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Production of Reactive Oxygen Species by Photosystem II as a Response to Light and Temperature Stress

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The effect of various abiotic stresses on photosynthetic apparatus is inevitably associated with formation of harmful reactive oxygen species (ROS). In this review, recent progress on ROS production by photosystem II (PSII) as a response to high light and high temperature is overviewed. Under high light, ROS production is unavoidably associated with energy transfer and electron transport in PSII. Singlet oxygen is produced by the energy transfer form triplet chlorophyll to molecular oxygen formed by the intersystem crossing from singlet chlorophyll in the PSII antennae complex or the recombination of the charge separated radical pair in the PSII reaction center. Apart to triplet chlorophyll, triplet carbonyl formed by lipid peroxidation transfers energy to molecular oxygen forming singlet oxygen. On the PSII electron acceptor side, electron leakage to molecular oxygen forms superoxide anion radical which dismutes to hydrogen peroxide which is reduced by the non-heme iron to hydroxyl radical. On the PSII electron donor side, incomplete water oxidation forms hydrogen peroxide which is reduced by manganese to hydroxyl radical. Under high temperature, dark production of singlet oxygen results from lipid peroxidation initiated by lipoxygenase, whereas incomplete water oxidation forms hydrogen peroxide which is reduced by manganese to hydroxyl radical. The understanding of molecular basis for ROS production by PSII provides new insight into how plants survive under adverse environmental conditions.

Keywords: photoinhibition, heat inactivation, singlet oxygen, free oxygen radicals, lipid peroxidation

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INTRODUCTION

Photosystem II (PSII) is water-plastoquinone oxidoreductase embedded in the thylakoid membrane that catalyzes light-driven H_2O oxidation to O_2 and plastoquinone (PQ) reduction to plastoquinol (PQH_2; Dau et al., 2012; Vinyard et al., 2013; Nelson and Junge, 2015; Suga et al., 2015; Najafpour et al., 2016). In this reaction, primary charge separation between the chlorophyll monomer (Chl_{D1}) and pheophytin ($Pheo_{D1}$) of D1 protein forms $^1[Chl_{D1}^{\bullet+}Pheo_{D1}^{\bullet-}]$ radical pair which is fast stabilized by the oxidation of the weakly coupled chlorophyll dimer P_{D1} and P_{D2} (P680) forming $^1[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ radical pair (Cardona et al., 2012). $^1[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ radical pair is stabilized by the electron transport from $Pheo_{D1}$ to the tightly bound plastoquinone Q_A forming $Q_A^{\bullet-}$ and from the redox active tyrosine residue D1:161Y (Y_Z) to $P680^{\bullet+}$ forming $Y_Z^{\bullet}$. Electron transport

form $Q_A^{\bullet-}$ to loosely bound plastoquinone Q_B and the reduction of $Y_Z^{\bullet}$ by the proton-coupled electron transport from the Mn_4O_5Ca cluster forms reducing and oxidizing equivalent at Q_B and Mn_4O_5Ca cluster, respectively. When two reducing equivalents are formed at Q_B site, its protonation forms plastoquinol (PQH_2) which is liberated to PQ pool via channels (Lambreva et al., 2014). Formation of four oxidizing equivalents in the Mn_4O_5Ca cluster causes four-electron oxidation of two H_2O to O_2 which is released via channels into the lumen (Vogt et al., 2015).

Light-driven processes comprising both energy transfer and electron transport are accompanied by formation of reactive oxygen species (ROS). In the energy transfer, singlet oxygen ($^1O_2$) is formed by the energy transfer from triplet chlorophyll to O_2 (Triantaphylides and Havaux, 2009; Pospíšil, 2012; Fischer et al., 2013). In electron transport, ROS are formed by the consecutive one-electron reduction of O_2 and by the concerted two-electron oxidation of H_2O on the PSII electron acceptor and donor sides, respectively (Pospíšil, 2009). The one-electron reduction of O_2 forms superoxide anion radical ($O_2^{\bullet-}$) which dismutes spontaneously or enzymatically to hydrogen peroxide (H_2O_2) and subsequently is reduced to hydroxyl radical ($HO^{\bullet}$) via Fenton reaction. The two-electron oxidation of water forms H_2O_2 which is oxidized and reduced to $O_2^{\bullet-}$ and $HO^{\bullet}$, respectively. Non-enzymatic and enzymatic scavenging systems have been engaged to eliminate ROS and thus control level of ROS formed under various types of abiotic (adverse environmental conditions such as high light, high and low temperatures, UV-radiation, and drought) and biotic (herbivores and pathogens such as viruses, bacteria, and fungi) stresses.

Under moderate stress, when scavenging system maintains ROS level low, ROS serves as signaling molecules which activate an acclimation response and programmed cell death (Apel and Hirt, 2004; Dietz et al., 2016). Several lines of evidence have been provided that ROS play a crucial role in intracellular signaling from the chloroplast to the nucleus under high light (Gollan et al., 2015; Laloi and Havaux, 2015) and high temperature (Sun and Guo, 2016). However, due high reactivity of ROS toward proteins and lipids, ROS diffusion is limited. It seems to be unlikely that ROS might transmit signal from the chloroplast to the nucleus. It is considered that products of protein oxidation and lipid peroxidation might serve as signaling molecules (Fischer et al., 2012). As ROS formed by energy transfer ($^1O_2$) and electron transport (H_2O_2) are produced simultaneously, it seems to be likely that their action in signaling pathways interferes. It was demonstrated that H_2O_2 antagonizes the $^1O_2$ signaling pathways in the *flu* Arabidopsis mutant (Laloi et al., 2007).

Under severe stress, when scavenging system is unable to sufficiently eliminate undesirable ROS formation, PSII proteins and lipids might be oxidized by ROS. Several lines of evidence were provided in the last three decades on the oxidative damage of PSII proteins by ROS under high light (Aro et al., 1993) and high temperature (Yamamoto et al., 2008). It is widely accepted that $^1O_2$ is major ROS responsible for oxidative modification of PSII proteins. Contrary, H_2O_2 has low capability to oxidize PSII protein; however, when free or protein-bound metals are available, $HO^{\bullet}$ formed by Fenton reaction oxidizes nearby proteins. It has to be pointed that experimental evidence on PSII protein oxidation was obtained *in vitro* and thus it remains to be clarified whether oxidative modification of PSII proteins by ROS occurs *in vivo*. Apart to involvement of ROS in PSII protein damage, the inhibition of *de novo* protein synthesis by ROS was proposed under high light (Nishiyama et al., 2006) and high temperature (Allakhverdiev et al., 2008). Whereas PSII protein oxidation is widely described, limited evidence has been provided on lipid peroxidation near PSII. It was shown that $^1O_2$ formed in PSII initiates lipid peroxidation in the thylakoid membrane (Triantaphylides et al., 2008).

In this review, an update on the latest findings on molecular mechanism of ROS formation at high light and high temperature is presented. In spite of the fact that molecular mechanism of ROS formation is substantially different at high light and high temperature, high light regularly combined with high temperature might bring about more serious impact on ROS formation.

HIGH LIGHT

When light energy which is driving force for photosynthetic reactions exceeds the photosynthetic capacity, a light-induced decline in photochemical activity in PSII denoted as photoinhibition occurs. Limitations in the energy transfer and electron transport result in the generation of ROS. Limitation in energy transfer occurs, when the excess energy absorbed by chlorophyll in the PSII antennae complex is not fully utilized in the PSII reaction center by charge separation. Under these conditions, singlet chlorophyll might be converted to deleterious triplet chlorophyll. To prevent formation of triplet chlorophyll, quenching of singlet chlorophyll to heat is maintained directly by xanthophylls or indirectly by the rearrangement of Lhcb protein by PsbS (Ruban et al., 2012). However, when quenching of singlet chlorophyll is not sufficient, singlet chlorophyll is converted to triplet chlorophyll which transfers energy to O_2 forming $^1O_2$. Limitation in electron transport on the PSII electron acceptor side is accompanied by full reduction of PQ pool. As the Q_B site becomes unoccupied by PQ due to the full reduction of PQ pool, forward electron from Q_A to Q_B is blocked. Under these conditions, back electron transport from $Q_A^{\bullet-}$ to Pheo and consequent recombination of $Pheo^{\bullet-}$ with $P680^{\bullet+}$ forms deleterious triplet chlorophyll which transfer to O_2 forming $^1O_2$. Under highly reducing conditions, double reduction and protonation of Q_A might result in the release of Q_AH_2 from its binding site. To prevent double reduction of Q_A, electron from $Q_A^{\bullet-}$ leaks to O_2 forming $O_2^{\bullet-}$. Superoxide anion radical is eliminated by its spontaneous and enzymatic dismutation to H_2O_2. In the interior of the thylakoid membrane, $O_2^{\bullet-}$ is eliminated by the intrinsic SOD activity of cyt b_{559}, whereas $O_2^{\bullet-}$ which diffuse out the thylakoid membrane is eliminated by FeSOD attached to the stromal side of the thylakoid membrane at the vicinity of PSII. Limitation in electron transport on the PSII electron donor side is associated with incomplete H_2O oxidation catalyzed by the Mn_4O_5Ca cluster. Incomplete H_2O oxidation results in the formation of H_2O_2 which serves as precursor for

$HO^{\bullet}$. Under conditions, when H_2O_2 is not properly eliminated by catalase, $HO^{\bullet}$ is formed by Fenton reactions catalyzed by iron and manganese on the PSII electron acceptor and donor sides, respectively.

Singlet Oxygen

Singlet oxygen is formed by the triplet-triplet energy transfer from triplet chlorophyll or triple carbonyl to O_2. Triplet-triplet energy transfer from triplet chlorophyll to O_2 occurs in both the PSII antennae complex and the PSII reaction center. In the PSII antennae complex, triplet chlorophyll is formed by the photosensitization reaction, whereas in PSII reaction center triplet chlorophyll is formed by the charge recombination of triplet radical pair $^3[P680^{\bullet+}Pheo^{\bullet-}]$. Triplet-triplet energy transfer from triplet carbonyl to O_2 proceeds during lipid peroxidation initiated by ROS formed by light. Whereas $^1O_2$ formation by the energy transfer from triplet chlorophyll is well documented and represents the main source of $^1O_2$ at high light, $^1O_2$ formation by the energy transfer from triplet carbonyls is rarely evidenced and has marginal contribution to the overall $^1O_2$ formation.

Triplet Chlorophyll

Light energy absorbed by chlorophylls is transferred from the PSII antennae complex toward the PSII reaction center (van Amerongen and Croce, 2013). However, when energy transfer is limited, chlorophylls might serve as photosensitizers which form $^1O_2$ by the energy transfer from their triplet state to O_2 (**Figure 1A**). To prevent this, chlorophylls are coupled with carotenoids which have capability to quench triplet chlorophylls. Carotenoids consist of carotenes (β-carotene) and their oxygenated derivatives xanthophylls (lutein, zeaxanthin; Domonkos et al., 2013). In the PSII antennae complex, lutein and zeaxanthin play a crucial role in triplet chlorophyll quenching (Dall'Osto et al., 2006, 2012). Whereas lutein is permanently coordinated to Lhcb proteins, zeaxanthin is accumulated under high light by the reversible de-epoxidation of violaxanthin and is either free in the thylakoid membrane or bound to Lhcb protein (Havaux and Niyogi, 1999; Pinnola et al., 2013). Four xanthophyll binding sites were documented in the monomeric (Lhcb4-6) and the trimeric (LHCII) antenna proteins of PSII (Liu et al., 2004). Xanthophylls bound in both L1 (lutein) and L2 (lutein in LHCII and lutein or zeaxanthin in monomeric Lhcb4-6 proteins) sites can efficiently quench the neighboring triplet chlorophylls. Lutein in L1 (Lut620) and L2 (Lut621) are coupled with chlorophylls Chl610-Chl614 and Chl602- Chl604, respectively. The quenching of triplet chlorophylls 602 and 603 by lutein in L2 is highly efficient, whereas lutein in L1 site had no effect on quenching of triplet chlorophyll 612 (Ballottari et al., 2013). To maintain effective quenching of triplet chlorophyll by carotenoids, carotenoids has to be properly distanced and oriented from chlorophylls. Triplet-triplet energy transfer from chlorophylls to carotenoids is mediated by Dexter mechanism (Dexter, 1953), which needs overlap between the electron clouds of the donor and acceptor. When distance or orientation of carotenoid and chlorophyll is changed, the capability of carotenoids to quench excitation energy of triplet chlorophylls is diminished (Cupellini et al., 2016). Under such conditions, when O_2 is in the proximity of triplet chlorophyll, the transfer of excitation energy from triplet chlorophyll to O_2 forms $^1O_2$. Comparison of the monomeric and the trimeric antenna proteins of PSII showed that the monomeric antenna proteins (Lhcb6 > Lhcb5 > Lhcb4) produced more $^1O_2$ as compared to trimeric antenna proteins (LHCII; Ballottari et al., 2013).

When electron transport on the PSII electron acceptor side is limited due to the slow electron transport to the Q_A and Q_B, several types of charge recombination of $[P680^{\bullet+}\ Q_A^{\bullet-}]$ and $^1[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ radical pairs occur. Whereas $[P680^{\bullet+}\ Q_A^{\bullet-}]$ radical pair recombines solely to the ground state P680, primary radical pair $^1[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ formed by the reverse

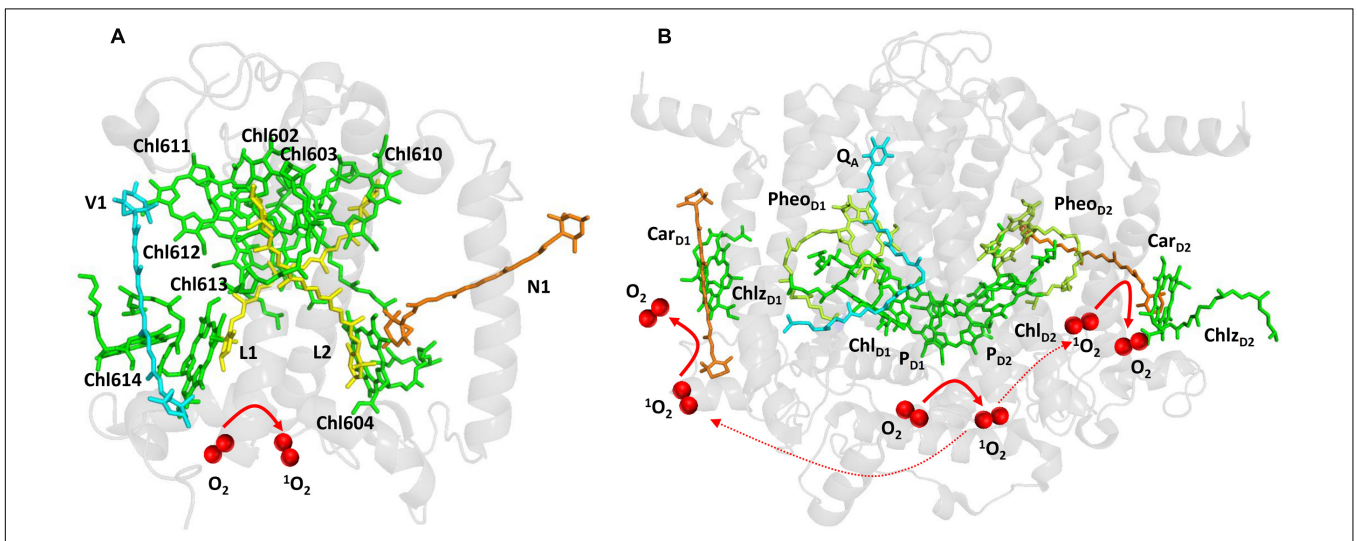

FIGURE 1 | Light-induced formation of $^1O_2$ in the antennae complex (A) and the reaction center **(B)** of PSII. The figures were made with Pymol (DeLano, 2002) using the structure for LHCII from *Spinacia oleracea* (PDB ID: 1rwt; Liu et al., 2004) and PSII from *Spinacia oleracea* (PDB ID: 3JCU; Wei et al., 2016).

electron transport from $Q_A^{\bullet-}$ to $Pheo_{D1}$ either recombines to the ground state P680 or converts to the triplet radical pair $^3[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ by change in the spin orientation. Recombination of triplet radical pair $^3[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ forms triplet chlorophyll $^3P680^*$ delocalized on the weakly coupled chlorophyll dimer P_{D1} and P_{D2} (Fischer et al., 2013; Telfer, 2014). Evidence has been provided that triplet state is localized on the Chl_{D1} at low temperature (Noguchi et al., 2001). The formation of $^3Chl_{D1}$ was proposed to occur either directly by the charge recombination of the triplet radical pair $^3[P680^{\bullet+}Pheo_{D1}^{\bullet-}]$ or by the triplet energy transfer from $^3P680^*$ to Chl_{D1}. As two β-carotenes (Car_{D1} and Car_{D2}) are distanced from chlorophyll dimer P_{D1} and P_{D2}, β-carotenes are not able to quench triplet chlorophyll $^3P680^*$ (**Figure 1B**).

Triplet Carbonyl

Lipid peroxidation initiated by radical ROS ($O_2^{\bullet-}$, $HO^{\bullet}$) forms the primary and the secondary lipid peroxidation products. The primary lipid peroxidation product are lipid hydroperoxides (lipid hydroperoxy fatty acids, LOOH) which decompose to the secondary lipid peroxidation products lipid hydroxides (hydroxy fatty acids, LOH), reactive carbonyl species (RCS), and electronically excited species. Hydrogen abstraction from polyunsaturated fatty acid by $HO^{\bullet}$ forms lipid alkyl radical ($L^{\bullet}$) which interacts with O_2 forming lipid peroxyl radical ($LOO^{\bullet}$). Lipid peroxyl radical abstracts hydrogen from the adjacent polyunsaturated fatty acid forming LOOH. Lipid hydroperoxide is stable; however, under oxidizing or reducing condition it is oxidized or reduced to $LOO^{\bullet}$ or alkoxyl radical ($LO^{\bullet}$). Cyclization or recombination of $LOO^{\bullet}$ forms high energy intermediates, dioxetane, or tetroxide. High energy intermediates are highly unstable and decomposite to triplet excited carbonyls ($^3L^*$) which might transfer triplet energy to O_2 forming $^1O_2$. Alternatively, tetroxide might directly decompose to $^1O_2$ via the Russell mechanism. Evidence has been provided that $^1O_2$ is formed through lipid peroxidation under light stress in spinach PSII membranes deprived by the Mn_4O_5Ca cluster (Yadav and Pospíšil, 2012a). The authors demonstrated that the oxidation of lipids by highly oxidizing $P680^{\bullet+}$ and $TyrZ^{\bullet}$ caused $^1O_2$ formation via the Russell mechanism. It has to be noted that amount of $^1O_2$ formed by the triplet-triplet energy transfer from triplet chlorophyll is considerably higher than from triplet carbonyl.

Superoxide Anion Radical

Superoxide anion radical is formed by the one-electron reduction of O_2 on the PSII electron acceptor side (**Figure 2**). Pheophytin ($Pheo_{D1}^{\bullet-}$), tightly bound plastosemiquinone ($Q_A^{\bullet-}$), loosely bound plastosemiquinones ($Q_B^{\bullet-}$ or $Q_C^{\bullet-}$), free PQ ($PQ^{\bullet-}$), and ferrous iron of LP form of cyt b_{559} were proposed to serve as electron donors to O_2 (Ananyev et al., 1994; Cleland and Grace, 1999; Pospíšil et al., 2004, 2006; Yadav et al., 2014). As $Pheo_{D1}^{\bullet-}$ has highly negative redox potential, the reduction of O_2 by $Pheo_{D1}^{\bullet-}$ is thermodynamically feasible; however, its short lifetime makes the diffusion limited reduction of O_2 less reasonable. Contrary, plastosemiquinones ($Q_A^{\bullet-}$, $Q_B^{\bullet-}$) does not fulfill thermodynamic criteria due to their more positive redox potential, whereas they accomplish the kinetic criteria due their long lifetime. However, due to the different concentration of O_2 and $O_2^{\bullet-}$, the standard redox potential of $O_2/O_2^{\bullet-}$ redox couple is shifted according Nernst equation to more positive and thus the reduction of O_2 by plastosemiquinones becomes feasible (Pospíšil, 2009). The observation that exposure of isolated D1/D2/cyt b_{559} complexes which lacks Q_A to high light causes a significant rate of cytochrome (III) reduction revealed that $Pheo_{D1}^{\bullet-}$ has capability to reduces O_2. The detection of $O_2^{\bullet-}$ in isolated thylakoids by a voltammetric method showed $O_2^{\bullet-}$ production by the tightly bound plastosemiquinone $Q_A^{\bullet-}$ (Cleland and Grace, 1999). Experimental evidence has been recently provided on the reduction of O_2 by the loosely bound plastosemiquinones (Yadav et al., 2014). The authors demonstrated that plastosemiquinone is formed by the one-electron reduction of plastoquinone at the Q_B site and the one-electron oxidation of plastoquinol by cyt b_{559} at the Q_C site. Apart to cofactors involved in the linear transport, the ferrous heme iron of LP form of cyt b_{559} was shown to reduce O_2 forming $O_2^{\bullet-}$ (Pospíšil et al., 2006).

It has been demonstrated that PsbS knock-out rice mutants produced more $O_2^{\bullet-}$ compared to WT under high light (Zulfugarov et al., 2014). The authors proposed that the lack of PsbS may cause shift in the midpoint redox potential of $Q_A/Q_A^{\bullet-}$ redox couple to more negative value and thus enhance $O_2^{\bullet-}$ production by $Q_A^{\bullet-}$. The D1 protein phosphorylation which is associated with the migration of damaged PSII complexes from the grana to the stroma lamellae during D1 protein repair cycle was shown to decrease $O_2^{\bullet-}$ production (Chen et al., 2012). The author proposed that the D1 protein phosphorylation causes conformation change of D1 protein and thus modifies the binding of loosely bound plastosemiquinone to Q_B site. Consequently, the alternation of Q_B site brings about the decrease in $O_2^{\bullet-}$ formed by the loosely bound plastosemiquinone $Q_B^{\bullet-}$. In agreement with this proposal, it has been recently demonstrated that $O_2^{\bullet-}$ production is enhanced in STN8 kinase knock-out rice mutants under high light (Poudyal et al., 2016). It has been proposed that enhancement in $O_2^{\bullet-}$ production is due to the absence of conformational changes caused by STN8 kinase-induced phosphorylation. Using PsbY knock-out Arabidopsis plants, it has been shown that redox potential property of cyt b_{559} is controlled by PsbY protein (von Sydow et al., 2016). It has to be explored whether PsbY protein controls $O_2^{\bullet-}$ production.

Hydrogen Peroxide

Hydrogen peroxide is formed by the one-electron reduction of $O_2^{\bullet-}$ and the two-electron oxidation of H_2O on the PSII electron acceptor and donor sides, respectively (**Figure 2**). Hydrogen peroxide formation by the one-electron reduction of $O_2^{\bullet-}$ occurs as dismutation or is maintained by plastosemiquinone. In the dismutation, two $O_2^{\bullet-}$ are simultaneously reduced and oxidized forming H_2O_2 and O_2, respectively. In the spontaneous dismutation, the interaction of two $O_2^{\bullet-}$ is restricted due to repulsion of the negative charge on the molecule, whereas the interaction of the protonated form of superoxide, hydroperoxyl radical ($HO_2^{\bullet}$), either with $O_2^{\bullet-}$ or $HO_2^{\bullet}$ is feasible. Spontaneous dismutation has been recently monitored

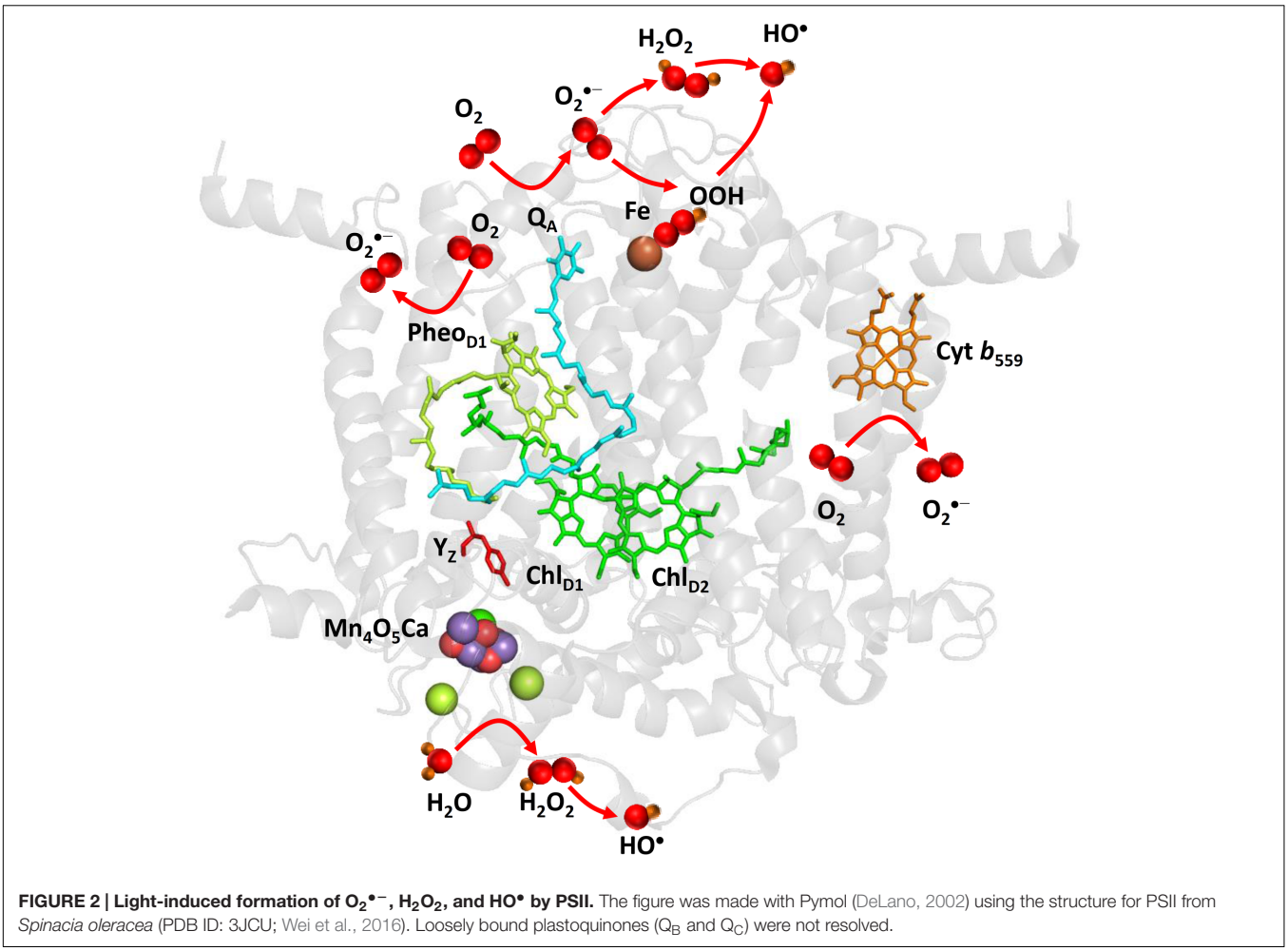

FIGURE 2 | Light-induced formation of $O_2^{\bullet-}$, H_2O_2, and $HO^{\bullet}$ by PSII. The figure was made with Pymol (DeLano, 2002) using the structure for PSII from *Spinacia oleracea* (PDB ID: 3JCU; Wei et al., 2016). Loosely bound plastoquinones (Q_B and Q_C) were not resolved.

by real-time detection of H_2O_2 in PSII membrane under high light using highly sensitive and selective osmium-horseradish modified electrode (Prasad et al., 2015). In the enzymatic dismutation, reduction and oxidation of $O_2^{\bullet-}$ is associated with the redox change of the redox active metal center which serves as a superoxide oxidase (SOO) and superoxide reductase (SOR), respectively. It was demonstrated that the 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 peroxide; Pospíšil et al., 2004) (**Figure 3A**). Evidence has been provided that the ferric and ferrous heme irons of cyt b_{559} exhibit the SOO and the SOR activities, respectively (Tiwari and Pospíšil, 2009; Pospíšil, 2011). Apart to dismutation, free $PQ^{\bullet-}$ in PQ pool was proposed to participate in H_2O_2 formation. Hydrogen peroxide was shown to be formed by reduction of $O_2^{\bullet-}$ by free $PQ^{\bullet-}$ (Borisova-Mubarakshina et al., 2015). The authors showed that H_2O_2 formed in PQ pool regulates the size of PSII antenna complex at high light. Furthermore, evidence has been provided that H_2O_2 might be formed by reduction $^1O_2$ of by PQH_2 (Khorobrykh et al., 2015). It was demonstrated that $^1O_2$ generated by photosensitizer Rose Bengal interacts with PQH_2 forming H_2O_2. The authors proposed that H_2O_2 formed by reduction of $^1O_2$ by PQH_2 in the thylakoid membrane might cause dimerization of the protein kinase STN7 and thus activates the enzyme.

Hydrogen peroxide formation by the two-electron oxidation of H_2O is maintained by the Mn_4O_5Ca cluster when the complete four-electron oxidation of H_2O to O_2 is limited. Whereas all four manganese are redox active in four-electron oxidation of H_2O to O_2, the incomplete oxidation of H_2O to H_2O_2 involves two redox active manganese. The two-electron oxidation of H_2O has been proposed to involve the transition from either S_2 to S_0 state or S_1 to S_{-1} state. Evidence has been provided that release of chloride from its binding site near to the Mn_4O_5Ca cluster enhanced H_2O_2 formation (Bradley et al., 1991; Fine and Frasch, 1992; Arato et al., 2004). A nucleophilic attack of hydroxo group on oxo group was proposed as an attractive model for formation of hydroperoxo species. It is proposed that nucleophilic attack of hydroxo group coordinated to Mn(4) and Cl(2) and oxo group coordinated to Ca forms hydroperoxo intermediate (**Figure 3B**). The hydroxo group is formed by deprotonation of the H_2O substrate coordinated to to Mn(4) and Cl(2), whereas the oxo group is formed by

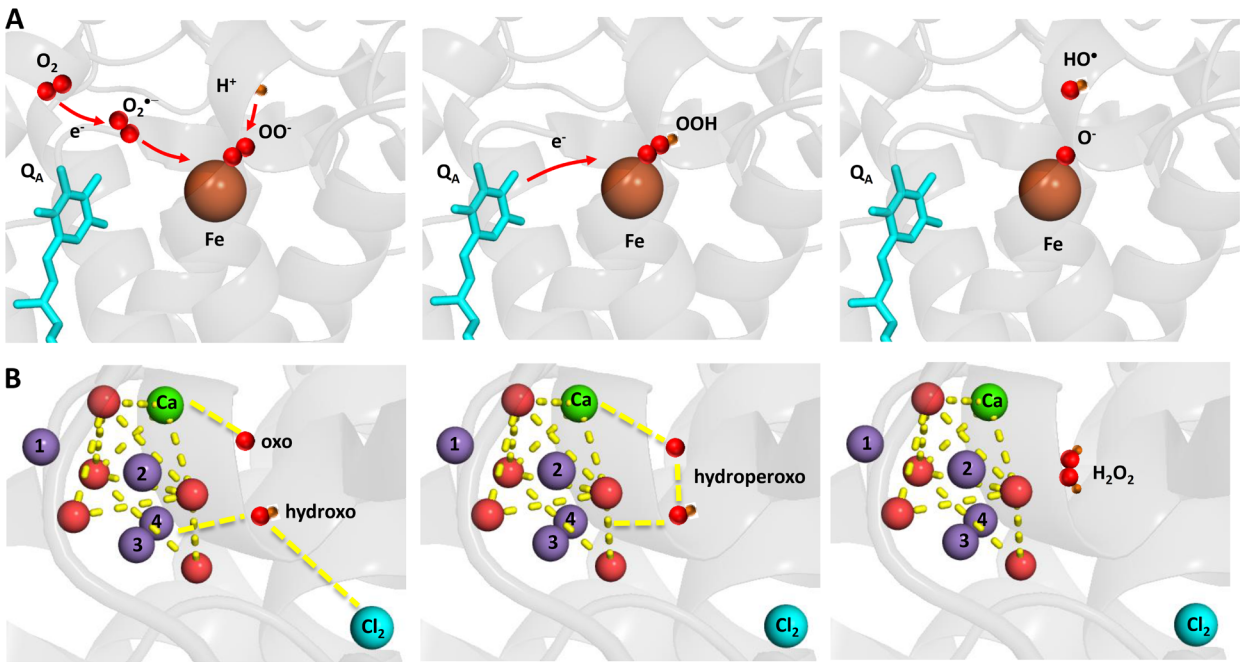

FIGURE 3 | Light-induced formation of bound peroxide and HO• on the PSII electron acceptor (A) donor **(B)** sides. The figure was made with Pymol (DeLano, 2002) using the structure for PSII from *Spinacia oleracea* (PDB ID: 3JCU; Wei et al., 2016).

double deprotonation of H_2O substrate coordinated to Ca. A nucleophilic attack of manganese-coordinated hydroxo group on the calcium-coordinated electrophilic oxo group forms a peroxide intermediate that substitutes Cl(2) in coordination to Mn(4). Chloride controls accessibility of H_2O substrate to Mn(4) and the nucleophilicity of hydroxo group and thus interaction of hydroxo and oxo groups. Water substrate, which serves as a precursor for the hydroxo group, enters into the catalytic site, when the Cl(2) binding site becomes opened to the solvent H_2O due to its release.

Hydroxyl Radical

Hydroxyl radical is formed by the one-electron reduction of H_2O_2 formed on the both PSII electron acceptor and donor sides (**Figure 2**). Hydroxyl radical formation by the one-electron reduction of free H_2O_2 and bound peroxide on the PSII electron acceptor side was shown to be maintained by free iron and the non-heme iron, respectively (Pospíšil et al., 2004). The authors demonstrated that 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• via ferric iron-oxo intermediate (**Figure 3A**).

Hydroxyl radical formation by the one-electron reduction of H_2O_2 on the PSII electron donor side is likely to be maintained by manganese. From thermodynamic point of view, the reduction of H_2O_2 by manganese is not feasible. It was proposed that the reduction of H_2O_2 by manganese becomes thermodynamically more favorable by (1) the coordination of manganese to the protein due to the decrease in the redox potential of manganese and (2) the pH decrease in the lumen due to the increase in the standard redox potential of H_2O_2/HO• redox couple (Pospíšil, 2012). It was demonstrated that PSII membranes depleted by chloride shows higher HO• formation compared to control PSII membranes (Arato et al., 2004). Based on the observation that HO• formation was not completely suppressed by exogenous SOD, the authors proposed that HO• is formed by reduction of H_2O_2 produced by the incomplete water oxidation on the PSII electron donor side.

HIGH TEMPERATURE

When PSII is exposed to high temperature, decline in the PSII activity denoted as heat inactivation occurs (Mathur et al., 2014). Heat inactivation occurs on the both PSII electron acceptor and donor sides. On the PSII electron donor side, heat inactivation is associated with the inhibition of water oxidation accompanied with release of PsbO, PsbP, and PsbQ proteins, calcium, chloride, and manganese from their binding sites (Coleman et al., 1988; Enami et al., 1994; Pospíšil et al., 2003; Barra et al., 2005). On the PSII electron acceptor side, heat inactivation is linked to the inhibition of electron transport from Q_A to Q_B (Pospíšil and Tyystjarvi, 1999). The authors demonstrated that increase in the midpoint redox potential of $Q_A/Q_A^{\bullet-}$ redox couple is responsible for the inhibition of Q_A to Q_B electron transport. Contrary to high light, ROS formation at high temperature is not driven by energy absorbed by chlorophylls; however, it is associated with heat-induced structural and functional changes in the thylakoid membrane. On the PSII electron acceptor side, $^1O_2$ is formed decomposition of high energy intermediates formed by

lipid peroxidation. On the PSII electron donor side, incomplete H_2O oxidation forms H_2O_2 which is reduced by manganese to $HO^•$ via Fenton reaction.

Singlet Oxygen

Singlet oxygen is formed by the triplet-triplet energy transfer from $^3L^*$ to O_2 produced by the decomposition of high energy intermediates, dioxetane, or tetroxide, formed during lipid peroxidation (Havaux et al., 2006; Pospíšil and Prasad, 2014). The observation that elimination of $HO^•$ formation by mannitol did not suppress $^1O_2$ formation revealed that lipid peroxidation is unlikely initiated by $HO^•$ (Pospíšil et al., 2007). More recently, it has been demonstrated that inhibition of lipoxygenase by catechol and caffeic acid in *Chlamydomonas* cells prevented $^1O_2$ formation (Prasad et al., 2016). Singlet oxygen was proposed to be generated at the lipid phase near the Q_B site (Yamashita et al., 2008). It was pointed that PQH_2 formed by reduction of PQ by stromal reducing compound might cause ROS production which can damage D1 protein (Marutani et al., 2012).

Hydrogen Peroxide

Hydrogen peroxide is formed by the two-electron oxidation of H_2O on the PSII electron donor side (**Figure 4**). It was proposed that the release of extrinsic proteins (PsbO, PsbP, and PsbQ) leads to the inadequate accessibility of water to the Mn_4O_5Ca cluster and consequently to the formation of H_2O_2 (Thompson et al., 1989). Indeed, it was demonstrated using the amplex red fluorescent assay that exposure of PSII membranes to high temperature (40°C) results in H_2O_2 formation (Yadav and Pospíšil, 2012b). The authors demonstrated that the binding of acetate to the Mn_4O_5Ca cluster in the competition with chloride and blockage of water channel prevented H_2O_2 formation. Based on these observations, it was suggested that the release of chloride from its binding site near to the Mn_4O_5Ca cluster leads to uncontrolled accessibility of H_2O to the Mn_4O_5Ca cluster. To maintain controlled four-electron oxidation of H_2O to O_2, the accessibility of H_2O to the Mn_4O_5Ca cluster has to be regulated. Chloride coordinated to amino acids nearby the Mn_4O_5Ca cluster controls the accessibility of H_2O to the metal center und thus maintain proper four-electron oxidation of H_2O to O_2. However, when chloride is released from its binding site, the delivery of H_2O to the Mn_4O_5Ca cluster is unrestricted and incomplete oxidation of O_2 to H_2O_2 occurs. Crystal structure of PSII from cyanobacteria *Thermosynechococcus vulcanus* reveals that two chlorides are located at distances of 6.67 and 7.40 Å from the Mn_4O_5Ca cluster (Umena et al., 2011). To avoid oxidation of nearby amino acid, diffusion of H_2O_2 into the lumen has to be restricted to the channels. As H_2O_2 is larger polar molecule similar to H_2O, it seems to be likely that H_2O_2 diffuse into the lumen via water channels. However, when H_2O_2 leaks from the water channels, it might interact with manganese and formed $HO^•$.

Hydroxyl Radical

Hydroxyl radical is formed by the one-electron reduction of H_2O_2 formed on the PSII electron donor side (**Figure 4**). It was demonstrated by the EPR spin trapping spectroscopy that the exposure of PSII membranes to high temperature results in $HO^•$ formation (Pospíšil et al., 2007). The authors showed that $HO^•$ production is completely suppressed by exogenous catalase and metal chelator desferal revealing that $HO^•$ is formed via the metal-catalyzed Fenton reaction. Furthermore, the observation that the addition of exogenous calcium and chloride prevented $HO^•$ formation reveals that $HO^•$ is produced by the Mn_4O_5Ca cluster. This proposal was confirmed by the observation that no $HO^•$ formation was observed in PSII membranes deprived by the Mn_4O_5Ca cluster (Yamashita et al., 2008). As the replacement of chloride by acetate at its binding site near to the Mn_4O_5Ca cluster and the blockage of water channel prevented $HO^•$ formation in a similar manner as H_2O_2 formation, it was assumed that chloride plays a crucial role in $HO^•$ formation (Yadav and Pospíšil, 2012b). The authors proposed that H_2O_2 formed by the incomplete H_2O oxidation is reduced to $HO^•$ via the Fenton reaction mediated by free manganese released from the Mn_4O_5Ca cluster. The release of manganese from its binding site at high temperature was reported using atomic absorption (Nash et al., 1985) and EPR (Coleman et al., 1988; Pospíšil et al., 2003) spectroscopy. Detailed study using X-ray absorption spectroscopy showed that decomposition of the Mn_4O_5Ca cluster occurs in two steps (Pospíšil et al., 2003). In the first step, two manganese are released

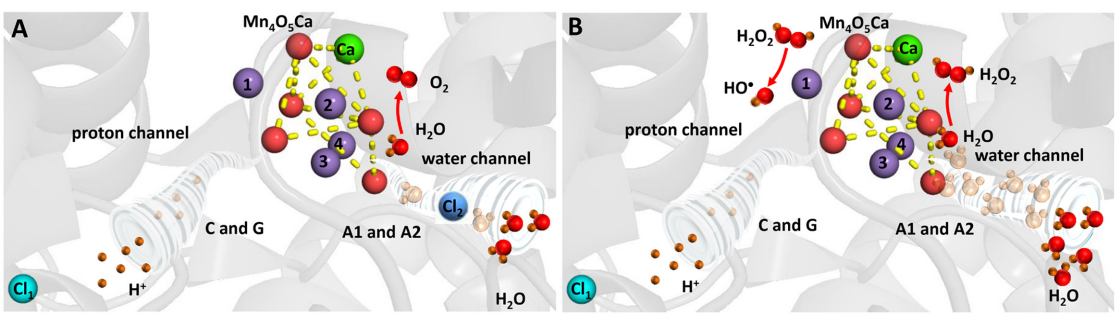

FIGURE 4 | Heat-induced formation of H_2O_2 and $HO^•$ on the PSII electron donor side. (A) Chloride controls accessibility of H_2O to the Mn_4O_5Ca cluster and maintains complete oxidation of H_2O to O_2. **(B)** Removal of chloride results in uncontrolled accessibility of H_2O to the Mn_4O_5Ca cluster and incomplete oxidation of H_2O to H_2O_2. The figure was made with Pymol (DeLano, 2002) using the structure for PSII from *Spinacia oleracea* (PDB ID: 3JCU; Wei et al., 2016).

from their binding sites into the lumen remaining two manganese connected by a di-μ-oxo bridge, whereas in the second phase the remaining two manganese are liberated form PSII.

PHYSIOLOGICAL RELEVANCE OF ROS FORMATION

Role of ROS in Retrograde Signaling

Both $^1O_2$ and H_2O_2 formed in the thylakoid membrane were proposed to be involved in retrograde signaling (Dietz et al., 2016). Role of $^1O_2$ in acclimation and programmed cell death was demonstrated in green algae (Erickson et al., 2015) and higher plants (Triantaphylides and Havaux, 2009; Laloi and Havaux, 2015). In higher plants, *fluorescent* (*flu*) and *chlorina 1* (*ch1*) Arabidopsis mutants were advantageously used due to their high capability to form $^1O_2$. It was proposed that the $^1O_2$ level determines whether acclimation response or programmed cell death is triggered (Laloi and Havaux, 2015).

At low $^1O_2$ level, acclimation response is mediated by β-cyclocitral formed by oxidation of β-carotene (Ramel et al., 2013a; Havaux, 2014). It was demonstrated that exposure of WT Arabidopsis plants to β-cyclocitral caused expression of $^1O_2$ related gene (Ramel et al., 2012). In agreement with this finding, it was shown that concentration of β-cyclocitral is enhanced in *ch1* Arabidopsis plants under acclimation (Ramel et al., 2013b). Further, evidence was provided on the role of jasmonic acid in acclimation response. It was demonstrated that jasmonate-deficient Arabidopsis mutant (*delayed-dehiscence 2*) was more resistant to light and jasmonate biosynthesis was pronouncedly lowered under acclimation (Ramel et al., 2013b). Based on these observations, the authors proposed that downregulation of jasmonate biosynthesis plays a crucial role in the triggering of acclimation response (Ramel et al., 2013c).

At high $^1O_2$ level, programmed cell death is dependent on the plastid proteins EXECUTER1 (EX1) and EXECUTER2 (EX2; Lee et al., 2007) and OXIDATIVE SIGNAL INDUCIBLE1 (OXI1) encoding an AGC kinase (Shumbe et al., 2016). Several lines of evidence on the involvement of EX1 and EX2 in programmed cell death were provided using *flu* Arabidopsis mutant (Lee et al., 2007). In this mutant, $^1O_2$ is formed by triplet-triplet energy transfer from the triplet chlorophyll precursor protochlorophyllide to O_2 (op den Camp et al., 2003). Even if EX1 and EX2 are located in chloroplast, it was proposed that jasmonic acid formed by $^1O_2$-initiated lipid peroxidation mediates genetically controlled programmed cell death response via these two plastid proteins (Przybyla et al., 2008). The initiation of $^1O_2$ signaling has been recently demonstrated close to EX1 in the grana margins nearby the site of chlorophyll synthesis and $^1O_2$ formation (Wang et al., 2016). As $^1O_2$ signaling depends on the FstH protease, the authors proposed that $^1O_2$ signaling is linked to D1 repair cycle. Apart to EX1 and EX2, it has been shown recently that *OXI1* kinase is involved in $^1O_2$ signaling in *ch1* Arabidopsis mutant (Shumbe et al., 2016). In this mutant, $^1O_2$ is formed by triplet-triplet energy transfer from the triplet chlorophyll formed in PSII to O_2 (Krieger-Liszkay, 2005). As *OXI1* kinase is localized at the cytosol at the cell periphery or in the nucleus, it seems to be likely that oxylipins mediate signal transduction from chloroplast to cytosol (Shumbe et al., 2016).

Hydrogen peroxide formed under high light was demonstrated to play a crucial role in signaling associated with acclimation and programmed cell death (Foyer and Noctor, 2009; Karpinski et al., 2013; Gollan et al., 2015). It is well established that H_2O_2 regulates expression of genes by the activation of protein kinase signaling pathways. It was proposed that precursor of jasmonic acid, 12-oxo phytodienoic acid (OPDA), mediates signal transduction from chloroplast to cytosol (Tikkanen et al., 2014). It has been recently demonstrated that H_2O_2 formed in PQ pool triggers signal transduction from the chloroplast to the nucleus via protein kinase signaling pathways leading to the regulation of the PSII antenna size during the acclimation response (Borisova-Mubarakshina et al., 2015).

Our knowledge on the involvement of ROS in retrograde signaling at high temperature is highly limited. While the physiological relevance of light-induced $^1O_2$ to acclimation and programmed cell death is described to some extent, no evidence was provided on the role of $^1O_2$ formed under high temperature to plant stress response. However, it seems to be likely that $^1O_2$ might oxidize lipid, protein or pigment forming specific oxidation products and thus initiates signal transduction from the chloroplast to the nucleus in the signaling cascade pathway. Contrary to $^1O_2$, H_2O_2 was shown to be an important component in heat stress-activated gene expression. Hydrogen peroxide was demonstrated to be involved in the synthesis of heat shock proteins (Volkov et al., 2006). More experimental data are required to pronouncedly progress our understanding of multiple signaling pathways involved the in response to heat stress.

Role of ROS in Oxidative Damage

At high light, proteins and lipids might be oxidized by ROS formed in PSII. PSII proteins were evidenced to be oxidatively modified in the following order D1 > D2 > Cyt b559 > CP43 > CP47 > Mn_4O_5Ca cluster (Komenda et al., 2006). Amino acid oxidation at the lumen exposed AB-loop of D1 protein forms 24 kDa C-terminal and 9 kDa N-terminal fragments, whereas amino acid oxidation in the stromally exposed D-de loop of the D1 protein form 23-kDa N-terminal and 9-kDa C-terminal fragments (Edelman and Mattoo, 2008). Identification of naturally oxidized amino acid in D1 protein using mass spectrometry was shown nearby to the site of ROS production (Sharma et al., 1997; Frankel et al., 2012, 2013). Whereas D1 protein oxidation was pronouncedly studied *in vitro*, limited evidence was provided on D1 protein oxidation *in vivo* (Shipton and Barber, 1994; Lupinkova and Komenda, 2004). Regardless of a broad range of evidence on PSII protein oxidation obtained *in vitro*, the plausibility of these processes *in vivo* has to be clarify. An efficient repair cycle for D1 protein, which includes proteolytic degradation of damaged D1 protein and its replacement with a newly synthetized D1 copy is essential for maintaining the viability of PSII (Komenda et al., 2012; Mulo et al., 2012; Jarvi et al., 2015). Apart to involvement of ROS in PSII protein damage under high light, ROS were shown to suppress the synthesis *de novo* of proteins with the

elongation step of translation as primary target (Nishiyama et al., 2006). However, considering the limited ROS diffusion, it seems to be more likely that ROS produced in the stroma might oxidize the translational elongation factors involved in D1 repair cycle. Unbound chlorophylls released to the stroma from their binding sites during PSII protein damage or chlorophyll precursors during chlorophyll synthesis are likely candidates for $^1O_2$ formation due to the lack of effective quenching of triplet excitation energy by carotenoids. To avoid $^1O_2$ formation, unbound chlorophylls might be temporarily coordinated to early light-induced proteins (ELIPs). In agreement with this proposal, it was demonstrated that small CAB-like proteins prevent $^1O_2$ formation during PSII damage, most probably by the binding of unbound chlorophylls released from the damaged PSII complexes (Sinha et al., 2012). Lipids associated with membrane proteins were shown to be oxidized by ROS. The initiation of lipid peroxidation by $^1O_2$ comprises the insertion of $^1O_2$ to double bond of polyunsaturated fatty acid, whereas $HO^{\bullet}$ initiates lipid peroxidation by hydrogen abstraction from polyunsaturated fatty acid. It has been demonstrated that primary (LOOH) and secondary (LOH, RCS, and electronically excited species) lipid peroxidation products are formed at high light. Formation of hydroxy fatty acid was demonstrated in Arabidopsis plants (Triantaphylides et al., 2008). The authors showed that oxidation of polyunsaturated fatty acid by $^1O_2$ leads to formation of LOOH which further forms LOH isomers (10-HOTE and 15-HOTE).

At high temperature, limited evidence was provided on the oxidation of proteins and lipids by ROS. It was demonstrated that exposure of thylakoid membranes to high temperature caused cleavage of D1 protein forming 9 kDa C-terminal and 23 kDa N-terminal fragments (Yoshioka et al., 2006). The authors demonstrated that FtsH protease is involved in the cleavage of the D1 protein at high temperature. Furthermore, it was reported that $^1O_2$ formed at Q_B site by the recombination of $LOO^{\bullet}$ formed by the lipid peroxidation caused the D1 protein degradation by the interaction with D-*de* loop of the D1 protein in a similar manner as under high light (Yamashita et al., 2008). As experimental evidence for oxidative damage of PSII protein by endogenous ROS was obtained predominantly *in vitro*, it is unclear whether the PSII protein oxidation at high temperature occurs *in vivo*. Apart to involvement of ROS in PSII protein oxidation, the inhibition of *de novo* protein synthesis by ROS was proposed at high temperature (Allakhverdiev et al., 2008). Lipid peroxidation is associated with formation of RCS. It was demonstrated that malondialdehyde is formed in Arabidopsis plants exposed to heat stress (Yamauchi et al., 2008).

CONCLUSION AND PERSPECTIVES

Under environmental conditions, abiotic stresses adversely affect plant growth and survival. The impact of high light on the photosynthetic apparatus is considered to be of particular significance as light reactions of photosynthesis are inhibited prior to other cell functions are impaired. However, under environmental conditions, plants are exposed to combination of multiple stresses. High light stress is often associated with high temperature causing global warming which is one of the most important characteristics of accelerated climatic changes. Extensive research over the last 10 years focused on the structural and functional changes of the photosynthetic complexes in response to high light, high temperature or their combination. The exploration of molecular mechanism of ROS production by PSII helps to understand the adaptive processes by which plants cope with high light and high temperature stresses.

AUTHOR CONTRIBUTIONS

The PP wrote and approved manuscript for publication.

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