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REVIEW

Reactive oxygen species in photosystem II: relevance for oxidative signaling

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Abstract

Reactive oxygen species (ROS) are formed in photosystem II (PSII) under various types of abiotic and biotic stresses. It is considered that ROS play a role in chloroplast-to-nucleus retrograde signaling, which changes the nuclear gene expression. However, as ROS lifetime and diffusion are restricted due to the high reactivity towards biomolecules (lipids, pigments, and proteins) and the spatial specificity of signal transduction is low, it is not entirely clear how ROS might transduce signal from the chloroplasts to the nucleus. Biomolecule oxidation was formerly connected solely with damage; nevertheless, the evidence appears that oxidatively modified lipids and pigments are be involved in chloroplast-to-nucleus retrograde signaling due to their long diffusion distance. Moreover, oxidatively modified proteins show high spatial specificity; however, their role in signal transduction from chloroplasts to the nucleus has not been proven yet. The review attempts to summarize and evaluate the evidence for the involvement of ROS in oxidative signaling in PSII.

Keywords Chloroplast-to-nucleus retrograde signaling · Lipid peroxidation · Protein oxidation · Reactive oxygen species

Introduction

In the field environment, plants are exposed to various types of abiotic (high light, heat, cold, drought, flooding, salinity, heavy metals) and biotic (pathogens) stresses (Suzuki et al. 2014; Demidchik 2015). To survive under these conditions, plants have developed an extensive signaling network that regulates gene expression in the nucleus (Apel and Hirt 2004; Laloi and Havaux 2015; Gollan et al. 2015; Dietz et al. 2016; Dogra et al. 2018). As a response to different environmental stresses, reactive oxygen species (ROS) are formed in the chloroplast, by photosystem II (PSII) localized in the appressed region of the thylakoid membrane (grana stacks), and photosystem I (PSI) localized in the non-appressed region of the thylakoid membrane (grana margins and stroma lamellae) (Asada 2006; Triantaphylides and Havaux 2009; Fischer et al. 2013; Telfer 2014; Pospíšil 2016; Khorobrykh et al. 2020). It is generally accepted that ROS play a role in signal transduction from chloroplasts to the nucleus (chloroplast-to-nucleus retrograde signaling) (Suzuki et al. 2012; Schmitt et al. 2014; Noctor and Foyer 2016; Liebthal and Dietz 2017; Foyer 2018). To keep ROS and subsequently signaling in balance, plants developed an antioxidant network, including both the non-enzymatic (low-molecular-weight antioxidants) and enzymatic (superoxide dismutase, catalase, peroxidase) systems (Foyer and Noctor 2005; Kumar et al. 2020; Bassi and Dall'Osto 2021). Under moderate stress, when the antioxidant network can keep ROS level low (balance between ROS formation and scavenging is shifted towards ROS scavenging), ROS maintain signal transduction which activates an acclimation response to advance stress tolerance. Under severe stress, when the antioxidant network is unable to sufficiently eliminate ROS formation either due to an increase in ROS formation or a decrease in antioxidant capacity (balance between ROS formation and scavenging is moved towards ROS formation), ROS mediate signal transduction which leads to the programmed cell death (Foyer et al. 2017; Foyer 2018).

Under high light, ROS are formed by energy transfer and electron transport reactions in PSII. In the energy transfer mechanism, triplet excitation energy transfer from triplet-excited chlorophyll to molecular oxygen (O_2) produced singlet oxygen ($^1O_2$) (Telfer 2005; Krieger-Liszkay et al. 2008; Pospíšil 2012). In the electron transport mechanism, a consecutive one-electron reduction of O_2

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forms superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^{\bullet}$), whereas a concerted two-electron oxidation of water is associated with the formation of H_2O_2, which is reduced to $HO^{\bullet}$ (Pospíšil 2009). Although it is well known that ROS formed in PSII under high light can trigger a wide range of gene expression, it is not apparent (1) how ROS can diffuse for long distance from PSII to the nucleus and (2) how spatial specificity in the transcriptional regulation can be accomplished.

As the grana stacks are tightly packed with a high density of lipids, pigments, and proteins, biomolecule oxidation in PSII occurs to a large extent. It is well accepted that both radical ($HO^{\bullet}$) and non-radical ($^1O_2$) ROS might oxidize lipids, pigments, and proteins. In the radical ROS, the high reactivity of ROS is due to the presence of an unpair electron ($HO^{\bullet}$), which tends to pair up the unpaired electron by abstraction of a hydrogen atom from biomolecule. In the non-radical ROS, the high-energy state ($^1O_2$) is used to incorporate two oxygen atoms into the biomolecule. Due to the high reactivity with surrounding biomolecules, ROS have a very short lifetime (ns to µs) and, thus, can diffuse only for short distances (nm) in the grana stacks (Table 1). As the lifetime and diffusion of ROS depend on the environment nearby the site of ROS formation, PSII located in the grana stacks composed of lipids and tightly packed pigment-protein complexes is an unsuitable environment for long-distance diffusion.

As other metabolically active cellular compartments (chloroplasts, mitochondria, peroxisomes, cytosol, and plasma membrane) produce ROS, the site of ROS formation will not be recognizable by the nucleus. Thus, many ROS ($O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$) lack specific information about the site of their formation; however, some ROS ($^1O_2$) might carry spatial specificity. It is well known that $O_2^{\bullet-}$, H_2O_2, and $HO^{\bullet}$ are not formed solely in the chloroplasts; however, different compartments of cells contribute to their overall cellular formation. On the other hand, as $^1O_2$ is formed predominantly in PSII, thus, $^1O_2$ might be considered as a specific signaling molecule towards the site of ROS formation. However, as triplet-excited carbonyl which might be formed in different cellular compartments, might transfer triplet excitation energy to O_2, spatial specificity of $^1O_2$ might be lost under certain circumstances. As ROS might be formed in different cellular compartments, ROS exhibit low spatial specificity towards the site of ROS formation (Moller and Sweetlove 2010).

Due to diffusion limitation and low spatial specificity, it is unlikely that ROS formed in PSII serve as direct retrograde signaling molecules that transduce the signal from PSII to the nucleus. It seems more likely that fragments of fatty acid, isoprenoid, and amino acid chains formed by fragmentation of oxidatively modified lipids, pigments, and proteins are more appropriate candidates for signaling molecules. Because of their limited reactivity towards other biomolecules, oxidized lipids, pigments, and proteins are more stable and, thus, can diffuse for long distance. Due to more complexity of oxidatively modified biomolecules which might uniquely determine the site of oxidative modification in the cell, oxidized lipids, pigments, and mostly proteins exhibit spatial specificity to selectively regulate nuclear genes. Here, we evaluate evidence that biomolecule fragments arising from the cleavage of oxidatively modified biomolecules exhibit the necessary diffusion and spatial specificity for signal transduction from chloroplast to the nucleus and thus are the most appropriate candidate to regulate specific genes expression under environmental stresses.

ROS formation by PSII

Light-driven processes in PSII are accompanied by the formation of ROS by energy transfer and electron transport reactions. In the energy transfer mechanism, triplet excitation energy transfer from triplet-excited chlorophyll to O_2 forms $^1O_2$ (Krieger-Liszkay et al. 2008; Triantaphylides and Havaux 2009; Telfer 2014). Triplet-excited state is formed either on chlorophylls localized in the PSII antenna complex or on the weakly coupled chlorophyll dimer P_{D1} and P_{D2} (P680) in the PSII reaction center. In the electron transport mechanism, a consecutive one-electron reduction of O_2 forms $O_2^{\bullet-}$, H_2O_2, and $HO^{\bullet}$ at the stromal side of PSII, and a concerted two-electron oxidation of water on the lumenal side of PSII form H_2O_2, which might be further reduced to $HO^{\cdot}$ (Pospíšil 2009). At the stromal side of PSII, a one-electron reduction of O_2 occurs through the redox-active cofactors pheophytin ($Pheo_{D1}^{\bullet-}$) and the plastosemiquinones at the Q_A ($Q_A^{\bullet-}$) and Q_B ($Q_B^{\bullet-}$) sites. Subsequently, $O_2^{\bullet-}$ might

Table 1 Cellular lifetime and cellular diffusion distance for reactive oxygen species

	Cellular lifetime	Cellular diffusion distance	Membrane permeability	Compartment
$^1O_2$	Hundreds ns	Hundreds nm	Yes	Grana ⇒ stroma
$O_2^{\bullet-}$	Units µs	Units µm	No	Grana ⇒ stroma ⇒cytosol
H_2O_2	Tens ms	Tens mm	Yes	Grana ⇒ stroma ⇒ cytosol ⇒ nucleus
$HO^{\bullet}$	Units ns	Units nm	No	Grana

either dismutate to free H_2O_2 or interact with the non-heme iron to form bound peroxide (Pospíšil et al. 2004). Both free and bound peroxide can be reduced to $HO^{\bullet}$ by free iron or non-heme iron. At the lumenal side of PSII, a concerted two-electron oxidation of water is maintained by the Mn_4O_5Ca cluster. When manganese is in the reduced state (Mn^{2+}), H_2O_2 is reduced to $HO^{\bullet}$. From a spatial point of view, ROS are formed at 4 different areas: (1) P_{D1} and P_{D2}-binding domain localized between D and E transmembrane helixes of D1 and D2 proteins, (2) $Pheo_{D1}$-binding domain localized at C transmembrane helix of D1 protein, (3) Q_A and Q_B-binding domain localized in the hydrophilic D-*de* loop region, which connects the D and E transmembrane helices of the D1 and D2 proteins on the stromal side of PSII, and (4) Mn_4O_5Ca cluster-binding domain localized in the C-terminal region of the D1 and D2 proteins on the lumenal side of PSII (Fig. 1).

$^1O_2$ formation at P_{D1} and P_{D2}-binding domain

Singlet oxygen is formed by the triplet–triplet energy transfer from triplet-excited chlorophyll to O_2. In the PSII antenna complex, triplet-excited chlorophyll is formed by the intersystem crossing from singlet-excited chlorophyll when the orientation of electron spin is changed. To prevent the formation of triplet-excited chlorophyll, either singlet-excited chlorophyll or triplet-excited chlorophyll is quenched by coupled carotenoids such as carotenes (β-carotene) and their oxygenated derivatives xanthophylls (lutein, zeaxanthin). However, when chlorophylls are only weakly coupled or uncoupled with carotenoids, carotenoids cannot quench triplet-excited chlorophyll, and thus, triplet-excited chlorophyll transfers excitation energy to O_2. In the PSII reaction center, triplet-excited chlorophyll is formed by charge recombination of triplet radical pair $^3[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ formed by a change in the spin orientation of singlet radical

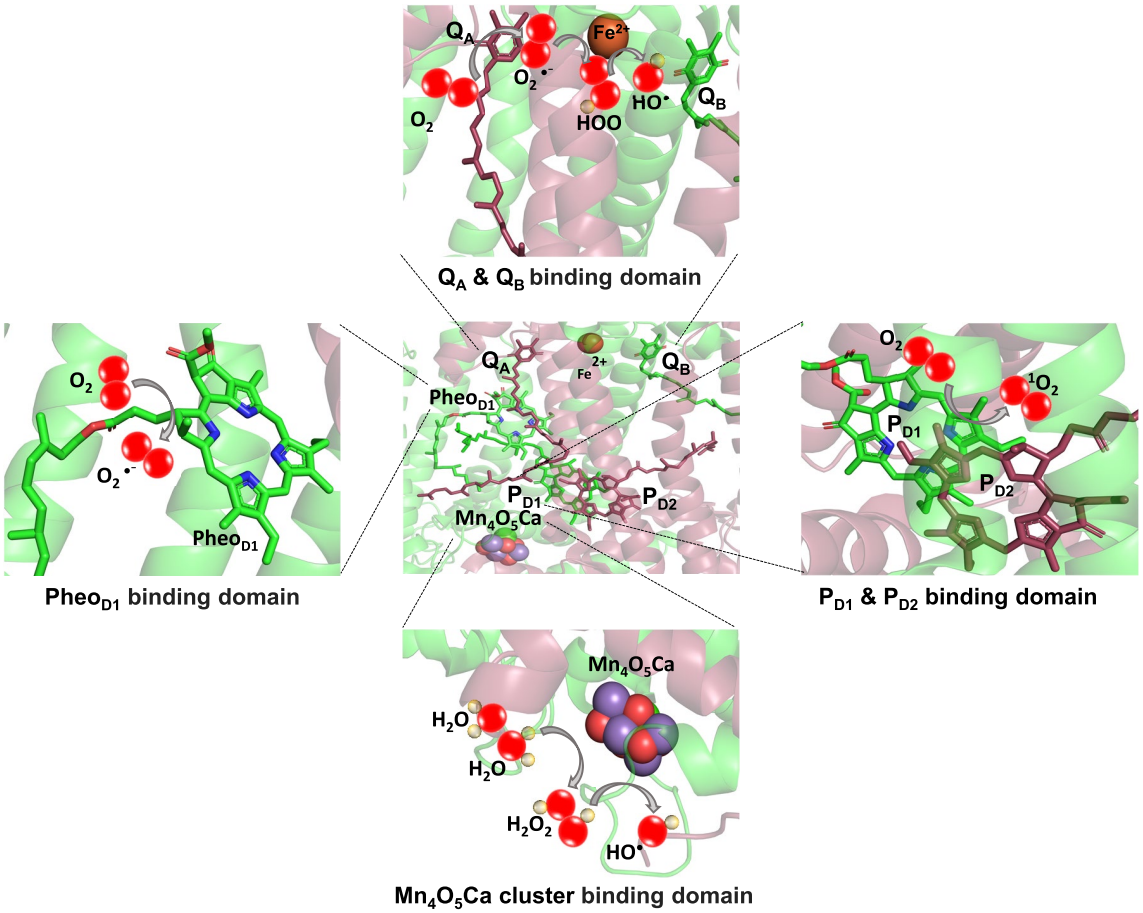


Fig. 1 ROS formation at binding sites of the redox-active cofactors in PSII. Four binding sites of ROS formation were identified: (1) P_{D1} and P_{D2}-binding domain localized between D and E transmembrane helixes of D1 and D2 proteins. (2) $Pheo_{D1}$-binding domain localized at C transmembrane helix of D1 protein. (3) Q_A and Q_B-binding domain localized in the hydrophilic D-*de* loop region, which connects the transmembrane helices D and E of the D1 and D2 proteins on the stromal side of PSII. (4) Mn_4O_5Ca cluster-binding domain localized in the C-terminal region of the D1 and D2 proteins on the lumenal side of PSII. The image was completed with Pymol (DeLano 2002) using the structure for PSII from *Spinacia oleracea* (PDB ID: 3JCU) (Wei et al. 2016)

pair $^{1}[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ (Vass 2012; Tyystjarvi 2013). As P_{D1} and P_{D2} dimer are not coupled with carotenoids (Car_{D1} and Car_{D2}), β-carotenes are not able to quench triplet-excited chlorophylls, and thus, the transfer of excitation energy from triplet-excited chlorophylls to O_2 might occur (Fig. 1). Apart from triplet-excited chlorophyll, triplet-excited carbonyl might transfer excitation energy to O_2 (Pospíšil and Yamamoto 2017; Pospíšil et al. 2019). Triplet-excited carbonyls are formed by the breakdown of high-energy intermediates (dioxetane or tetroxide) formed by the decomposition of lipid or protein hydroperoxides (Miyamoto et al. 2014; Pospíšil et al. 2014). Lipid and protein hydroperoxides are produced during lipid peroxidation and protein oxidation. While $^{1}O_2$ formation by the triplet–triplet energy transfer from triplet-excited carbonyls is negligible compared to triplet-excited chlorophyll, it might occur when ROS initiate lipid peroxidation and protein oxidation in different sites of the thylakoid membrane, even in those where chlorophyll is not located.

$O_2^{\bullet-}$ formation at $Pheo_{D1}$-binding domain

Superoxide anion radical is formed by one-electron reduction of O_2 by $Pheo_{D1}^{\bullet-}$ at $Pheo_{D1}$-binding domain (Fig. 1). The reduction of O_2 by $Pheo_{D1}^{\bullet-}$ is highly feasible from the thermodynamic point of view (the midpoint redox potential of $Pheo_{D1}/Pheo_{D1}^{\bullet-}$ redox couple is highly negative); however, less possible in terms of kinetic considerations (short lifetime of $Pheo_{D1}^{\bullet-}$ is insufficient for the diffusion-limited reduction). Due to the negative charge on molecule, $O_2^{\bullet-}$ has limited diffusion away from the site of production. When protons are available, protonated form of superoxide radical, hydroperoxyl radical ($HO_2^{\bullet}$), is formed. Due to the lack of negative charge on the molecule, $HO_2^{\bullet}$ can diffuse farther away from $Pheo_{D1}$.

$O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$ formation at Q_A and Q_B-binding domain

Superoxide anion radical is formed by one-electron reduction of O_2 by $Q_A^{\bullet-}$ and $Q_B^{\bullet-}$ at Q_A- and Q_B-binding domains, respectively (Fig. 1). The reduction of O_2 by $Q_A^{\bullet-}$ and $Q_B^{\bullet-}$ is from the thermodynamic perspective less feasible (the midpoint redox potential of $Q_A/Q_A^{\bullet-}$ redox couple is close to 0 mV); however, highly probable from the kinetic point of view (long lifetimes of $Q_A^{\bullet-}$ and $Q_B^{\bullet-}$ are sufficient for the diffusion-limited reduction of O_2). As Q_A and Q_B-binding domains are near the membrane edge, the availability of O_2 is appropriate. Apart from the reduction of free O_2, the reduction of O_2 bound to the non-heme iron by $Q_A^{\bullet-}$ was proposed to be more advantageous due to the better accessibility of O_2 to the non-heme iron and decrease of the redox potential of $O_2/O_2^{\bullet-}$ redox couple (Fantuzzi et al. 2022). Superoxide anion radicals dismutate either to free H_2O_2 (non-enzymatic dismutation) or interact with the non-heme iron to form bound peroxide (enzymatic dismutation). In non-enzymatic dismutation, the dismutation of two $O_2^{\bullet-}$ is limited due to the repulsion of the negative charges. However, when $O_2^{\bullet-}$ is protonated to $HO_2^{\bullet}$, the lack of negative charge on the molecule makes the dismutation feasible. In the enzymatic dismutation, reduction and oxidation of $O_2^{\bullet-}$ are associated with the redox changes of the non-heme iron, which serves as a superoxide oxidase (SOO) and superoxide reductase (SOR), respectively (Pospíšil 2014). In the SOR reaction, interaction of $O_2^{\bullet-}$ with the non-heme iron results in the oxidation of the ferrous iron and the formation of ferric-peroxo species, which is protonated to ferric-hydroperoxo species (bound hydroperoxide). Both free and bound peroxides are reduced to $HO^{\bullet}$ by free iron or non-heme iron, respectively. The free iron reduces H_2O_2 to $HO^{\bullet}$ and OH^{-} in the Fenton reaction. As the Q_A and Q_B-binding domain is close to the membrane edge, the presence of free transitional metals (mainly Fe^{2+}) cannot be ruled out. Alternatively, the reduction of bound peroxide (ferric iron-hydroperoxo intermediate) formed by the interaction of $O_2^{\bullet-}$ with the ferrous non-heme iron forms $HO^{\bullet}$ via ferric iron-oxo intermediate.

H_2O_2 and $HO^{\bullet}$ formation at Mn_4O_5Ca cluster-binding domain

Hydrogen peroxide is formed by two-electron oxidation of water by the Mn_4O_5Ca cluster (Fig. 1). The incomplete two-electron oxidation of water to H_2O_2 occurs when the complete four-electron oxidation of water to O_2 is limited. While four-electron oxidation of water to O_2 is catalyzed by four redox-active manganese ions, two redox-active manganese ions oxidize water to H_2O_2. Incomplete oxidation of water is caused by the uncontrolled delivery of water to the Mn_4O_5Ca cluster. The release of chloride from its binding site near the Mn_4O_5Ca cluster leads to uncontrolled accessibility of H_2O to the Mn_4O_5Ca cluster. Hydrogen peroxide is guided from the catalytic center into the lumen via water channels (Weisz et al. 2017). However, H_2O_2 might be reduced by Mn^{2+} released from the Mn_4O_5Ca cluster to $HO^{\bullet}$ and OH^{-} (Pospíšil et al. 2007; Yamashita et al. 2008).

Direct ROS signaling in PSII

Due to the limited diffusion of ROS in the thylakoid membrane, direct signal transduction from the sites of ROS formation in PSII to the nucleus is questionable. The actual ability of ROS to diffuse out to any distance is determined by the rate of diffusion and the presence of biomolecules (lipids, pigments, and proteins) capable of reacting with

ROS. The diffusion rate depends on ambient temperature and viscosity of the environment and, thus, is considered relatively constant inside the thylakoid membrane. On the opposite side, the presence of biomolecules may vary considerably depending upon the site of ROS formation. As the grana stacks are highly packed with lipids, pigments, and proteins, the reaction of ROS with biomolecules in this area occurs within a very short diffusion distance at the site of ROS formation. Thus, the diffusion of ROS from PSII to the nucleus and the direct oxidation of a transcription factor by ROS seem unlikely. These considerations are in an agreement with imaging of ROS formation obtained by confocal laser scanning microscopy using a fluorescent probe which shows that ROS are localized solely in the chloroplasts located at the periphery of the cells (Fig. 2).

As ROS carry no information on the site of their formation, a fundamental question arises how might the nucleus determine the site of ROS formation. While only some ROS ($^1O_2$) might carry some spatial specificity under certain circumstances, many ROS ($O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$) are rather unspecific about the site of their formation. As $^1O_2$ is formed by an energy transfer mechanism where triplet excitation energy is transferred from triplet-excited chlorophyll to O_2, $^1O_2$ formation is expected to be solely associated with chloroplast, particularly with PSII. Evidence has been provided that apart from triplet-excited chlorophyll, triplet-excited carbonyl might transfer excitation energy to O_2 (Pospíšil et al. 2019). It was demonstrated that $^1O_2$ is formed by energy transfer from triplet-excited carbonyl to O_2 in PSII membranes deprived of the Mn_4O_5Ca cluster (Pathak et al. 2017). However, as triplet-excited carbonyl is formed by the decomposition of cyclic (1,2-dioxetane) and linear (tetroxide) high-energy intermediates produced during lipid peroxidation and protein oxidation, triplet-excited carbonyl might be formed in different cellular compartments. Contrary, ROS ($O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$) formed by electron transport reaction are unspecific towards the site of their formation as these ROS are produced in different cell compartments (mitochondria, peroxisomes, cytosol, plasma membrane).

Singlet oxygen signaling

Chloroplast-to-nucleus retrograde signaling by $^1O_2$ is improbable due to high reactivity to lipids, pigments, and proteins. Due to high reactivity, $^1O_2$ has a short cellular lifetime (hundreds of ns) and a short cellular diffusion distance (hundreds of nm) (Table 1). Singlet oxygen reacts with lipids, pigments, and proteins to form endoperoxides and hydroperoxides (Di Mascio et al. 2019). Endoperoxides are formed by the cycloaddition of $^1O_2$ to polyunsaturated fatty acids and amino acids, whereas lipid and protein hydroperoxides are produced by the ene reaction with polyunsaturated fatty and amino acids. Lipid and protein hydroperoxides are oxidized and reduced to lipid and protein peroxyl and alkoxyl radicals, respectively. Within a diffusion distance of hundreds of nm, $^1O_2$ can diffuse out of the grana stacks (granum size of 300 nm) into the chloroplast stroma. Indeed, $^1O_2$ produced by PS II in thylakoid membranes isolated from Arabidopsis was detected via reactions with a hydrophilic spin-probe TEMPD (2,2,6,6-tetramethyl-4-piperidone)

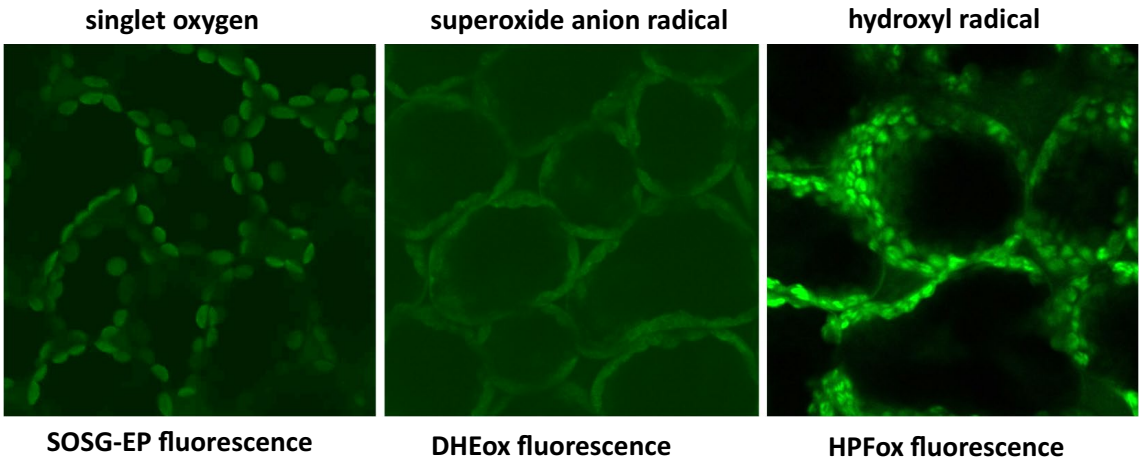


Fig. 2 Imaging of ROS formation in Arabidopsis leaves. The imaging of $^1O_2$, $O_2^{\bullet-}$, and $HO^{\bullet}$ in leaves was performed by confocal laser scanning microscopy using singlet oxygen sensor green (SOSG) ($^1O_2$), dihydroxy ethidium (DHE) ($O_2^{\bullet-}$), and 3′-p-(hydroxyphenyl) fluorescein (HPF) ($HO^{\bullet}$) fluorescent probes. The reaction of fluorescent probes with ROS forms oxidized fluorescent probes (SOSG-EP, DHEox, and HPFox) providing the fluorescences. The fluorescent probes SOSG (50 µM), DHE (100 µM) and HPF (10 µM) were infiltrated into leaf and exposed to high light (1000 µmol photons m^{-2} s^{-1}) for 30 min. The fluorescent probes were excited by a 488 nm argon laser and the fluorescence was detected in the spectral range 505–525 nm (SOSG, HPF) and 505–605 nm (DHE) (Prasad et al. 2018; Kumar et al. 2018)

yielding long-living paramagnetic TEMPONE (2,2,6,6-tetramethyl-4-piperidone-1-oxyl) detectable by electron paramagnetic resonance spectroscopy (Ferretti et al. 2018). Reaction of $^1O_2$ with the hydrophilic TEMPD confirms that $^1O_2$ is present in the aqueous phase.

Superoxide anion radical signaling

Even if $O_2^{\bullet-}$ has low reactivity to lipids, pigments, and proteins, signal transduction from chloroplasts to the nucleus by $O_2^{\bullet-}$ is impossible due to the negative charge on the molecule. As a result of low reactivity, $O_2^{\bullet-}$ has a long cellular lifetime (units of µs) and a long cellular diffusion distance (units of µm) (Table 1). Even if $O_2^{\bullet-}$ has oxidizing property (E_0´ of $O_2^{\bullet-}/H_2O_2 = 0.89$ V), the anionic form of the superoxide radical is not capable of oxidizing lipids, pigments, and proteins. The exceptions are an iron–sulfur cluster and aromatic amino acids (tyrosine and tryptophan). In the iron–sulfur cluster, $O_2^{\bullet-}$ oxidizes ferrous to ferric iron (Liochev and Fridovich 1994). In the aromatic amino acids, $O_2^{\bullet-}$ reacts with the phenoxyl radical of tyrosine or indolyl radical of tryptophan formed by abstraction of hydrogen atom from either the oxygen atom of the hydroxyl group of the phenyl ring of tyrosine or the nitrogen atom of the amine group of the indole ring of tryptophan (Davies 2016). Within the diffusion distance of units of µm, $O_2^{\bullet-}$ can diffuse out of the chloroplast (chloroplast size of 3–5 µm) into the cytosol. However, $O_2^{\bullet-}$ has to cross the inner and outer chloroplast membrane to reach the cytosol. As $O_2^{\bullet-}$ has a negative charge at neutral pH, it cannot cross the membrane due to the electrostatic repulsion of the negatively charged membrane (Guskova et al. 1984). The loss of negative charge due to the protonation of $O_2^{\bullet-}$ to $HO_2^{\bullet}$ allows diffusion across the membrane; however, $HO_2^{\bullet}$ is more reactive compared to $O_2^{\bullet-}$, and thus, $HO_2^{\bullet}$ can directly abstract hydrogen atom from lipids, pigments, and proteins. The capability of $HO_2^{\bullet}$ to abstract hydrogen atom from lipids, pigments, and proteins is due to the more positive redox potential (E_0´ $HO_2^{\bullet}/H_2O_2$ redox couple 1.06 V) and the lack of a negative charge on the molecule.

Hydrogen peroxide signaling

Chloroplast-to-nucleus retrograde signaling by H_2O_2 can occur due to low reactivity to lipids, pigments, and proteins. As a consequence of low reactivity, H_2O_2 has a long cellular lifetime (tens of ms) and a long cellular diffusion distance (tens of mm). It is well established that H_2O_2 is poorly reactive, with almost no capability to oxidize lipids, pigments, and proteins (Halliwell and Chirico 1993; Davies 2016). The cellular diffusion distance of tens of mm facilitates diffusion of H_2O_2 from chloroplast to nucleus. As a non-radical and uncharged molecule, H_2O_2 can cross the membrane by free diffusion or by aquaporins known as peroxiporins (membrane channels formed by transmembrane proteins) (Bienert et al. 2007). It has been proposed that H_2O_2 passes through the chloroplast membrane and directly transduces the signal to the nucleus (Mubarakshina et al. 2010). It was shown that H_2O_2 diffuses out of chloroplasts through the chloroplast membrane via aquaporins (Borisova et al. 2012). Hydrogen peroxide formed by the PQ-pool was shown to control *lhcb* gene expression, which is responsible for the synthesis Lhcb proteins (Borisova-Mubarakshina et al. 2015). It has been demonstrated in photosynthetic *Nicotiana benthamiana* epidermal cells that H_2O_2 diffuses from chloroplasts to nucleus directly via stromules and, thus, controls the gene expression during acclimation to high light. Based on the analogy with the OxyR-binding domain of H_2O_2 in bacteria *Escherichia coli* which contains two cysteines, the authors proposed that H_2O_2 oxidizes two cysteines of the transcriptional factor to form a disulfide bridge which causes the conformation changes of transcriptional factor to activate/deactivate genes (Exposito-Rodriguez et al. 2017).

Hydroxyl radical signaling

The involvement of $HO^{\bullet}$ in chloroplast-to-nucleus retrograde signaling might be likely ruled out due to the high reactivity to lipids, pigments, and proteins. As a result of high reactivity, $HO^{\bullet}$ has a short cellular lifetime (units of ns) and a short cellular diffusion distance (units of nm) (Table 1). High reactivity to biomolecules is caused by the highly positive redox potential of the $HO^{\bullet}/H_2O$ redox couple (E_0´$(HO^{\bullet}/H_2O) = 2.3$ V, pH 7). In polyunsaturated fatty acids, the abstraction of a hydrogen atom from the carbon atom next to the double bond causes the production of lipid alkyl radicals. In aliphatic amino acids (glycine, alanine, valine, leucine, isoleucine, and proline), the initiation of oxidation by $HO^{\cdot}$ occurs through the abstraction of a hydrogen atom at the carbon atom forming protein alkyl radicals. The oxidation of the aromatic amino acids (tyrosine and tryptophan) occurs by the abstraction of a hydrogen atom by $HO^{\bullet}$ at the oxygen atom of the hydroxyl group of the phenyl ring forming phenoxyl radical (tyrosine) and the nitrogen atom of the amine group of the indole ring forming indolyl radical (tryptophan). The formation of lipid and protein alkyl radicals by $HO^{\bullet}$ initiates a cascade of reactions leading to lipid peroxidation and protein oxidation, respectively. It is generally accepted that $HO^{\bullet}$ reacts with polyunsaturated fatty acids and amino acids nearby the production site, with limited diffusion to other targets far from the production site.

Oxidative signaling

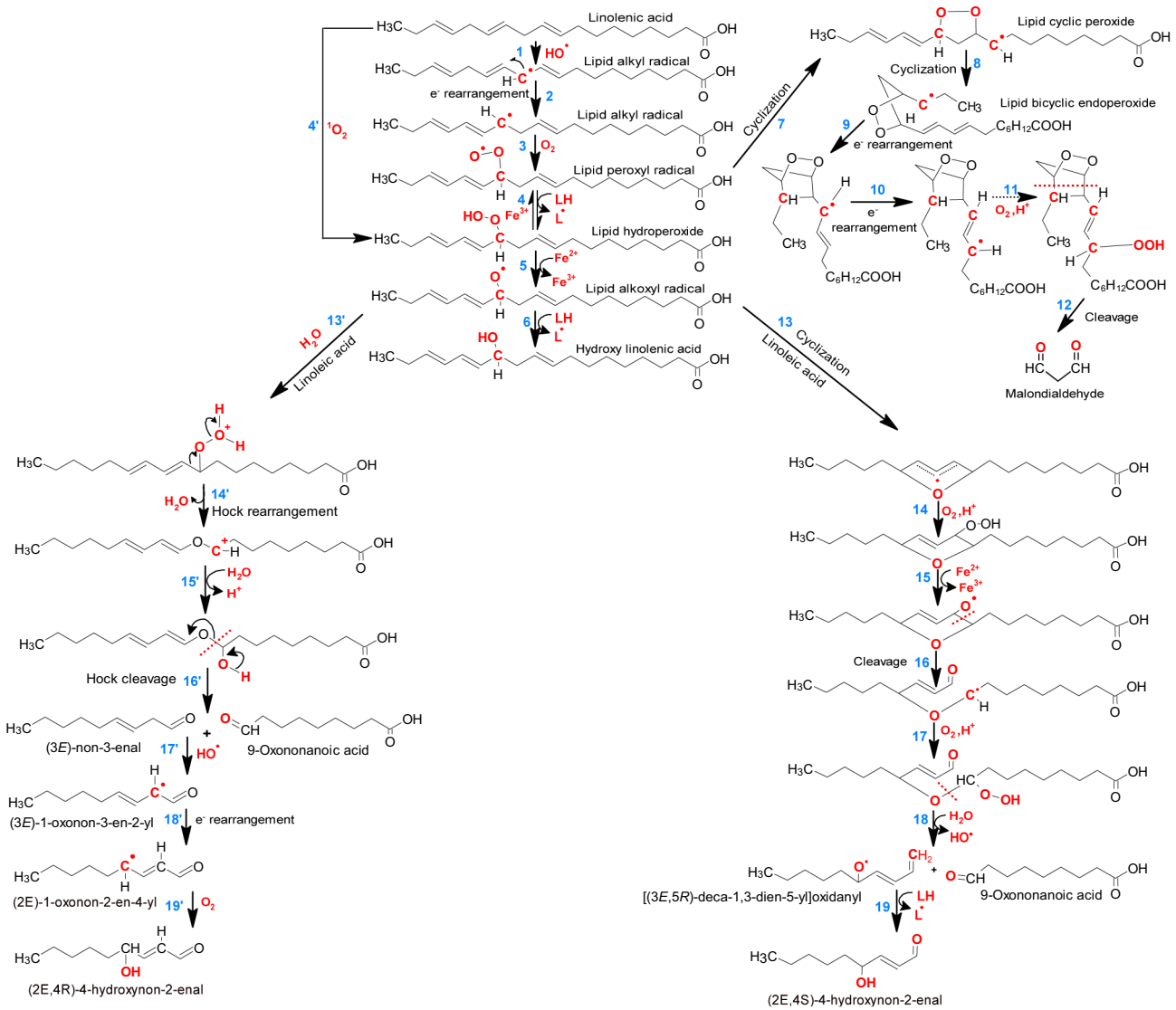
Oxidatively-modified biomolecules by ROS formed in PSII might transduce the signal to the nucleus in oxidative signaling. As the oxidation causes the cleavage of fatty acid, isoprenoid, and amino acid chains, fragments of lipids, pigments, and proteins are typically small molecules that might penetrate through the membrane. Due to their lower reactivity towards other biomolecules, their cellular lifetime and cellular diffusion are enough to transduce the signal for a long distance. As the length and saturation of fatty acid chains do not differ significantly between the cellular compartments, the spatial specificity of oxidative signaling by lipid is less compared to proteins. As each protein has a unique structure arising from the unambiguous sequence of amino acids with definite characteristics given by the size, shape, polarity, and charge, oxidative signaling by protein has a high spatial specificity. The signal transduction from PSII to the nucleus by oxidized lipids, pigments, and proteins might occur either directly or at multiple levels. In the direct signaling pathway, biomolecule fragments can diffuse out of the thylakoid membrane, move through the stroma, cross inner and outer chloroplast membranes, and via cytosol diffuse to the nucleus. In the cytosol or nucleus, oxidized biomolecules interact with transcription factors which are proteins that bind to DNA in order to modulate the gene expression by promoting or suppressing transcription. In the multiple levels signaling pathway, the targets by oxidized lipids, pigments, and proteins are unknown.

Oxidative signaling by lipids

The crystal structure of cyanobacterial homodimeric PSII at 2.9 Å resolution showed the position of 25 lipid molecules per monomer comprising of 18 galactolipids (11 monogalactosyl-diacylglycero, MGDG and 7 digalactosyl-diacylglycerol, DGDG), 5 sulfoquinovosyl-diacylglycerol (SQDG), and 2 phosphatidyl-glycerol (PG) (Guskov et al. 2009). Several types of unsaturated fatty acids of lipids, such as oleic acid (18:1), linoleic acid (18:2), and linolenic acid (18:3), were identified in PSII. As the fatty acids in PSII span the membrane from the stromal to the lumenal side of PSII, the double bond in unsaturated fatty acids is prone to ROS formed at different binding sites of the redox-active cofactors in PSII. Several lipids (MGDG18, SQDG-3, SQDG4, and PG3 PG22) were found to be located near Q_A and Q_B-binding domain. Particularly, SQDG-3 is close to the Q_B-binding site at a position about 10 Å away from Q_B.

Lipid oxidation by ROS

Due to double bonds in unsaturated fatty acids, lipids are easily oxidized by both radical ($HO^{\bullet}$) (Type I reaction) and non-radical ($^1O_2$) (Type II reaction). Oxidation of lipids by ROS forms primary products of lipid peroxidation which decompose to secondary products of lipid peroxidation. Lipid hydroperoxide (hydroperoxy fatty acids), a primary product of lipid peroxidation, is formed by the addition of two oxygen atoms in fatty acid (Niki et al. 2005) (Fig. 3). In the radical reaction, the abstraction of weakly bonded hydrogen atoms from polyunsaturated fatty acid by $HO^{\bullet}$ forms lipid alkyl radical (carbon-centered radical), which reacts with O_2 at a diffusion-limited rate forming lipid peroxyl radical (Yin et al. 2011). When lipid peroxyl radical abstracts a hydrogen atom from nearby polyunsaturated fatty acid, lipid hydroperoxide is created (Girotti 1998). In the non-radical reaction, the addition of $^1O_2$ to double bonds of polyunsaturated fatty acid forms lipid hydroperoxide via ene reaction (Di Mascio et al. 2019). When reducing (Fe^{2+}) and oxidizing (Fe^{3+}) compounds are lacking, lipid hydroperoxide is relative stability. The relative stability of lipid hydroperoxide is caused by the lack of unpaired electrons which allows to lipid hydroperoxide migrate from the site of formation in PSII and translocate the signal from the thylakoid membrane to stroma. Lipid hydroperoxide decomposes to hydroxy fatty acids and reactive carbonyl species, a secondary product of lipid peroxidation (Fig. 3). Both hydroxy fatty acids and reactive carbonyl species contain one additional oxygen atom in fatty acid in the form of hydroxy and carbonyl groups, respectively. When reduced transition metals (Fe^{2+}, Mn^{2+}, Cu^{+}) are present close to lipid hydroperoxide, it is reduced to lipid alkoxyl radical (Yin et al. 2011). Hydroxy fatty acids are formed by the abstraction of a hydrogen atom from a nearby fatty acid by lipid alkoxyl radical while another lipid alkyl radical is formed. In the presence of oxidized transition metals (Fe^{3+}, Mn^{3+}, Cu^{2+}), lipid hydroperoxide is oxidized back to lipid peroxyl radical. Reactive carbonyl species such as malondialdehyde (MDA) and 4-hydroxy-(E)-2-nonenal (HNE) are formed by the cyclization of lipid peroxyl and alkoxyl radicals, respectively. The cyclization of lipid peroxyl radical forms lipid cyclic peroxide with unpaired electron on the carbon atom and rearrangement of the unpaired electron form lipid bicyclic endoperoxide. Lipid bicyclic endoperoxide decomposes to MDA. Similarly, HNE is formed by the reactions comprising the formation of lipid endoperoxide by cyclization of lipid alkoxyl radical. Furthermore, HNE is formed by the Hock rearrangement via oxononanoic acid intermediate.



Oxidative signaling by lipid peroxidation product

It is well documented that MDA and HNE serve as signaling molecules (Mano et al. 2019; Farmer and Mueller 2013). The signaling functions of MDA and HNE originate from their capacity to react with nucleophilic moieties of the amino acid (Lys, Arg, Cys, and His) and thereby modified the function of target molecules (transcription factor). Malondialdehyde exists in two forms with different chemical reactivity. Anionic enolate aldehyde with low chemical reactivity is the dominating form at high pH, whereas protonated enol aldehyde and dialdehyde with high chemical reactivity are the dominating forms at low pH (Ayala et al. 2014). It was proposed that two forms with different chemical reactivities might modulate gene expression in different ways (Weber et al. 2004).

Oxidative signaling by pigments

The crystal structure of PSII from thermophilic cyanobacteria *Thermosynechococcus elongatus* showed that β-carotene molecules are located in the PSII core antenna (CP47 and CP43 proteins) and the PSII reaction center. Nine β-carotenes are bound to the PSII core antenna (4 β-carotenes in CP43 and 5 β-carotenes in CP47), whereas two β-carotenes are bound in the PSII reaction center (1 β-carotene to D1 and 1 β-carotene to D2 protein) (Loll et al. 2005).

Pigment oxidation by ROS

Oxidation of β-carotene by $^1O_2$ leads to the production of volatile ketonic and aldehydic derivatives of β–carotene such

◂**Fig. 3** Lipid oxidation by ROS. Abstraction of hydrogen atom from the carbon atom next to the double bond generates a lipid alkyl radical (reaction 1). An unpaired electron on the carbon atom is rearranged to nearby carbon atom (reaction 2). The reaction of lipid alkyl radical with molecular oxygen (O_2) forms lipid peroxyl radical (reaction 3). Abstraction of hydrogen atom from an adjacent lipid by lipid peroxyl radical forms lipid hydroperoxide while another lipid alkyl radical is formed. In the presence of oxidized transition metals (Fe^{3+}), lipid hydroperoxide is oxidized back to lipid peroxyl radical (reaction 4). The addition of $^1O_2$ to the double bond of lipid via ene reaction forms lipid hydroperoxide (reaction 4′). In the presence of reduced transition metals (Fe^{2+}), lipid hydroperoxide forms lipid alkoxyl radical (reaction 5). Abstraction of hydrogen atom from an adjacent lipid by lipid alkoxyl radical forms hydroxy fatty acids (reaction 6). Cyclization of lipid peroxyl radical forms lipid cyclic peroxide with the unpaired electron localized on carbon atom (reaction 7) which further cyclize to form lipid cyclic endoperoxide (reaction 8). Rearrangement of the unpaired electron within the lipid cyclic endoperoxide forms lipid bicyclic endoperoxide (reaction 9) followed by another electron rearrangement (reaction 10). The lipid bicyclic endoperoxide reacts with O_2 to form lipid peroxyl radical followed by abstraction of hydrogen atom from adjacent lipid to form lipid bicyclic endoperoxy hydroperoxide (reaction 11). Cleavage of lipid bicyclic endoperoxy hydroperoxide forms MDA (reaction 12). Cyclization of lipid alkoxyl radical from linoleic acid forms lipid cyclic alkoxyl radical (reaction 13) or react with water molecule to form acidified lipid hydroperoxide (reaction 13′). The lipid cyclic alkoxyl radical reacts with O_2 in the presence of H^+ to form lipid cyclic hydroperoxide (reaction 14). Acidified lipid hydroperoxide leaves the group when the C–C bond rearranges to C–O bond as Hock rearrangement to form lipid carbonium ion (reaction 14′). The lipid cyclic hydroperoxide in the presence of reduced transition metal (Fe^{2+}) forms lipid cyclic alkoxyl radical (reaction 15). Hydrolysis of unstable carbonium ion forms hydroxy fatty acid (reaction 15′). Cleavage of lipid cyclic alkoxyl radical forms lipid alkyl radical (reaction 16). Hock cleavage of hydroxy lipid forms oxononanoic acid and (*3E*)-non-3-enal (reaction 16′). The lipid alkyl radical reacts with O_2 in the presence of H^+ to form lipid hydroperoxide (reaction 17). Abstraction of hydrogen atom from the carbon atom by $HO^•$ forms lipid alkyl radical [(*3E*)-1-oxonon-3-en-2-yl radical] (reaction 17′). Hydrolysis of lipid hydroperoxide forms 9-oxononanoic acid and lipid alkoxyl radical (reaction 18). The electron rearrangement forms lipid alkyl radical at another carbon atom (reaction 18′). Abstraction of hydrogen atom by lipid alkoxyl radical from another lipid forms HNE (reaction 19). The lipid alkyl radical reacts with O_2 to form HNE via intermediates (lipid peroxyl, lipid hydroperoxide, and lipid alkoxyl radical) (intermediates not shown) (reaction 19′)

as β–ionone and β–cyclocitral, respectively (Ramel et al. 2013). The cycloaddition of $^1O_2$ with diene forms β–carotene-7,10-endoperoxide, which is cleaved to β–cyclocitral (Fig. 4). As chlorophylls in the PSII core antenna are strongly coupled with carotenoids (β-carotenes and xanthophylls), the formation of triplet-excited chlorophyll is prevented limiting $^1O_2$ formation. However, as two β-carotenes in the PSII reaction center (Car_{D1} and Car_{D2}) are distanced from chlorophyll dimer P_{D1} and P_{D2}, the inability of β-carotenes to quench triplet-excited chlorophyll results in $^1O_2$ formation. In agreement with this consideration, it is considered that oxidation of β-carotene by $^1O_2$ takes place predominantly in the PSII reaction center.

Oxidative signaling by pigment oxidation product

Based on the observation that exogenous application of β-cyclocitral on Arabidopsis plants modified the expression of a large set of genes, it was proposed that β-cyclocitral serves as a signaling molecule that mediates gene responses (Ramel et al. 2012). As β-cyclocitral is formed specifically by $^1O_2$ and the majority of the genes affected by β-cyclocitral was identified as $^1O_2$-responsive genes, it was concluded that β-cyclocitral is an intermediate in the signaling initiated by $^1O_2$. β-cyclocitral contains a carbonyl group adjacent to a double bond that can oxidize sulfur and nitrogen atoms which are present in many biomolecules. As the β-carbon in the α,β-unsaturated carbonyl group is methylated in β-cyclocitral, β-cyclocitral is less reactive to biomolecules and, thus, might diffuse for long distance. β-cyclocitral can diffuse easily out of the PSII reaction center either into the lumen or the stroma (D'Alessandro and Havaux 2019). When β-cyclocitral diffuses into the lumen, it is protonated due to the acidic environment in the lumen (pH 4.5–6.5). The protonated β-cyclocitral is oxidized to β-cyclocitric acid (Fig. 4). We suggest that manganese in the oxidized state (Mn^{3+} or Mn^{4+}) at Mn_4O_5Ca cluster might cause oxidation of β-cyclocitral to β-cyclocitric acid at the luminal side of the thylakoid membrane. It was proposed that β-cyclocitric acid can diffuse from the lumen to the stroma using transporters (D'Alessandro and Havaux 2019). When β-cyclocitral diffuses into the stroma, it remains in the aldehydic form due to alkaline (pH 7–8) and reducing environment in the stroma. From the chloroplast, β-cyclocitral diffuses into the cytosol and subsequently into the nucleus. Two signaling pathways comprising Methylene Blue Sensitivity 1 (MBS1) and TGA II transcription factors were described. In MBS1 signaling pathway, MBS1 transcription factor located in the cytosol is oxidized by β-cyclocitral and diffuses to the nucleus where it regulates $^1O_2$ responsible genes (Shumbe et al. 2017). In TGA II signaling pathway, β-cyclocitral oxidizes SCARECROW-like 14 (SCL14) transcription regulator in the nucleus which interacts with TGAII transcription factors. The SCL14/TGA II complex enhances the transcriptional levels of the ANAC102 transcription factor which controls the downstream ANAC002, ANAC031, and ANAC081 transcription regulators (D'Alessandro et al. 2018) which affect $^1O_2$-responsive genes and genes responsible for the synthesis of redox-active antioxidant enzymes. β-cyclocitral can play an important role as a signaling molecule stimulating gene expression with protective functions that can enhance chloroplast antioxidant capacity (D'Alessandro et al. 2018).

Oxidative signaling by proteins

Oxidatively modified proteins involved in oxidative signaling are typically peptides comprising several tens of

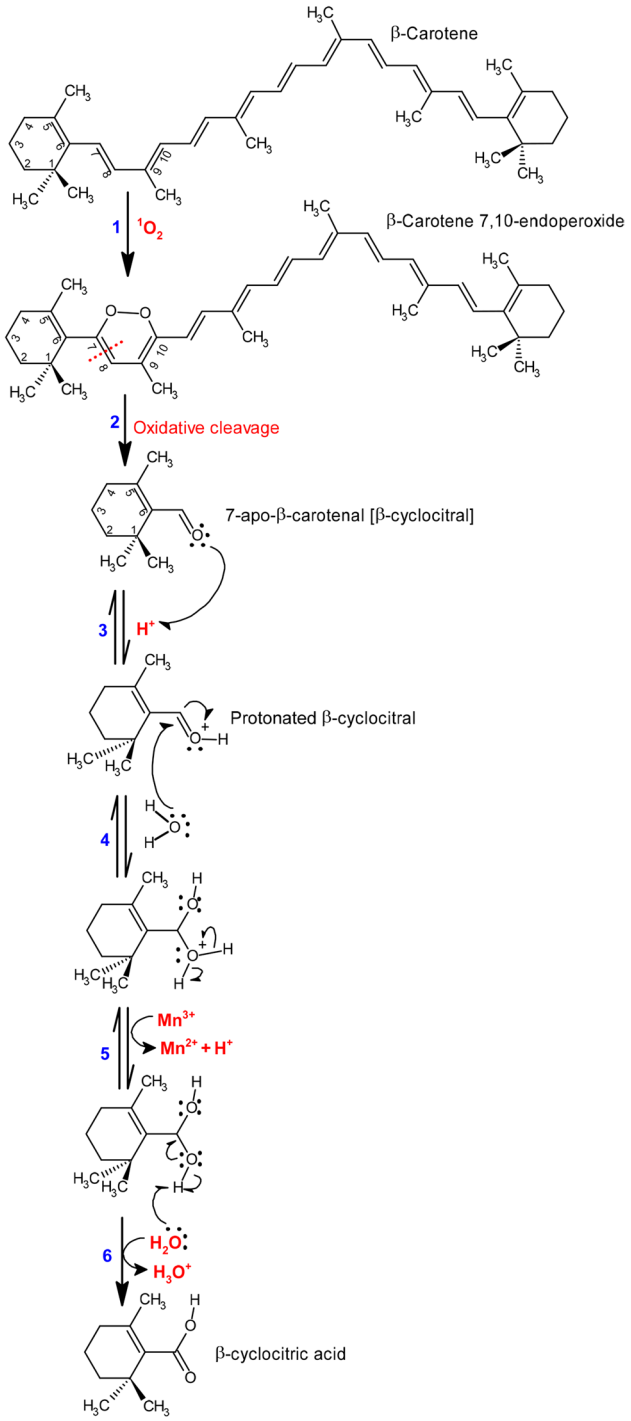


Fig. 4 Pigment oxidation by ROS. Addition of $^1O_2$ to double bond at carbon 7 and carbon 10 position forms β-carotene endoperoxide (reaction 1). Oxidative cleavage of the double bond between carbon 7 and carbon 8 forms 7-apo-β-carotenal (β-cyclocitral) (reaction 2). Protonation on the oxygen atom of the carbonyl forms actives carbonyl (reaction 3). Attack of nucleophilic oxygen in the water to the electrophilic carbon in the C=O breaks the π bond and transfers the electrons to the positive oxygen (reaction 4). Deprotonation of the oxonium ion in the presence of transition metal (Mn^{3+}) forms the hydrate (reaction 5). Abstraction of the proton from the hydrate by a base (water molecule) forms β-cyclocitric acid (reaction 6)

amino acids in length (5 to 100 amino acids). As amino acid sequence unambiguously determines peptides, oxidative signaling by proteins exhibits high spatial specificity. When an amino acid is oxidatively modified, the structure of peptides with a small number of amino acids might change. A type of oxidative modification of particular amino acid depends on the type of ROS which initiates oxidation. Thus, it is likely that peptide oxidized by radical ROS ($HO^\bullet$) activates one group of genes in the nucleus, whereas the same peptide oxidized by non-radical ROS ($^1O_2$) triggers another group of genes in the nucleus. Here, we propose that protein fragments (peptides) arising from the proteolytic cleavage of oxidatively modified proteins exhibit the necessary spatial specificity for signal transduction from chloroplast to the nucleus and, thus, are the most appropriate candidates to regulate specific genes expression.

Protein oxidation by ROS

Proteins are oxidized as a result of different chemical modifications comprising the oxidation (the addition of one oxygen atom in amino acid, OH) (general oxidation, + 15.99 Da), peroxidation (addition of two oxygen atoms in amino acid, OOH) (double oxidation, + 31.99 Da), and carboxylation (the formation or addition of carbonyl group in amino acid, C=O) (Stadtman and Levine 2003; Takamoto and Chance 2006; Bachi et al. 2013). Redox-active amino acids oxidized by both radical ($O_2^{\bullet-}$, $HO^\bullet$) and non-radical ($^1O_2$) ROS are aromatic amino acids (tyrosine, tryptophan) and sulfur-containing amino acids (cysteine and methionine). In the radical ROS pathway, oxidation of these residues by $HO^\bullet$ results in the formation of side-chain radicals such as phenoxyl radical (tyrosine), indolyl radical (tryptophan), thiyl radical (cysteine), and sulfide radical cation (methionine), which further react with O_2 to form peroxyl radicals or another radical to give non-radical products (Davies 2016). In the non-radical ROS pathway, the addition of $^1O_2$ to the aromatic ring of aromatic amino acid forms hydroperoxide via endoperoxide, whereas the addition of $^1O_2$ to sulfur-containing amino acids form peroxide (with a negative charge on oxygen atom and positive charge on sulfur atom) (Di Mascio et al. 2019). Even if histidine is not an aromatic amino acid, it contains an aromatic ring and, thus, is oxidized by $^1O_2$. Similar to aromatic amino acids, the addition of $^1O_2$ to the aromatic ring of histidine forms endoperoxide which decomposes to hydroperoxide (Di Mascio et al. 2019).

Aromatic amino acid oxidation by ROS

Protein hydroperoxide (hydroperoxy amino acids) is formed by the addition of two oxygen atoms in amino acid by O_2, $O_2^{\bullet-}$, or $^1O_2$ (Fig. 5). The formation of hydroperoxy amino acids can occur on alanine moiety (by addition of O_2) or

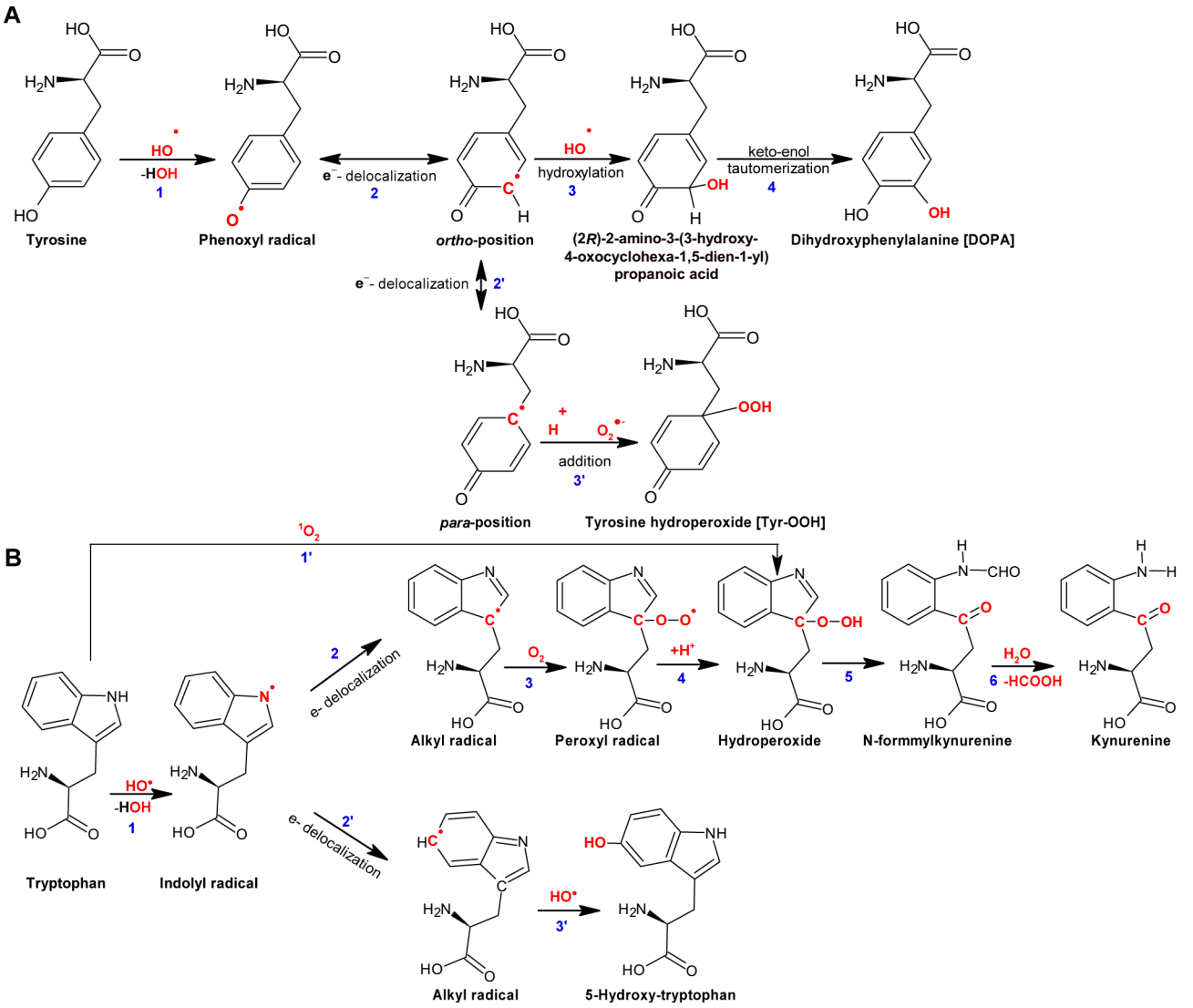


Fig. 5 Protein oxidation by ROS. **A** Tyrosine oxidation. Abstraction of hydrogen atom from the hydroxyl group of the phenyl ring of tyrosine by $HO^{\bullet}$ forms tyrosyl radical (reaction 1). Delocalization of an unpaired electron from the oxygen to a carbon atom of the phenyl ring forms alkyl radical at ortho-position (reaction 2) or at para-position (reaction 2′). Addition of $HO^{\bullet}$ to the alkyl radical at ortho-position forms (2R)-2-amino-3-(3-hydroxy-4-oxocyclohexa-1,5-dien-1-yl) propanoic acid (reaction 3) and addition of $O_2^{\bullet-}$ to alkyl radical at para-position forms the tyrosine hydroperoxide (reaction 3′). Keto-enol tautomerization of the (2R)-2-amino-3-(3-hydroxy-4-oxocyclohexa-1,5-dien-1-yl)propanoic acid forms the dihydroxyphenylalanine [DOPA] (reaction 4). **B** Tryptophan oxidation. Abstraction of hydrogen atom from the nitrogen atom of the indolel ring of tryptophan by $HO^{\bullet}$ forms alkyl radical at nitrogen atom (reaction 1). Delocalization of an unpaired electron from the nitrogen to the carbon atom of the pyrrole ring of indole (reaction 2) or to the carbon atom of the benzene ring of indole forms alkyl radical at carbon atoms (reaction 2′). Addition of O_2 to the alkyl radical at carbon atom of the pyrrole ring of indole forms peroxyl radical (reaction 3). Addition of $HO^{\bullet}$ to alkyl radical at the carbon atom of benzene ring forms hydroxy-tryptophan (reaction 3′). Abstraction of a hydrogen atom from an adjacent amino acid by peroxyl radical (reaction 4) or addition of $^1O_2$ to carbon atom of the pyrrole ring of indole with double bond forms hydroperoxide (reaction 1′). Decomposition of hydroperoxide forms N-formmylkynurenin (reaction 5). Further decomposition of N-formmylkynurenin forms kynurenine (reaction 6)

aromatic ring (by addition of $O_2^{\bullet-}$ or $^1O_2$) of the aromatic amino acids (tyrosine and tryptophan). Abstraction of a hydrogen atom from carbon atom at alanine moiety is more feasible than from an aromatic ring. In the aromatic ring pathway, $HO^{\bullet}$ abstracts a hydrogen atom from the oxygen atom of the phenyl ring (tyrosine) and the nitrogen atom of the indole ring (tryptophan). In tyrosine, a hydrogen atom abstraction from the hydroxyl group of the phenyl ring of tyrosine by $HO^{\bullet}$ forms phenoxyl radical (oxygen-centered radical with the unpaired electron localized on oxygen

atom), followed by delocalization of an unpaired electron from the oxygen to carbon atom of the phenyl ring forming tyrosine alkyl radical at ortho-position or at para-position (carbon-centered radical with the unpaired electron localized on carbon atom). The addition of $O_2^{\bullet-}$ to carbon-centered radical at the para-position leads to the formation of tyrosine hydroperoxide. Alternatively, alkyl radical at the ortho-position might react with $HO^{\bullet}$ to form hydroxy-tyrosine (dihydroxyphenylalanine, DOPA). In tryptophan, $HO^{\bullet}$ abstracts a hydrogen atom from the amine group of the indole ring forming indolyl radical (nitrogen-centered radical with the unpaired electron localized on nitrogen atom). The delocalization of an unpaired electron from the nitrogen to a carbon atom of the indole ring forms a tryptophan alkyl radical (carbon-centered radical) to which the addition of O_2 forms a tryptophan peroxyl radical (oxygen-centered radical). After the abstraction of another hydrogen atom from an adjacent amino acid by tryptophan peroxyl radical, tryptophan hydroperoxide is formed. Alternatively, $^1O_2$ addition to double bonds forms tryptophan hydroperoxide (Davies 2003; Gracanin et al. 2009). Tryptophan hydroperoxide might decompose to N-formylkynurenine, which subsequently degrades into kynurenine. Alternatively, the addition of $HO^{\bullet}$ to tryptophan alkyl radical at the carbon atom of indole ring forms hydroxy-tryptophan. (Hawkins and Davies 2019).

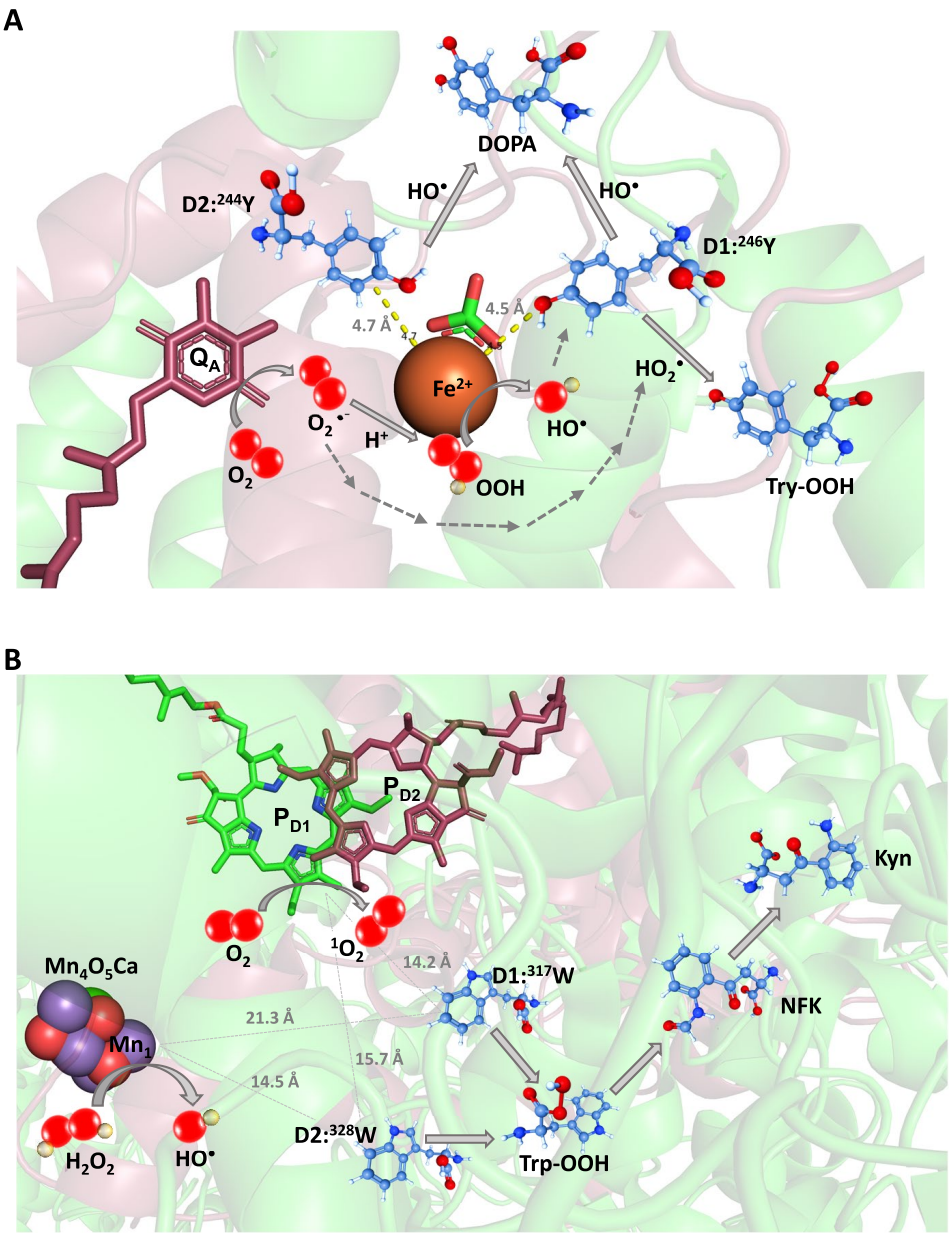


Fig. 6 Aromatic amino acid oxidation at binding sites of the redox-active cofactors in PSII. Two sites of aromatic amino acid oxidation by ROS were indentified: **A** the D-*de* loop region of the D1 and D2 proteins on the stromal side of PSII (Q_A and Q_B-binding domain), and **B** the C-terminal region of the D1 and D2 proteins on the lumenal side of PSII (Mn_4O_5Ca cluster-binding domain). In **A** tyrosines D1:^{246}Y (the distance of 4.5 Å from the non-heme iron) and D2:^{244}Y (the distance of 4.7 Å from the non-heme iron) localized in the stroma-exposed D-*de* loop region of D1 and D2 proteins are oxidized by $HO^{\bullet}$ to dihydroxyphenylalanine (DOPA). In this reaction, hydrogen abstraction from the hydroxyl group of the phenyl ring of D1:246Y and D2:244Y forms a phenoxyl radical, which is followed by delocalization of an unpaired electron from the oxygen to a carbon atom of the phenyl ring. The addition of another $HO^{\bullet}$ to the phenyl ring forms DOPA. In **B** tryptophans D1:^{317} W (the distance of 14.2 Å from P_{D1} and 21.3 Å from the Mn_4O_5Ca cluster) and D2:^{328}W (the distance of 15.7 Å from P_{D2} and 14.2 Å from the Mn_4O_5Ca cluster) localized at the lumen-exposed C terminus of D1 and D2 proteins are oxidized by $^1O_2$ or $HO^{\bullet}$ to tryptophan hydroperoxide (Trp-OOH) which decomposes to N-formylkynurenine (NFK) and kynurenine (Kyn)

Oxidative signaling by protein oxidation product

Due to specific oxidative modification on a particular amino acid residue (tyrosine and tryptophan), EXECUTER1 (EX1) and D1/D2 proteins are unique candidates for signaling molecules. Below oxidation of tryptophan in EX1 protein EX1:^{643}W to N-formylkynurenine, oxidation of tyrosines in D1 and D2 proteins D1:^{246}Y and D2:^{244}Y to DOPA, and oxidation of tryptophan in D1 and D2 proteins D1:^{317}W and D2:^{328}W to N-formylkynurenine (Fig. 6) are discussed as a plausible oxidative modification important for signaling to activate genes expression. Even if oxidative modification of aromatic amino acids and proteolytic degradation of protein are documented, evidence on the translocation of oxidized proteins from chloroplast to the nucleus which is essential for signal transduction has not been provided yet.

EXECUTER1 protein

Protein signal transduction was proposed to be mediated by EXECUTER1 (EX1) protein oxidized by $^1O_2$ (Kim et al. 2008; Kim and Apel 2013; Kim 2020). The authors suggested that $^1O_2$-mediated EX1 oxidation should be considered as a general mechanism of retrograde signaling, and that fragments of oxidized EX1 proteins might function as signals. EX1 protein localized in the grana margins was demonstrated to interact with PSII core proteins, chlorophyll synthesis enzymes (protochlorophyllide oxidoreductase enzymes), metalloprotease FtsH protease, and protein elongation factors (Wang et al. 2016). Using Arabidopsis fluorescent in blue light (flu) mutant, which accumulates protochlorophyllide (Pchlide) in the dark (an intermediate in the chlorophyll biosynthesis pathway which acts as a photosensitizer in the light forming $^1O_2$), it was demonstrated that EX1 protein is oxidized by $^1O_2$ (Lee et al. 2007). It has been recently demonstrated that tryptophan located in the DUF3506 domain of EX1 protein (EX1:^{643}W) is oxidized by $^1O_2$ forming tryptophan hydroperoxide, hydroxy-tryptophan, and N-formylkynurenine (Dogra et al. 2019). It was proposed that oxidatively modified EX1 protein is proteolytically cleaved by the ATP-dependent zinc metalloprotease FtsH (Wang et al. 2016). It is not obvious whether tryptophan oxidation initiates proteolytic degradation of EX1 protein. Interestingly, the substitution of tryptophan with leucine or alanine which is insensitive to $^1O_2$ inhibits EX1-dependent gene expression. It was assumed that tryptophan oxidation is required for signaling, and that EX1 degradation by FtsH initiates libration of a signaling molecule which activates gene expression.

D1 protein

Signal transduction mediated by D1 protein was described in *Synechococcus* sp. Strain PCC 7942 (Stelljes and Koenig 2007). The authors demonstrated that a C-terminal fragment of D1 protein binds to the *psbAI* promoter and, thus, regulates transcription of the *psbA* gene. Based on the analogy with cyanobacteria, it is likely that the C-terminal fragment of D1 protein might be involved in signaling within the chloroplasts (intra-chloroplast signaling) and, thus, likely regulate the *psbA* gene in the chloroplast. Light-induced tryptophan modification of D1:^{317}W localized at lumen-exposed C terminus was shown to form N-formylkynurenine in PSII (Dreaden et al. 2011; Kasson et al. 2012). The authors proposed that oxidative modification of tryptophan can play a role in oxidative signaling in the D1 repair cycle under high light. Later, oxidative modifications to the D1 and D2 proteins were described in detail using high-resolution tandem mass spectrometry (Frankel et al. 2012, 2013; Kale et al. 2017; Kumar et al. 2021). In this context, it is interesting that oxidized aromatic amino acid residues are localized primarily near the sites of ROS formation at the stroma-exposed D-*de* loop region (Q_A and Q_B-binding domain) and lumen-exposed C terminus (Mn_4O_5Ca cluster-binding domain). Tyrosines D1:^{246}Y and D2:^{244}Y localized in the stroma-exposed D-*de* loop region and tryptophans D1:^{317}W and D2:^{328}W localized at lumen-exposed C terminus were shown to be oxidized under high light (Kale et al. 2017; Kumar et al. 2021). The oxidative-modified D1 protein is enzymatically cleaved into fragments by specific proteases, the ATP-independent serine protease Deg (Deg1, 5, and 8 are in the lumen, whereas Deg2 is located at PSII stromal side) and the ATP-dependent zinc-metalloprotease FtsH (located at PSII stromal side) (Yoshioka and Yamamoto 2011; Komenda et al. 2012; Jarvi and Suorsa 2015; Kato and Sakamoto 2018). It has been a longstanding question how D1 synthesis is associated with oxidative modification of D1 protein. Here, we propose that D1 protein fragments arising from the proteolytic cleavage of oxidatively modified D1 proteins exhibit the necessary specificity for signal transduction and, thus, are the most appropriate candidate to regulate *psbA* translation. In agreement with this proposal, it has been recently demonstrated that light-induced *psbA* translation is triggered by PSII damage via the autoregulatory circuit (Chotewutmontri and Barkan 2020). The authors proposed that D1 autoregulates *psbA* translation by interaction with HCF244/OHP1/OHP2 assembly complex which consists of one-helix proteins, OHP1 and OHP2 (light-harvesting-like protein 2 and 6) (in cyanobacteria HliD and HliC) and HCF244 (in cyanobacteria Ycf39). It is possible that the fragment products of D1 protein might play a signaling role in the PSII repair cycle; however, experimental evidence has not been yet demonstrated in higher plants.

Conclusion

The formation of ROS by energy transfer and electron transport in PSII is often associated with lipid, pigment and protein damage which can lead to programmed cell death. Here, we propose that ROS can initiate cell signaling by oxidation of biomolecules associated with the cell acclimation. While the importance of lipophilic signaling molecules (oxidized lipids and pigments) in chloroplast-to-nucleus retrograde signaling has been evidenced, the role of oxidized proteins in signal transduction from chloroplast to nucleus has not been demonstrated. Thus, the oxidative modification of specific amino acids by ROS might appear to induce new pathways in retrograde signaling. This review tried to bring the first view into this issue and define the conditions when oxidative modification of protein by ROS formed in PSII is accompanied by the cell signaling. Clarification of the mechanism underlying the complexity of ROS signaling pathways might help understand how the plant can survive under exposure to a variety of abiotic and biotic stresses.

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