that multiple H₂O₂-generating stimuli induce the expression of Arabidopsis OX11 (oxidative signal-inducible1) gene encoding a serine/threonine protein kinase that is essential for activation of AtMPK3 and AtMPK6 (Rentel et al., 2004). The *Oxi1* null mutants exhibited hypersensitivity to virulent fungal infections and were compromised in the elicitor and ROS-induced MAPK stimulation. Later studies identified OX11 as a key signaling element in both respiratory-burst-produced H₂O₂- and chloroplast-generated ¹O₂-dependent signaling pathways (Rentel et al., 2004; Shumbe et al., 2016). The H₂O₂ signaling pathway is integrated with the components of MAPK pathway to regulate gene expression in defense and hypersensitive responses. Conversely, the ¹O₂-dependent stimulation of OX11 affects the jasmonate signaling pathway that controls the ¹O₂-linked cell death pathways (Shumbe et al., 2016). Nevertheless, the OX11 signal transduction pathway functions independently of the ¹O₂-EX-dependent signaling pathway in cell death observed in the *flu* mutants (op den Camp et al., 2003).

Another example of MAPK signaling related to the retrograde signaling was established in O₂ deficiency experiments. O₂ deprivation of Arabidopsis stimulates mitochondrial production of ROS that move to the cytosol for transient activation of AtMPK3 and AtMPK6 and initiate retrograde signaling between mitochondria and nucleus (Chang et al., 2012). Moreover, AtMPK6 is strongly expressed under high-light stress (800 μmol quanta m⁻² s⁻¹) and regulates the expression of *ERF6* and *ERF104* transcription factors as components of the chloroplast-to-nucleus retrograde signaling that might be crucial in plant tolerance to fluctuating light conditions (Vogel et al., 2014). Taken together, these reports indicate that the ROS-induced retrograde signaling pathways act as important regulators of plant defense against multiple abiotic stresses.

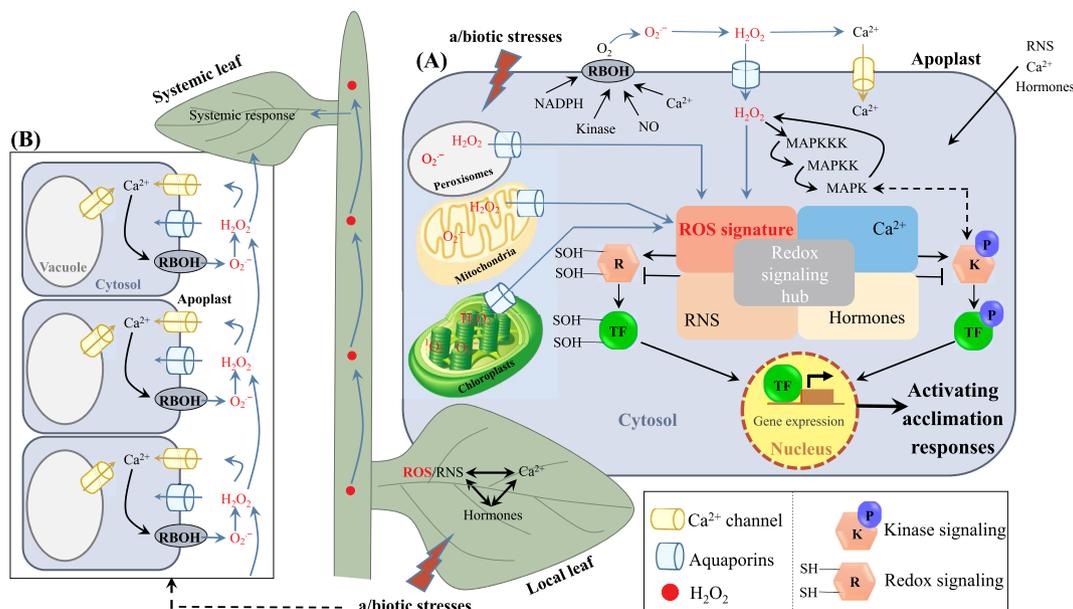


Fig. 5. A simplified model of cellular ROS networks regulating abiotic and biotic stress responses locally and systemically. **(A)** These networks may involve ROS signals produced in different subcellular organelles during abiotic or biotic stresses that trigger reactions outside of the organelle. To initiate the specific responses to developmental and environmental signals, the ROS signals work up- or downstream from many other secondary messengers such as RNS, Ca²⁺, hormones and MAPK signaling in addition to numerous feed-forward and feed-back regulations in an interwoven way that places ROS-induced redox signaling in the core of cellular reactions to a specific stimulus. **(B)** A schematic representation of ROS-mediated intercellular and long-distance communication mediating systemic responses in plants. When a local leaf is exposed to abiotic or biotic stress, it increases cytosolic Ca²⁺ concentration which in turn stimulates RBOH (respiratory burst oxidase homolog) and consequently ROS production. The ROS accumulate in the apoplast, get sensed by the adjacent cell, and activate its ROS/Ca²⁺-activated Ca²⁺ channels, thus triggering Ca²⁺ fluxes and producing ROS in the neighboring cell via RBOH. This phenomenon of ROS/Ca²⁺-activated Ca²⁺ flux that in turn causes RBOH activation and produces apoplastic ROS, and the subsequent process of ROS wave propagation throughout the plant, leads to the activation of systemic acquired acclimation/systemic acquired resistance in the systemic leaf.

5.2. ROS-induced retrograde signaling in response to biotic stresses

Being sessile, plants evolved complex defense and stress acclimation mechanisms that can be initiated in the tissue(s) exposed to stress conditions and transferred to the distal parts not directly exposed to stress. The defense or adaptation mechanisms being triggered in non-infected tissues are called systemic acquired resistance (SAR) or systemic acquired acclimation (SAA), respectively, and both are important in avoiding harmful effects to the whole plant (Alvarez et al., 1998). The ROS involvement in systemic signaling as a component of plant immunity is well known, conferring protection to plants against multiple biotic (e.g. pathogen attack) and abiotic (high light, wounding) stresses (Fig. 5) (Xia et al., 2015).

Induction of the default death pathway [i.e. programmed cell death (PCD)] of a single cell or a group of cells as part of SAR is aimed at restricting disease spread from the infection point; the hypersensitive response to pathogens is the best-studied PCD process in plants (Dangl and Jones, 2001). Increases in the ROS production, accumulation and concomitant signal are necessary for PCD. During a plant–pathogen interaction, the activation of ROS generation and accumulation in various cellular compartments occur in a highly specific manner. For example, in chloroplasts and peroxisomes with the highest rate of ROS production even under non-stress conditions, plants increase ROS production and suppress ROS scavenging mechanisms as a trigger for the PCD onset (op den Camp et al., 2003). However, ROS production in the apoplast (that has low antioxidant buffering) does not induce PCD without suppression of ROS scavengers, indicating the absolute requirement for the coordinated production of ROS and downregulation of ROS scavenging in PCD regulation. Evidence comes from exposure to ozone (Kangasjärvi et al., 2005) or ¹O₂ (Leisinger et al., 2001) that induces ROS signaling, hypersensitive response and SAR. However, in contrast to ozone that enters leaves by diffusion through open stomata and rapidly encounters the cell walls and plasma membrane, ¹O₂ is

primarily produced in the lipid interior of the thylakoid membrane. The cell death/disease resistance pathways induced by the chloroplast-generated ¹O₂ have been studied in the Arabidopsis *flu* mutants (Przybyla et al., 2008). As discussed above, these *flu* mutants accumulate the chlorophyll precursor protochlorophyllide when grown under low light and rapidly accumulate ¹O₂ when transferred from low to high light (op den Camp et al., 2003). The authors suggested that the bleaching response in the *flu* mutant seedlings after exposure to ¹O₂ was not caused by a direct oxidative harm, but was a result of PCD. We already explained that the two nuclear-encoded chloroplast proteins EXECUTER1 (EX1, *executer1/flu* double mutant) and EX2 participate in the ¹O₂-coordinated signaling pathways; inactivation of EX1 prevented the ¹O₂-induced death of *flu* seedlings as well as growth inhibition in mature plants (Wagner et al., 2004). Although suppression of EX1 protein in wild-type Arabidopsis treated with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) also prevented cell death similarly to the findings in the *flu* mutant, the stimulation of ¹O₂ production by DCMU activated a set of genes in wild-type plants that differed from the genes upregulated in the *flu* mutant (Flors et al., 2006). These findings suggest that ¹O₂ can stimulate the retrograde signaling pathway, but it remains unclear how such pathways operate in plants (other than Arabidopsis wild-type vs. *flu* mutants); also, the connection between DCMU and ¹O₂ production is not clear. Nevertheless, based on the pharmacological data available, it appears that ROS removal during pathogen attack reduces PCD (Desikan et al., 1998; Levine et al., 1994); however, transgenic tobacco with decreased APX or CAT expression has enhanced PCD upon bacterial exposure (Mittler et al., 1999).

Other evidence also points to the important role of H₂O₂ that, in contrast to other ROS, can diffuse into cells and activate defense responses, including PCD. A sustained increase in H₂O₂ generation has been reported as a key factor mediating PCD in a dose- and time-dependent manner. During incompatible responses, when PCD is initiated, the generation of H₂O₂ occurs in a biphasic way, with the initial and

then delayed burst of H₂O₂ production (Mittler et al., 2011). The ROS waves link these two phases of ROS burst and propagate systemically the signals from local tissues via the cell-to-cell relay mechanisms (Fig. 5) (Choudhury et al., 2016). In contrast, during compatible interactions, only the first H₂O₂ peak occurs and pathogens can infect the host plant (Baker and Orlandi, 1995; Torres et al., 2006).

In Arabidopsis, the oxidative burst in pathogen-treated leaves was reported to provoke a burst in distal non-infected parts, leading to systemic immunity through the activation of defense-related genes (e.g., GSTs and Gpx) and responses, including PCD (Levine et al., 1994). H₂O₂ modulates the cellular redox state by influencing the recycling of reduced (GSH) and oxidized (GSSG) glutathione forms, with glutathione being associated with induction of pathogenesis-related transcripts (Foyer and Noctor, 2011). Similarly, transgenic tobacco deficient in CAT accumulated H₂O₂ during photosynthesis and exhibited the induction of defense proteins (PR-1, GP_x) locally as well as systemically (Chamnonpol et al., 1996).

Significant attention has also concentrated on the role of salicylic acid in PCD induction and the constitutive expression of pathogenesis-related proteins associated with SAR. Accumulation of H₂O₂ was associated with accumulation of salicylic acid as well, and it was suggested that both ROS and antioxidants (CAT and GSH) were involved in the salicylic acid signaling, whereby H₂O₂ would function downstream of salicylic acid in the pathogenesis-related gene induction (Vandenabeele et al., 2002).

The central role of the MAPK signaling pathway during plant-pathogen interactions has also been well established. For instance, tobacco mosaic virus infection in tobacco (*Nicotiana tabacum*) leaves is known to activate SIPK/WIPK (salicylic acid-/wounding-induced protein kinase) (Zhang and Klessig, 1998) that is linked to the MAPK pathway for subsequent defense responses (Zhang and Liu, 2001). Thus, overexpression of NtMEK2 initiates oxidative burst and cell death similar to the hypersensitive response (Yang et al., 2001). The authors reported that virus-induced gene silencing of NtMEK2 and SIPK/WIPK strongly reduced *N* gene-mediated resistance against tobacco mosaic virus (Jin et al., 2003). Consistent with these findings, NtMEK1 has also been associated with pathogen defense response and hormone signaling (Liu et al., 2003). By using transgenic approaches, several studies reported that AtMPK3, AtMPK4 and AtMPK6 are stimulated by fungal and bacterial PAMPs (pathogen-associated molecular patterns) and ROS (Desikan et al., 2001; Kovtun et al., 2000; Nühse et al., 2000; Petersen et al., 2000). Arabidopsis *MPK4*-silenced plants showed increased resistance to virulent pathogens; AtMPK4 is required for jasmonic acid-mediated gene expression (Petersen et al., 2000). Conversely, *atmpk6* mutant plants exhibited decreased resistance to avirulent pathogens, even though several pathogenesis-related defense genes were expressed similarly to wild-type plants (Menke et al., 2004). A combination of genetic and biochemical approaches suggested that MEKK1-MKK4/MKK5-MPK3/MPK6 function downstream of flagellin receptor FLS2 (flagellin sensing 2), and the transient expression analysis revealed that the overexpression of MEKK1 kinase domain or constitutively active MKK4/MKK5 made leaves resistant to fungal and bacterial pathogens (Asai et al., 2002). Several other studies reported that SIPK-mediated MAPK cascade regulates harpin-induced cell death in *N. tabacum* (Samuel et al., 2005) and INF1-induced cell death in *N. benthamiana* (Takahashi et al., 2007). Further, it has been shown that plant recognition of pathogens/PAMPs (such as bacterial flagellin-derived flg22) triggers rapid production of ROS (via AtRbohD) and activation of MAPKs, two early signaling events after plant sensing of invading pathogens (Jones and Dangl, 2006), and plays an essential role in ROS-related gene expression and other physiological responses, including PCD. However, recent experimental work by Xu et al. (2014) employed chemical and genetic approaches to decipher the complex role of MAPK during such signaling events; it identified that flg22-triggered oxidative burst in Arabidopsis was independent of AtMPK3/AtMPK6. In Arabidopsis mutant plants lacking *AtRbohD*, flg22-triggered ROS burst was

entirely blocked, but AtMPK3/AtMPK6 stimulation was unimpaired. Therefore, authors suggested that, in plant immunity, rapid oxidative burst and AtMPK3/AtMPK6 are two independent signaling events downstream of FLS2. Taken together, these results indicate that the relationship between ROS and MAPK signaling remains elusive and needs to be further investigated.

6. Conclusions and future perspective

Research in the field of ROS and redox biology continues to be exciting and challenging. The emerging concepts indicate that numerous types of oxidative modification/damage are involved in the ROS-induced redox signaling in plants. In this review, the novel biological roles of ROS in regulating many aspects of the plant life cycle and the environmental response mechanisms are discussed.

Despite the extensive and increasing knowledge, several questions remain to be addressed:

- (1) ROS waves and the associated signaling networks are long known to induce local and systemic signaling; however, it remains largely unclear how plant cells perceive and distinguish between different stimuli.
- (2) The specificity of a given ROS species in modulating diverse biological processes is an interesting topic for future exploration.
- (3) A long-term goal is to identify new signaling molecules, such as oxidized or aggregated proteins and to characterize how they feed into the cellular regulatory network.
- (4) Further research is required to understand how ROS interact with phytohormones to create molecular memories of stress.

Answering these key questions is essential to designing improved biotechnology-driven strategies for sustainable crop production in the fluctuating/stress environments. The well-crafted multidisciplinary approaches using advanced imaging, biochemical, genetic, and transgenic techniques will need to be employed in this quest.

Conflicts of interest

None declared.

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Author contribution

Muhammad Ansar Farooq conceived the idea, gathered the literature, prepared the figures and wrote the full paper. Adnan Khan Niazi, Javaid Akhtar and Saifullah edited and commented on the paper. Zahra Souri and Naser Karimi participated in writing some sections of the paper. Muhammad Farooq and Zed Rengel provided the technical guidance and editing support.

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