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Reactive oxygen species generation and signaling in plants

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The introduction of molecular oxygen into the atmosphere was accompanied by the generation of reactive oxygen species (ROS) as side products of many biochemical reactions. ROS are permanently generated in plastids, peroxisomes, mitochiondria, the cytosol and the apoplast. Imbalance between ROS generation and safe detoxification generates oxidative stress and the accumulating ROS are harmful for the plants. On the other hand, specific ROS function as signaling molecules and activate signal transduction processes in response to various stresses. Here, we summarize the generation of ROS in the different cellular compartments and the signaling processes which are induced by ROS.

Introduction

With introduction of molecular oxygen (O_2) into our atmosphere by O_2-evolving photosynthetic organisms early in the evolution of aerobic life, reactive oxygen species (ROS) have become an integral part of life. The activation or reduction of oxygen gives rise to reactive ROS that includes the singlet oxygen ($^1O_2$), superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical ($HO^\cdot$). Plants and other living organisms in the oxidizing environment constantly produce ROS in chloroplasts, mitochondria, peroxisomes and other sites of the cell because of their metabolic processes such as photosynthesis and respiration.

The generation of ROS in plants is triggered by different kinds of environmental stresses, such as high light, high or low temperature, salinity, drought, nutrient deficiency and pathogen attack. Plants and other living organisms have evolved a host of antioxidants and anti-oxidative enzymes and other small molecules to harmlessly dissipate ROS. Imbalance between ROS production and their detoxification by enzymatic and non-enzymatic reactions causes oxidative stress. As a result of higher net ROS formation, there is photooxidative damage to DNA, proteins and lipids and ultimately cell death. ROS also act as signaling molecules involved in growth and developmental processes, pathogen defense responses such as hypersensitive reaction and systemic acquired resistance, stress hormone production, acclimation and programmed cell death.[1]

Imbalance between ROS generation and safe detoxification represents metabolic states that frequently are referred to as oxidative stress. In biological systems, oxidative stress results from the presence of elevated levels of oxidizing agents that are able to abstract electrons from essential organic molecules and disturb cellular function. When ROS production exceeds antioxidizing capacity, this can lead to cell damage and ultimately cell death by ROS toxicity and/or specific ROS-activated cell-death-inducing signaling events.

Although dioxygen in its ground state is relatively unreactive, partial activation or reduction gives rise to ROS including $^1O_2$, O_2^-, H_2O_2 and $HO^\cdot$. The evolution of aerobic metabolic processes such as respiration and photosynthesis unavoidably led to the production of such ROS in mitochondria, chloroplast and peroxisomes along with the other cellular and extracellular compartments. The common feature among the different ROS types is their capacity to cause oxidative damage to proteins, DNA and lipids.

Chemistry of Oxygen in Biological Systems

Although molecular oxygen contains an even number of electron, it has two unpaired electron in its molecular orbital. These two electrons have the same spin quantum number, and if O_2 attempts to oxidize another atom or molecule by accepting a pair of electron from it, both new electrons must be of parallel spin so as to fit into the vacant orbital. Usually, a pair of electrons in an atomic or molecular orbital would have anti-parallel spins. This imposes an important restriction on oxidation by O_2. Molecular O_2 is usually constrained to one electron transfer reaction at a time.

A way to overcome spin restriction, O_2 molecule interacts with another paramagnetic center. Transition metals like Fe or Cu frequently have unpaired electrons.

$Fe^{II} + O_2 \rightarrow Fe^{III} + O_2^{-\cdot}$

In aqueous solution $O_2^{-\cdot}$ decays to H_2O_2

$O_2^{-\cdot} + O_2^{-\cdot} + 2H^+ \rightarrow H_2O_2 + O_2$

The protonation of $O_2^{-\cdot}$ produces the hydroperoxyl radical, a far more reactive species.

$O_2^{-\cdot} + H^+ \rightarrow HOO^\cdot$

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The decomposition of H_2O_2 can be a source of hydroxyl radical, $HO^{\cdot}$

$Fe^{III} + O_2^{-\cdot} \rightarrow Fe^{II} + O_2$

$Fe^{II} + H_2O_2 \rightarrow Fe^{III} + HO^- + HO^{\cdot}$

Production of Reactive Oxygen Intermediates in Plants

Organelles with a highly oxidizing metabolic activity or with an intense rate of electron flow, such as chloroplast, mitochondrium and peroxisome, are a major source of ROS production in plants. Along with these organelles, peroxidases and amine oxidases present in cell walls and NADPH oxidase located in the plasma membrane produce ROS, often in response to stress signals. Oxygen is continuously produced inside the chloroplast due to photosynthetic electron transport and simultaneously removed by reduction and assimilation.

Photoreduction of oxygen to the superoxide radical occurred due to reduced electron transport components associated with photosystem (PS)I and a reaction linked to the photorespiratory cycle in the peroxisome. When the availability of CO_2 is restricted inside the leaves due to various environmental stresses, ribulose-1,5-bisphosphate carboxylase/oxygenase catalyzes a competitive reaction in which oxygen is favored over CO_2 as a substrate. This oxygenation reaction leads to the formation of glycolate, which is transported to peroxisomes and produce H_2O_2 after subsequent oxidation by glycolate oxidase.

Plasma membrane NADPH-dependent oxidases contain a multimeric flavocytochrome that forms an electron transport chain capable of reducing O_2 to O_2^{-}. Inhibitors of this oxidase impair ROS production.[2] In addition to NADPH oxidase, pH dependent cell wall peroxidase, oxalate oxidase and amine oxidases have been proposed to produce ROS in the apoplast.[3,4]

Though mitochondria are the major source of ROS production in mammalian cells, in green tissues its contribution for ROS is not effective.[5] The mitochondrial electron transport chain can produce ROS, which can transfer a single electron to oxygen and produce O_2^{-}. The mitochondrial alternative oxidase (AOX) catalyses the O_2-dependent oxidation of ROS. Lack of AOX induction caused increased ROS production[6] and tobacco plants overexpressing AOX have small hypersensitive response lesions than wild type in response to virus infection.[7] H_2O_2 treatment of Arabidopsis cells and H_2O_2 accumulation in catalase–deficient tobacco lead to induction of antioxidant defenses and increased AOX levels in mitochondria.[8]

Formation of Singlet Oxygen in Plants

Oxygen in its ground state is not very reactive and does not have any deleterious effect. The ground state molecular oxygen is a triplet state ($^3O_2$) and in fact a biradical, as it has two unpaired electrons. Its two unpaired electrons have parallel spins (↑↑) that do not allow them to react with most molecules. However, if the triplet oxygen absorbs sufficient energy, the spin restriction is removed and the spin of one of its unpaired electrons is reversed. As a result there is generation of singlet oxygen ($^1O_2$), whose outermost pair of electrons has antiparallel spins (↑↓). Singlet oxygen molecules are also formed when superoxide radicals interact with hydroxyl radicals. The excitation energy required to produce $^1O_2$ from the triplet oxygen is 94 kJ mol^{-1}.[9] It has a short half-life of about 200 ns in cells with a possible diffusion distance of about 270 nm and could even diffuse out of the chloroplast into the cytosol.[9]

In plants, $^1O_2$ is mainly produced by the chlorophyll (Chl) and its tetrapyrrole metabolic intermediates in the presence of light. Chl, the most abundant pigment in land plants, is the main light absorbing pigment and is present both in the light harvesting complex (LHC) and the photosynthetic reaction centers. The excited state of these is long lived and allow conversion of the excitation energy to an electrochemical potential via charge separation. Inefficient transfer of energy results in the generation of triplet state Chl that reacts with triplet oxygen to produce the highly reactive $^1O_2$. In the light harvesting complex, the $^1O_2$ is quenched by the carotenoids (for further information on the photochemistry of carotenoids, see ref. 10.)

$^1O_2$ is produced near the reaction centers of the PSs. With increase in light intensity i.e., from the early morning to noon, light absorption by leaves increases almost linearly. However, the rate of photosynthesis reaches its maximum value much before the linear increase in light absorption ceases. Therefore plants end up absorbing more light than they could utilize in photosynthesis. This results in the over excitation of the photosynthetic apparatus. In the presence of excess light energy, the Q_A and Q_B (the first and second plastoquinone electron acceptors of PSII) in the electron transport chain is over-reduced[11] and because of that, charge separation cannot be completed between P680 and pheophytin. As a result the triplet state of the reaction center Chl P680 (^{3}P680) is favored[12,13] leading to the formation of $^1O_2$.[14] Normally when excess light is absorbed, an alternative dissipating pathway is activated that safely returns ^{1}Chl* to its ground state before it is converted to ^{3}Chl*. The excitation energy of excess ^{1}Chl* is dissipated by zeaxanthin or other carotenoids as heat in Chl and/or carotenoid binding protein complexes.[15-19] The carotenoids, which quench the excited state of Chl, must be in close proximity with triplet Chl i.e., within a maximum distance of 3.6 Å. In this spin exchange reaction, the triplet state of carotenoids is formed that can dissipate the excess energy as heat. In the reaction center, the distance between Chl and carotenoid is too large to allow triplet quenching. $^1O_2$, produced in the reaction center, directly reacts with carotenoids. The release of $^1O_2$ is also detected in isolated PS II particles[20] and in thylakoids.[21-24] $^1O_2$ is also generated from the cytochrome-*b_6f*-complex.[25]

Generation of Singlet Oxygen from Chlorophyll Biosynthesis Intermediates

Upon illumination, Chl biosynthesis intermediates i.e., protochlorophyllide (Pchlide) or protoporphyrin IX (Proto IX) produce $^1O_2$ in plants and cause oxidative damage.[21,22,26,27] Formation of reactive oxygen species, from Chl biosynthesis intermediates was also proposed by others.[28-35] The site of generation of $^1O_2$ is mostly in the thylakoids. This is because Chl biosynthesis intermediates

are partially hydrophobic, and consequently are loosely attached to the thylakoid membranes.[36-38] Although they are associated with the thylakoid membranes, these tetrapyrroles do not form pigment protein complexes and hence are not connected to the reaction center. Although some of the carotenoids are present in the lipid bilayer, a lot more are located in the pigment-protein complexes and they are spatially too far from Chl biosynthesis intermediates to quench their triplet states.[39,40] Synthesis of Chl biosynthetic intermediates is highly regulated so that intermediates are not overproduced in plants. However, Chl biosynthesis intermediates that are normally present in plants are capable of producing $^1O_2$ that cause oxidative damage in high light and several other stress conditions.[21]

Porphyrin-Generating Compounds

There are two important types of porphyrin-generating compounds. One consists of 5-aminolevulinic acid (ALA), the substrate of tetrapyrroles and the other is a group of diphenyl ethers that inhibit protoporphyrinogen oxidase activity, thereby deregulating the tetrapyrrole metabolism. Cercosporin, rose bengal and several other compounds could generate $^1O_2$ and O_2^{-}.[41,42]

5-Aminolevulinic acid. 5-Aminolevulinic acid (ALA) is the sole precursor of all tetrapyrroles i.e., Chl, hemes, sirohemes, and phytochromobilins. Tetrapyrrole intermediates are photosensitizers and generate radicals and ROS, especially $^1O_2$ in the presence of light. So plants regulate their own tetrapyrrole biosynthesis and degradation pathway to avoid the consequence of the excess generation of ROS. The major regulatory point is at the production of the initial precursor ALA. Therefore, ALA synthesis is the rate-limiting step of the tetrapyrrole biosynthetic pathway. ALA is formed from glutamyl-tRNA by the enzyme glutamyl-tRNA reductase (GluTR). In Arabidopsis this enzyme has three isoforms (HEMA1, HEMA2 and HEMA3) and their expression levels are different in different plant tissues. Pchlide, which accumulates in the dark, repress the ALA synthesis by feed-back inhibition.[43,44] However, when ALA is applied externally, green plants bypass the regulatory feedback inhibition of Pchlide pool and induce excess accumulation of Mg-tetrapyrroles in the dark.[31,32,45] When only ALA is applied externally, Pchlide is the major porphyrin that accumulates. But after ALA + Modulator (= a compound structurally related to tetrapyrrole molecule) treatments, several other types of porphyrins accumulate, depending upon the target site of the modulator.[33] ALA is added along with the modulator for providing the carbon skeleton to accumulate porphyrins. Eight molecules of ALA are required to form one molecule of tetrapyrrole. The mode of action of some of the modulators has been attributed to their metal chelating properties. Enzymes in the porphyrin synthesizing pathway essentially require certain metal ions for their activity. Another way by which some of these modulating chemicals may be acting is by stimulating enzyme activity, i.e. by behaving as cofactor analogs.

Diphenyl ethers. The diphenyl ethers (DPEs) are inhibitors of the enzyme protoporphyrinogen oxidase (protox),[46] an enzyme that converts protoporphyrinogen IX to Proto IX. The latter is an intermediate in Chl and heme biosynthetic pathway. DPEs cause plants to overaccumulate a large quantity of Proto IX.[47] Pchlide, Mg-Proto IX and Mg-Proto IX monomethylester (MPE) are also found to be elevated, but to a significantly less extent as compared to Proto IX, in tissues with inhibited protox activity. Though DPE entry into cells is light-independent, light and pigments are mandatory for their herbicidal action. Initial symptom of DPE damage is seen as water soaked spots on leaf tissue, followed by loss of leaf turgidity, bleaching and necrosis. More lipophilic DPEs like oxyfluorfen and acifluorfen-methyl have greater potency as herbicides than the more polar acifluorfen. This correlation may also be partly due to the greater ease of penetration through the cuticle by the more lipophilic molecules. DPEs can inhibit carotenoid synthesis, ATP formation, photosynthetic electron transport, and induce membrane peroxidation by causing massive accumulation of Proto IX.[48,49] Superoxide radical is not of primary importance in the development of DPE toxicity.[50-52] Oxyfluorfen added to isolated thylakoid membranes, in vitro, generates $^1O_2$ during illumination.[42] Treatment with the protox inhibitor acifluorfen-sodium (AF-Na) in the light induced the overaccumulation of protoporphyrinogen IX that migrates out of the chloroplast to the cytoplasm where it is oxidized to Proto IX by plasma membrane bound AF-Na-insensitive protoporphyrinogen oxidase.[47,53] A part of Proto IX so generated in the plasma membrane migrates back to the chloroplast and partitions between the cytoplasm and the chloroplast.[53,54] The $^1O_2$ generated by the photosensitization reaction of Proto IX creates necrotic spots and cell death by destroying the plasma membrane.[27] The DPE herbicide lactofen induces cell death and expression of PR1, PR5 and PR10 protein in soybean plants. The anthocyanin biosynthesis pathway genes i.e., chalcone synthase and chalcone reductase are also induced in lactofen treated samples.[55]

Type II and Type I Photosensitization Reactions of Tetrapyrroles. In type II photosensitization reaction, a sensitizer can transfer its excitation energy to a ground state oxygen molecule, resulting in $^1O_2$. ALA or DPE compounds induce overaccumulation of non-phototransformable Pchlide or Proto IX, respectively. In the presence of light, these tetrapyrroles generate $^1O_2$ through type II photosensitization reaction, which ultimately destroys the plant.[21,22,27] $^1O_2$ is quite selective and fails to react with molecules that are not enough electron-rich, and simply returns to the ground state.

The type I photosensitization involves hydrogen atom or electron transfer from the sensitizer to the substrate.[56] The resulting free radicals can subsequently react with O_2 to produce oxidized products or other reactive species. The products are often peroxides, which can in turn breakdown to induce free radical chain auto-oxidation, leading to further oxidation in a non-photochemical step.

$LOO^{\cdot} + LH \dashrightarrow LOOH + L,$

where L and $LOO^{\cdot}$ are lipid free radicals; LH is an unsaturated lipid and LOOH is a lipid hydroperoxide.

Sensitizers (Sens) can produce superoxide radical ($O_2^{-\cdot}$) by undergoing electron transfer processes with the substrate or O_2.

$^3Sens + Subs \dashrightarrow Sens^{-} + Subs_{ox}$

$Sens^{-} + O_2 \dashrightarrow Sens + O_2^{-\cdot}$

or

$^3Sens + O_2$ ----> $Sens^+ + O_2^{-}\cdot$.

These reactions produce $O_2^{-}\cdot$, which can subsequently give rise to the highly reactive hydroxyl radical (OH•). The hydroxyl radicals thus produced can react with organic molecules in a variety of ways or can initiate radical chain auto-oxidation.

Intracellular Destruction of Singlet Oxygen. The most efficient mechanism of detoxification of $^1O_2$ in plants involves carotenoids. The carotenoids reach the triplet excited state by absorbing the excess energy of $^1O_2$ which returns it to its triplet ground state ($^3O_2$). They finally dissipate the excess acquired energy as heat.[57] The physical quencher has to be lipid soluble and needs to be very close to the photosensitizer. Carotenoids, because of their conjugated double bonds, are the most abundant quenchers of $^1O_2$ in the pigment bed of the photosynthetic apparatus. Photosynthetic antenna systems have several xanthophylls i.e., lutein, violaxanthin, neoxanthin, and zeaxanthin. Out of these, lutein is the most abundant as it is needed for efficient quenching of ^{3}Chl*. Zeaxanthin is synthesized from violaxanthin under high-light stress by the violaxanthin deepoxidase enzyme and is involved in energy dependent quenching of Chl a fluorescence (see e.g., 40). Tocopherol is lipid soluble and is a minor but significant component of $^1O_2$ quenchers in the thylakoid membranes. The suppression of both zeaxanthin and tocopherol in the *npq1/ vte1* double mutant results in $^1O_2$-mediated lipid peroxidation in high light.[58,59] In the PSII reaction center, especially under high light regime, $^1O_2$ is quenched by β-carotene and α-tocopherol.[60]

Scavengers of $^1O_2$ are usually water soluble and are themselves oxidized or destroyed while detoxifying the ROS. The oxidized scavenger is re-reduced by a set of biochemical reduction reactions at a great cost to the cell. The cell has only limited capability to resynthesize the destroyed scavengers. Therefore, the cells become extremely prone to $^1O_2$ attack. Ascorbate is an example of $^1O_2$ scavenger that is oxidized after detoxification. It is predominantly present in the plastids. $^1O_2$ reacts with ascorbate to produce dehydroascorbate.[61] The latter is converted back to ascorbate by the dehydroascorbate reductase, and the glutathione reductase enzymes involved in the Halliwell-Asada pathway. Vitamin B6 (pyridoxine, pyridoxal, pyridoxamine) can efficiently scavenge $^1O_2$.[62,63] The fungus Cercospora secretes cercosporin, a $^1O_2$-generating photosensitizer into the extracellular matrix during plant infection.[63] The cercosporin secreted to the host cell by the fungus absorbs solar energy and transfers its energy to oxygen to generate $^1O_2$ that kills the host cell. However, the fungus itself is protected against $^1O_2$-mediated damage by the $^1O_2$-scavenger vitamin B6. In the same vein, the pyridoxine synthase is involved in tolerance to oxidative stress.[64] Similarly, exogenous vitamin-B6 protects protoplasts of the *flu* (fluorescence) mutants of *Arabidopsis thaliana* that generated $^1O_2$.[65] Flavonoids that are present in plants in high concentrations in the cytoplasm and isoprene that is mostly synthesized in the chloroplasts could also function as $^1O_2$ quenchers.[66-69] The water soluble chlorophyll binding protein (WSCP) binds to free Chl molecules as well as to its biosynthetic intermediates and does not allow them to get photoactivated to produce $^1O_2$. It acts as a physical barrier between free Chl molecules and molecular oxygen.[70]

Singlet Oxygen-induced Oxidative Damage in Mutants

Chlorophyll anabolic mutants. *Tigrina* mutant of barley accumulates 2-10 times more Pchlide in darkness than the wild type.[71] Homozygous *tigrina-d* mutants are fully green and viable if grown in continuous weak light, but show a green-white banded phenotype, when grown under light/dark cycles. They have normal level of protochlorophyllide oxidoreductase (POR) and when illuminated, the excess Pchlide causes photodynamic damage resulting in the formation of necrotic patches.[72] Runge et al.[73] isolated *xantha* mutants of Arabidopsis and classified them in two groups, mutants that are blocked in various steps of the Chl biosynthetic pathway prior to POR, and mutants that accumulate Pchlide in the dark. The etiolated PORA and PORB mutant seedlings accumulate significant amounts of non-phototransformable Pchlide in darkness and upon light exposure they show bleaching effect and germination defect.[74] However, overexpression of PORA and PORB results in the efficient transformation of non-phototransformable Pchlide to chlorophyllide (Chlide). Transgenic seedlings grown under far red light when transferred to white light are more resistant to photobleaching because of high POR proteins.[75]

The isolation and studies on Arabidopsis *flu* mutant by Klaus Apel's group confirm the role of Pchlide in $^1O_2$ generation; it leads to oxidative damage. In *flu* mutant there is a massive accumulation of Pchilde if those plants are grown under constant dark/light cycle and there is growth arrest and cell death because of generation of $^1O_2$. However if the plants are grown under continuous light, there is no accumulation of Pchlide, no generation of $^1O_2$ and plants behave like wild type plants. The FLU protein interacts with GulTR (HEMA1) and regulates the accumulation of Pchlide in darkness.[76] In the *flu* mutant there is no regulatory point at the GluTR level and there is a massive accumulation of Pchlide. Lee et al.[77] have revealed that the *TIGRINA d* gene of barley is an ortholog of the *FLU* gene of *Arabidopsis thaliana*. Pchlide-mediated $^1O_2$ formation leads to the induction of the early stress-responsive gene.[26] There is no change in amounts of other photosensitizers i.e, Proto IX, Mg -proto IX and MPE in the *flu* mutant. Two major stress reactions were observed when dark-grown *flu* plants were returned to light: a cell death response and a rapid inhibition of growth. Oxygenation derivatives of linolenic acid, by far the most prominent polyunsaturated fatty acid of chloroplast membrane lipids, start to accumulate rapidly in the *flu* mutant after the dark/light shift. The oxidation of linolenic acid is not caused by direct interaction with $^1O_2$ but instead occurs enzymatically. Thus, the development of stress symptoms in the *flu* mutant seems not to be attributable to cell damage caused by $^1O_2$ but rather appears to result from the more indirect role of this ROS. Vitamin B6 that quenches $^1O_2$ in fungi was able to protect *flu* protoplasts from cell death;[65] further, protoplasts of *flu* mutant depleted of both ethylene and salicylic acid had reduced cell death. However, when the gene *Executer1* (exe1) was mutated in the *flu* background, the *exe1/flu* double mutant accumulated free Pchlide in the dark like the *flu* mutant, but unlike the wild type plants. After transfer to light, *exe1/flu* generated $^1O_2$

in amounts similar to those of *flu* but grew like wild type when kept under non-permissive light-dark cycles.[78] In *flu* plants, the growth rate was reduced immediately after the beginning of re-illumination. The *exe1/flu* plants, however, grew like wild-type plants. Growth inhibition of *flu* plants was particularly striking when plants were transferred to repeated light-dark cycles, whereas the *exe1/flu* mutant continued to grow like wild-type plants.[78] Both assays demonstrate that the rapid bleaching of *flu* seedlings and the inhibition of growth after the release of $^1O_2$ are not by the toxicity of this ROS; further, these do not reflect photooxidative damage and injury, but instead result from the activation of genetically controlled responses that require the activity of the *Executer1* gene. The isolation of the Executer 2 protein also shows a similar kind of response in *flu* back ground.[79] Inactivation of executer proteins blocks the $^1O_2$-mediated signaling from the chloroplast to the nucleus that affects the normal plastid development in germinating seeds.[80] Coll et al.[81] have isolated another $^1O_2$-linked death activator (soldat8) that encodes the SIGMA6 factor of the plastid RNA polymerase, specifically abrogate $^1O_2$-mediated stress responses in young *flu* seedlings without grossly affecting $^1O_2$-mediated stress responses of mature *flu* plants. The other protein named PRL1 (Pleiotropic response locus 1) also affect the expression of $^1O_2$- responsive genes in Arabidopsis.[82]

Apart from Pchlide, early intermediates i.e., coproporphyrin also acts as a photosensitizer.[83-85] The antisense coproporphyrinogen oxidase (that converts coproporphyrinogen III to protoporphyrinogen IX) in tobacco plants, have an excessive amount of coproporphyrin. This oxidized porphyrin gives rise to photodynamic reactions, which affect cellular processes resulting in retarded growth and necrotic leaves.[84,85] The Arabidopsis coproporphyrinogen oxidase mutants (*lin2*; lesion initiation 2) had pale leaves and developed lesions on the young leaves.[83] 3,3-Diamino benzidine and trypan blue staining of the mutant leaves shows H_2O_2 accumulation and cell death. Seedlings homozygous for a null mutation in the *cpx1* gene of maize completely lack chlorophyll and develop necrotic lesions in the light.[86] The accumulation of uroporphyrin I in the uroporphyrinogen III cosynthase antisense barley plants results in necrotic leaves and ultimately cell death because of accumulation of ROS.[87] Like uroporphyrin I, uroporphyrin III, an oxidized derivative of uroporphyrinogen III, an intermediate of the chlorophyll biosynthesis pathway, also acts as a photosensitizer. Accumulation of uroporphyrin III leads to light-dependent necrosis in tobacco[30,88] and in maize.[89] Antisense tobacco plants of uroporphyrinogen decarboxylase have stunted growth with necrotic leaves and high *PR1* gene expression. The maize lesion mimics a mutant, coding for uroporphyrinogen decarboxylase that has necrotic spots in the leaves. Inhibition of protox in Arabidopsis leads to production of lesion-mimic phenotype, high endogenous level of salicylic acid and *PR1* gene expression.[90] Overexpression of plastidic protox leads to resistance to the DPE herbicide acifluorfen. The overexpressed plants did not show any necrotic leaves.[91] Tobacco plants having reduced ferrochelatase activity also show necrotic leaves in a light intensity dependent manner.[92]

Chlorophyll catabolic mutants. Intermediates involved in the Chl degradation pathway also produce ROS. Squash plants expressing the mature (lacking the N-terminal 21 amino acids) citrus chlorophyllase protein display a lesion-mimic phenotype when grown under natural light. The phenotype is caused by the accumulation of chlorophyllide, which is a photodynamic porphyrin molecule.[93] The Arabidopsis pheophorbide a oxygenase (PAO, also called *acd1*, accelerated cell death 1) mutant shows a cell death phenotype because of the accumulation of the Chl degradation intermediate pheophorbide a. The latter gets photoactivated in the presence of light and generates ROS that form lesions in the mutant plants. The lesions that form in *acd1* mutant leaves start mostly at the tip of the leaf and subsequently run down the leaf blade.[94] Hirashima et al.[95] also observed that the accumulation of pheophorbide a in dark-grown *acd1* antisense plants caused cell death. LLS1 (lethal leaf spot 1), the homologue of ACD1 (Accelerated cell death 1/ Pheophorbide a oxygenase) in maize, is responsible for Chl catabolism. The maize *lls1* mutant formed lesions when grown in the light.[96] Similarly the Arabidopsis red chlorophyll catabolite reductase (RCCR, also called *acd2*, Accelearated cell deah 2) mutant showed lesion formation in leaves and spontaneous cell death phenotype.[97] It is observed that the accumulation of H_2O_2 in the *acd2* mitochondria is causal for its cell death phenotype.[98] The lesion formation in *acd2* is caused by the accumulation of red chlorophyll catabolite (RCC) in darkness that generates $^1O_2$ in the presence of light.[99] Further work should be done to check whether the generation of H_2O_2 and $^1O_2$ are independent events or whether one leads to the other.

Abiotic stress-mediated ROS generation. One of the mechanisms that may lead to apoptosis upon extreme desiccation due to water-stress, salt-stress *etc.* is *via* ROS. In desiccated photosynthetic tissues, particular problems arise if excited Chl molecules are present but carbon fixation is limited by water deficiency. Under these conditions, electron flow continues, and excitation energy can be passed from photo-excited chlorophyll pigments to ground state oxygen ($^3O_2$) forming singlet oxygen ($^1O_2$). In addition, superoxide (O_2^-), hydrogen peroxides (H_2O_2) and the highly toxic hydroxyl radical (OH^-) can be produced by photosystem II.[100] ROS are also produced during normal metabolism in the electron transport chains of respiration and photosynthesis,[101] but desiccation greatly enhances their production.[102] To avoid $^1O_2$ formation, photosynthetic organisms can dissipate excess energy *via* non-photochemical quenching (NPQ). This is most likely to involve the xanthophyll cycle in which violaxanthin is stepwise de-epoxidized to antheraxanthin and then to zeaxanthin, while solar radiation is dissipated as heat.[103,104] In addition to their function as accessory pigments in photosynthesis, other carotenoids can also contribute to energy dissipation.[105] Moreover, antioxidants such as glutathione, ascorbate, tocopherol, and related enzymes such as superoxide dismutase, catalase, peroxidase and others scavenge ROS.[102]

NADPH Oxidases

The respiratory burst oxidase homologues (Rbohs) oxidize cytosolic NADPH and transfer the electron to O_2, thereby generating

superoxide which is subsequently converted to H_2O_2. Ten *RBOH* genes are present in the Arabidopsis genome, they encode plasmamembrane-localized proteins, where the apoplastic oxidase domain is responsible for superoxide generation in the apoplast and the N-terminal extension in the cytoplasm contains the regulatory regions calcium-binding EF-hands and phosphorylation domains.[106,107] Thus, there is a crosstalk between calcium and phosphorylation in controlling apoplastic ROS production.[108] Furthermore, NADPH oxidase undergoes S-nitrosylation and this is required for enzyme activity.[109,110] Rbohs are involved in defense against pathogen attacks, e.g. by activating hypersensitive responses and regulating innate immunity in plants[111-114] and extracellular lignin production (115, and ref. therein), but also in nodule formation in *Medicago truncatula*,[116] abiotic stress responses such as heat, cold, drought, salinity and high light.[117,118] The ROS signal can be delivered from cell to cell through diffusion; and this long distance signals may participate in systemic acquired resistance.[118,119] NADPH oxidase-mediated ROS production regulates polarized cell expansion in root hairs and pollen tip growth,[120,121] or promotes seed ripening.[122] RbohC and –D are highly expressed in shoot and roots and control most of the inducible ROS production; RbohC is particularly involved in root hair formation[120] and mechanosensing,[123] and RbohH and –J are specifically expressed in pollen.[121]

Oxidative Burst, ROS in Plant/Microbe Interaction

Most work has been performed for the role of NADPH oxidases in plant immunity. While ROS production increases rapidly after pathogen attack to establish local and systemic resistance Pogány et al.[124] described a dual role of ROS and RbohD in the Arabidopsis-Alternaria pathosystem. RbohD triggers death in cells that are damaged by fungal infection but simultaneously inhibits death in neighboring cells through the suppression of free salicylic acid and ethylene levels. Comparably, *Sclerotinia sclerotiorum*, a necrotrophic fungus with a broad host range, produces the key pathogenicity factor oxalic acid, which induces apoptotic-like programmed cell death in plant hosts. This induction requires ROS generation in the host, a process triggered by fungal secreted oxalic acid. Conversely, during the initial stages of infection, oxalic acid also dampens the plant oxidative burst. This scenario presents a challenge regarding the mechanistic details of oxalic acid function; as oxalic acid both suppresses and induces host ROS during the compatible interaction. Initially, S. *sclerotiorum via* oxalic acid generates a reducing environment in host cells that suppress host defense responses including the oxidative burst and callose deposition, akin to compatible biotrophic pathogens. Once infection is established, however, this necrotroph induces the generation of plant ROS leading to programmed cell death of host tissue, the result of which is of direct benefit to the pathogen.[125] These and other results indicate that reducing the cellular environment directly or indirectly suppresses the host-plant oxidative burst and defense mechanisms against pathogen infections.[125] A survey of the literature also suggest that ROS levels (mainly or exclusively produced by NADPH oxidases) are higher after infections with necrotrophic compared to biotrophic pathogens, although this requires a more detailed analysis. In general, low antioxidant activity has been reported for plants exposed to necrotrophic pathogens while biotrophic pathogens activate the antioxidant system to propagate in the living plant cells. This is consistent with the observations that ROS production by plants infected with beneficial microbes is low and antioxidant enzyme activities high.[126,127] Although ROS have been mainly associated with pathogen attack, ROS are also detected in other biotic interactions including beneficial symbiotic interactions with bacteria or mycorrhiza, suggesting that ROS production is a common feature of different biotic interactions.[128] ROS might have different functions during various steps of the beneficial symbiosis, however it is generally excepted that ROS accumulates during early phases of the interaction when the beneficial symbiosis is not yet stable and declines thereafter.[129] Whether this is caused by a general reduction in host defense processes once the two symbionts have been recognized as friends, or caused by an active repression from the microbe, is not known yet. Beneficial fungi or microbe are also known to protect plants against pathogens, e.g. by scavenging ROS, in particular when the plants are attacked by necrotrophic fungi. Finally, the important role of fungus-derived ROS for mycorrhiza formation has been nicely demonstrated for the *Epichloë festuca*/*Lolium perenne* symbiosis. Inactivation of the fungal NADPH oxidase-encoding *noxA* gene shifts the symbiosis from mutualistic to antagonistic, because fungal growth is no longer restricted.[130]

ROS and Signal Transduction

ROS sensors/receptors induce signaling cascades that lead to differential gene expression. This can occur directly through activating receptors, components of signaling pathways and/or even transcription factors in the nucleus. As ROS are short-lived, sensing must be quite efficient. Possible scenarios are: ROS are sensed at the apoplastic site of the plasma membrane (e.g. after the activation of NADPH oxidases), activate intercellular signaling and ultimately changes in gene expression pattern, or ROS activate signaling molecules within the cell or even organelles (e.g. by $^1O_2$ generated in plastids). There might be a "linear" signal transduction pathway, but ROS may also influence the signaling events along such a proposed pathway at different levels. It is likely that different signaling pathways merge and/or interact with each other. In contrast, there might be a general effect of ROS on the cellular redox homeostasis, in particular if the ROS concentration in the cell is quite high. Since changes in organellar ROS levels, such as $^1O_2$ in the plastids, lead to altered gene expression in the nucleus, ROS clearly initiate retrograde signaling from the plastids to the nucleus. However, there is also intensive cross-talk between the organelles themselves: for instance, under high light stress, mitochrondria re-oxidize excess reduction equivalents generated in the plastids to protect the plastids and its electron transfer chain from over-reduction.[131] The utilization of mitochrondria to reduce photosynthesis-derived reduction equivalents is one strategy to reduce the production of ROS under stress. Mitochrondrial enzymes also form part of the respiratory pathway to salvage glycolate from photorespiration.

Plant cells sense ROS *via* at least 3 different mechanisms:

1. Unidentified receptor proteins

2. Redox sensitive compounds including transcription factors, such as NPR1 or HSFs

3. Direct inhibition of phosphatases by ROS

ROS are sensed *via* yet unknown mechanisms or receptors. All ROS with signaling functions, i.e. H_2O_2, $^1O_2$, $OH^{\cdot}$, and $O_2^{\cdot-}$[132] must somehow interact with a cellular target to activate signaling events. Whether different ROS species are perceived by different perception mechanisms is unknown, however the specificity in the responses and the different locations, where ROS are generated, suggest different targets or perception mechanisms and therefore specificity. Downstream of the activation of putative receptors, it is likely that ROS perception is transduced *via* changes in the redox status of the signaling components. The information from the different ROS species can be either integrated or the signaling events are specific for individual ROS species.

To study apoplastic ROS sensing, the air pollutant ozone which generates ROS in the apoplast is a powerful tool. Different Arabidopsis ecotypes also show different sensitivities to ozone treatments, ranging from tolerant to extreme sensitive. Brosché et al.[133] perform quantitative traits loci (QTL) mapping to identify genes that regulated ozone sensitivity in natural populations. The responses induced by ozone are quite similar to those induced by pathogens or pathogen-associated molecular patterns suggesting that ozone in the apoplast triggers hypersensitive-like programmed cell death responses. Several mutants altered in hormone biosynthesis or signalling showed also changes in ozone-induced transcriptional responses.[134] Gauthier et al.[135] have identified two members of the cysteine-rich receptor-like kinase gene family and a leucine-rich repeat (LRR-RLK) protein in Arabidopsis which are transcriptionally induced after ozone treatment, and thus they could sense ROS through redox modifications of their extracellular domain. Corresponding knock-out lines lead to sensitivity to extracellular ROS resulting in subtle lesion formation upon ozone treatment indicating their involvement in ROS signaling. Some of them are specifically upregulated by extracellular ROS but not by high light leading to the production of $^1O_2$, suggesting specificity in the perception of different ROS species. Another candidate for ROS perception is the STIG1-like protein GRIM REAPER.[136]

Downstream signaling events associated with ROS sensing involve Ca^{2+} and Ca^{2+} binding protein such as calmodulin,[137-139] the activation of G-protein[140] and the activation of phospholipid signaling.[141-143] A serine/threonine protein kinase (Oxidative Signal Inducible 1; OXI1) has been shown to play a central role in ROS sensing by activating mitogen–activated-protein kinases (MAPKs) 3 and -6 through Ca^{2+}.[142] The expression of *OXI1* is induced in response to a wide range of H_2O_2-generating stimuli. OXI1 kinase activity is itself also induced by H_2O_2 *in vivo*.[142] The OXI1 protein kinase is required for plant immunity against *Pseudomonas syringae* in Arabidopsis.[144] OXI1, which belongs to the AGC kinases well characterized in mammalian systems,[143] is important for two oxidative burst-mediated processes: basal resistance to microbial pathogens and root hair growth. To identify possible components of the OXI1 signalling pathway, phosphoproteomic techniques were used to detect alterations in the abundance of phosphorylated proteins and peptides in an *oxi1* null mutant of Arabidopsis.[145] Five proteins, including a putative F-box and 3-phosphoinositide-dependent kinase 1 (PDK1), show reduced phosphorylation in the *oxi1* mutant, and may be direct or indirect targets of OXI1. Four proteins, including ethylene insensitive 2 and phospholipase Dγ, show increased phosphorylation in the *oxi1* mutant. Therefore, these are putative early signaling candidate proteins in the OXI1 pathway. The diverse activities of these proteins, including protein degradation and hormone signalling, may suggest crosstalk between OXI1 and other signal transduction cascades.[145] A MAPK cascade involving MAPK3/6 acts downstream of OXI1 and controls the activation of different defense mechanisms in response to ROS stresses.[1,146] MAPKs are also activated by PDK1 through the phospholipase-C/D-phosphatidic-acid pathway.[141] H_2O_2 activates several MAPKs.[147] In Arabidopsis, H_2O_2 activates the MAPKs, MPK3, and MPK6 via MAPKKK ANP1.[146] Overexpression of ANP1 in transgenic plants resulted in increased tolerance to heat shock, freezing and salt stress.[146] H_2O_2 also increases expression of the Arabidopsis nucleotide diphosphate (NDP) kinase 2.[148] Overexpression of AtNDPK2 reduced accumulation of H_2O_2 and enhanced tolerance to multiple stresses including cold, salt, and oxidative stress. The effect of NDPK2 might be mediated by the MAPKs, MPK3 and MPK6, because NDPK2 can interact and activate them.

The expression of different transcription factors is enhanced by ROS and includes members of the WRKY, Zat, RAV, GRAS and Myb families.[149-154] In *E. coli*, the transcription factor OxyR,[155] and in budding yeast, Yap1 play major roles[156] in oxidative stress signaling. OxyR and Yap1 are redox-sensitive transcription factors and modulate gene expression in response to oxidative stress. Different types of ROS react with different cysteinyl residues and can give rise to differently modified products, possibly explaining how ROS species can induce different sets of genes *via* the same transcription factor.[156,157] Microarray analysis of H_2O_2-induced gene expression indicates potential H_2O_2-responsive *cis*-elements in genes regulated by H_2O_2. Recent studies using knockout plants have revealed that the zinc-finger protein Zat12 is required for *Apx1* expression and plant protection during oxidative stress, and that the highly conserved zinc finger paralogs LOL1 and LSD1 have antagonistic effects on SOD and $O_2^{\cdot-}$ accumulation.[152] The transmembrane sensory kinase functions through its capacity to autophosphorylate a histidine residue in response to the presence or absence of an external stimulus. The phosphoryl group is subsequently transferred from the histidine to an aspartate residue in the response regulator. The induced conformational change in the response regulator alters its DNA binding affinity and thus promotes gene regulation of certain promoters. Recent work has identified human protein tyrosine phosphatase PTP1B to be modified by H_2O_2 at the active site cysteine.[158] A similar regulation likely occurs in plants because PTP1, an Arabidopsis PTP that can inactivate the Arabidopsis MPK6, can be inactivated by H_2O_2.[159] Also, phosphatases involved in abscisic acid (ABA) signaling within guard cells have been identified whose *in vitro* activity was modulated reversibly by H_2O_2.[160,161] Peleg-Grossman

et al.[162] have shown that cytoplasmic H_2O_2 prevents translocation of NPR1 to the nucleus and inhibits the induction of *PR* genes in Arabidopsis. NPR1 is a transcriptional coactivator and regulates salicylic acid-dependent gene expression.[163] NPR1 protein exists in the cytosol in oligomeric form. During pathogen attack the NPR1 protein is reduced to its monomeric state and translocated to the nucleus, where it binds a bZIP transcription factor of the TGA/OBF family.[164-166] The oligomeric state of the NPR1 protein is sustained by disulfide S-S bonds that involve Cys82 and Cys216.[164] The formation and dissipation of disulfide bonds is regulated by redox changes, including ROS production and their degradation by antioxidants.[167] Cytoplasmic ROS function maintains the NPR1 complex in its oligomeric state, excludes the NPR1 from the nucleus and thus inhibits *PR* gene expression.[162] Once activated, the NPR1-TGA1 system is an ideal example for a redox- and ROS-regulated signaling pair involved in local and systemic defense repair.[163] In addition, nitric oxide is a redox regulator of the NPR1/TGA1 system.[168]

ROS and Redox

Many cellular signaling events are based on redox reactions, therefore, it is likely that ROS is directly linked to or at least integrated into the cellular redox metabolism. ROS are harmful to cells because they cause the oxidation of lipids, proteins and DNA and other components in their environment. Consequently, it is important for a cell to maintain the redox homeostasis, e.g. by antioxidants (ascorbate and glutathione) and/or antioxidant enzyme systems. The antioxidants are predominantly maintained in the reduced state. Changes in the balance of reduced *vs*. oxidised forms of the antioxidants may be used as a sensor for changes in the environment, and changes in ROS levels may directly affect the redox situation in the cell. Elevated ROS levels may lead to the oxidation of the antioxidant systems and this results in changes in the redox balance in the cell or apoplast. However, it is not understood yet, how changes in ROS levels influences the redox situation and ultimately activate ROS/redox-induced signaling events. In the plastids, for instance, high light intensity induces ROS production and the reduction of the plastoquinone pool. Besides activation of protein kinases by the reduced plastoquinone pool and initation of a short-term photoacclimation, high light also induces changes in plastid and nuclear gene expression and this includes numerous genes involved in antioxidative processes and genes which code for ROS-scavenging enzymes.[1,169] Whether these two processes (ROS production and reduction of plastoquinone) are linked to each other, is unknown.

Specificity of ROS Effects

The ROS level is controlled by a complex protein network in all compartments to maintain redox balance. Mittler et al.[169] have shown that this network includes at least 152 genes in Arabidopsis. Recent studies demonstrates that different ROS signals contain a certain degree of specificity, i.e. the response depends on the ROS that accumulates in or around a cell.[170,171] Since chloroplasts, mitochondria and peroxisomes are the main ROS producers in a plant cell, the majority of the ROS-scavenging enzymes are located in these organelles. This includes the major cellular isoforms of the superoxide dismutases, ascorbate peroxidases and catalases, but also glutathione peroxidases, and peroxiredoxins (cf. 169). Thus besides the classical use of inhibitors or the isolation of mutants, manipulation of the antioxidant enzyme levels in specific cellular compartments by genetic tools can influence the accumulation of specific ROS in given cellular compartments.[149,150,151,172,173] Arabidopsis plants compromised in specific antioxidant enzymes in combination with inhibitor studies and the *flu* mutant allows comparative analyses of targets of $O_2^{\cdot-}$, H_2O_2, and $^1O_2$.[170] Powerful tools are comparative expression profile, proteome or metabolome analyses of these mutants or wild-type plants treated with ROS biosynthesis inhibitors.[26,149,173-180] Examples are the *flu* mutant which generates $^1O_2$ in plastids, the *cat2* mutant which accumulates H_2O_2 in peroxisomes, or plants overexpressing glycolate oxidase in the plastids, which generates H_2O_2 in plastids. Another examples is the *rbohC rbohD* double knockout line which is strongly impaired in apoplastic ROS production in response to pathogen attack, or the *rbohC* mutant impaired in root hair development due to the lack of apoplastic ROS production in the appropriate cells.[114] Considering the complex ROS scavenging network[169] and gene families involved in ROS production, large number of new mutants, mutant combinations or overexpressor lines need to be analyzed in the future.[169] There are also other problems in defining specificity in ROS signaling: For instance, transcriptional analyses from the *flu* mutant have shed some light on the specific effects of $^1O_2$,[26,181] but, unlike in the wild-type, the $^1O_2$ production is not associated with excess excitation of the photosystem II.[182] So far, these comparative studies clearly demonstrate that the cellular ROS responses depend on the type of ROS and the subcellular location where they are produced. The analyses also allowed the generation of a list of marker genes that were preferentially regulated by hydrogen peroxide, superoxide, or singlet oxygen of different cellular origin, whereas other genes were identified as general oxidative stress response markers (cf. 169).

ROS in the cytosol. Although the cytosol is not thought to be a major site of ROS production in plants is important in redox signal integration. Cytoplasmic NADPH is central for redox signaling because it generates reducing substrates for antioxidant enzymes that detoxify ROS. Furthermore, NADPH maintains the thiol/disulfide status and supplies electrons to ROS producing enzymes such as NADPH oxidases. Signaling from the apoplasts and from the organelles have to pass through the cytoplasm in order to alter gene expression in the nucleus. It is conceivable that ROS information, the redox state in the plant/cell is integrated into other regulators. An example for such a network is provided by Khandelwal et al.[183] They generated a redox network to identify genes whose expression is tightly coordinated during adjustment of the cell to a new environment. In their experiments they applied stress to the plastids and identified ten subnetworks which participate in the re-adjustment of the cellular redox homeostasis to the new conditions. Many of the genes in these subnetworks code for cytoplasmic proteins.

How these processes are coupled to ROS remains to be determined. Furthermore, Mhamdi et al.[184] showed that different NADPH-dehydrogenases play non-overlapping roles in some stress responses. Thus, specificity from the different ROS species and locations overlap with the integration of ROS signaling into the redox homeostasis.

A major problem in agriculture is the effect of biotic and abiotic stress responses on plant growth and development. A common theme within these environmental factors is the perturbation of ROS homeostasis. The great economical importance highlights the importance of the ROS signaling network. In particular the genetic approaches undertaken in the last decade might substantially contribute to understand the underlying mechanisms. This may provide also a tool for genetic engineering of crop plants.

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