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Review Article

Interdependence of tetrapyrrole metabolism, the generation of oxidative stress and the mitigative oxidative stress response

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ABSTRACT

Tetrapyrroles are involved in light harvesting and light perception, electron-transfer reactions, and as co-factors for key enzymes and sensory proteins. Under conditions in which cells exhibit stress-induced imbalances of photosynthetic reactions, or light absorption exceeds the ability of the cell to use photo-excitation energy in synthesis reactions, redox imbalance can occur in photosynthetic cells. Such conditions can lead to the generation of reactive oxygen species (ROS) associated with alterations in tetrapyrrole homeostasis. ROS accumulation can result in cellular damage and detrimental effects on organismal fitness, or ROS molecules can serve as signals to induce a protective or damage-mitigating oxidative stress signaling response in cells. Induced oxidative stress responses include tetrapyrrole-dependent and -independent mechanisms for mitigating ROS generation and/or accumulation. Thus, tetrapyrroles can be contributors to oxidative stress, but are also essential in the oxidative stress response to protect cells by contributing to detoxification of ROS. In this review, we highlight the interconnection and interdependence of tetrapyrrole metabolism with the occurrence of oxidative stress and protective oxidative stress signaling responses in photosynthetic organisms.

Contents

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Introduction

Tetrapyrroles are linear or cyclic molecules containing four pyrrole rings that are ubiquitously utilized as cofactors in all kingdoms. These molecules are involved in central metabolic processes, including respiration, methanogenesis and photosynthesis (reviewed in [1]). The most versatile tetrapyrrole cofactor is the porphyrin heme. This cyclic tetrapyrrole contains a central iron atom and is a major player in many cellular processes. Heme-bound proteins, i.e., hemoproteins, are involved in diverse functions ranging from oxygen transport to cellular signaling, energy transduction, lipid biosynthesis, and gene regulation, among others (reviewed in [1–3]). In photosynthesis, chlorophyll and the open-chain phycobilins are the most abundant and functionally important tetrapyrroles. Chlorophyll is present in the core photosystems of oxygenic photosynthetic organisms and the extended light-harvesting complexes of plants and algae (reviewed in [4–6]). Phycobilins are found in the light-harvesting phycobilisomes attached to the core photosystems of algae and cyanobacteria and phycobilins and related linear tetraypyrrole bilins serve as the chromophores of plant and bacterial photoreceptors (reviewed in [7]).

Tetrapyrrole biosynthesis has been studied in great detail and is outlined in many excellent reviews [1,8]. A central portion of tetrapyrrole synthesis yields products for chlorophyll synthesis and for production of heme and heme-derived tetrapyrroles, all of which are critical for photosynthesis and respiration. This part of tetrapyrrole synthesis includes the formation of protoporphyrin IX, a cyclic tetrapyrrole, after which the pathway bifurcates into the magnesium-dependent chlorophyll or iron-dependent heme branches (Fig. 1). The cleavage of heme and subsequent reduction of the biliverdin product yields bilins, which can act as chromophores for light-sensing photoreceptors or light-harvesting phycobiliproteins as introduced above. In this regard, tetrapyrroles are of special interest in the photosynthetic cell.

Photooxidative stress is a core part of a photosynthetic lifestyle. It can be caused by overreduction of the photosynthetic apparatus when light absorbed exceeds the needs for carbon accumulation or the capacity for electron transfer. When light is in excess, energy transfer from photoexcited chlorophyll in photosystem II to oxygen results in singlet oxygen ($^1O_2$) formation [9–11]. Other reactive oxygen species (ROS) form through distinct mechanisms, e.g., electron transfer from electron acceptors of photosystem I to oxygen instead of ferredoxin primarily leads to superoxide anion radical ($O_2^{\bullet -}$) production [12]. The relatively stable ROS hydrogen peroxide (H_2O_2) can be produced due to reduction of superoxide, and can be detoxified by catalases or peroxidases (reviewed in [13,14])(note: see Table 1 for description of these and other molecules involved in oxidative stress). However, H_2O_2 formation can also be catalyzed by metals such as iron to generate hydroxyl radical ($HO^{\bullet}$) in Fenton chemistry [15].

Besides chlorophyll, other tetrapyrroles can act as photosensitizers due to their ability to absorb light of different wavelengths. These molecules, thus, also pose a threat to the cell when they accumulate in their free form due to changes in their synthesis and utilization [16,17]. Central to cellular survival and productivity, therefore, is a need to mitigate any potential damage associated with the accumulation of free tetrapyrroles. Notably, an accumulation of tetrapyrroles in the cell, e.g., by a change in flow through biosynthetic pathways, leads to increased production and/or activity of ROS-detoxifying enzymes, including superoxide dismutase (SOD) and catalase enzymes [18]. Additionally, detoxification of redox-active heme can be achieved by heme-binding proteins through export, sequestration and/or degradation of heme (reviewed in [19]). On the contrary, some tetrapyrroles have been reported to have antioxidant properties and thus rather than causing damage to cells can support ROS scavenging [20]. These observations highlight the complex relationship between tetrapyrrole metabolism and oxidative stress. In this review, we primarily focus on the interdependence of tetrapyrroles and oxidative stress in photosynthetic organisms.

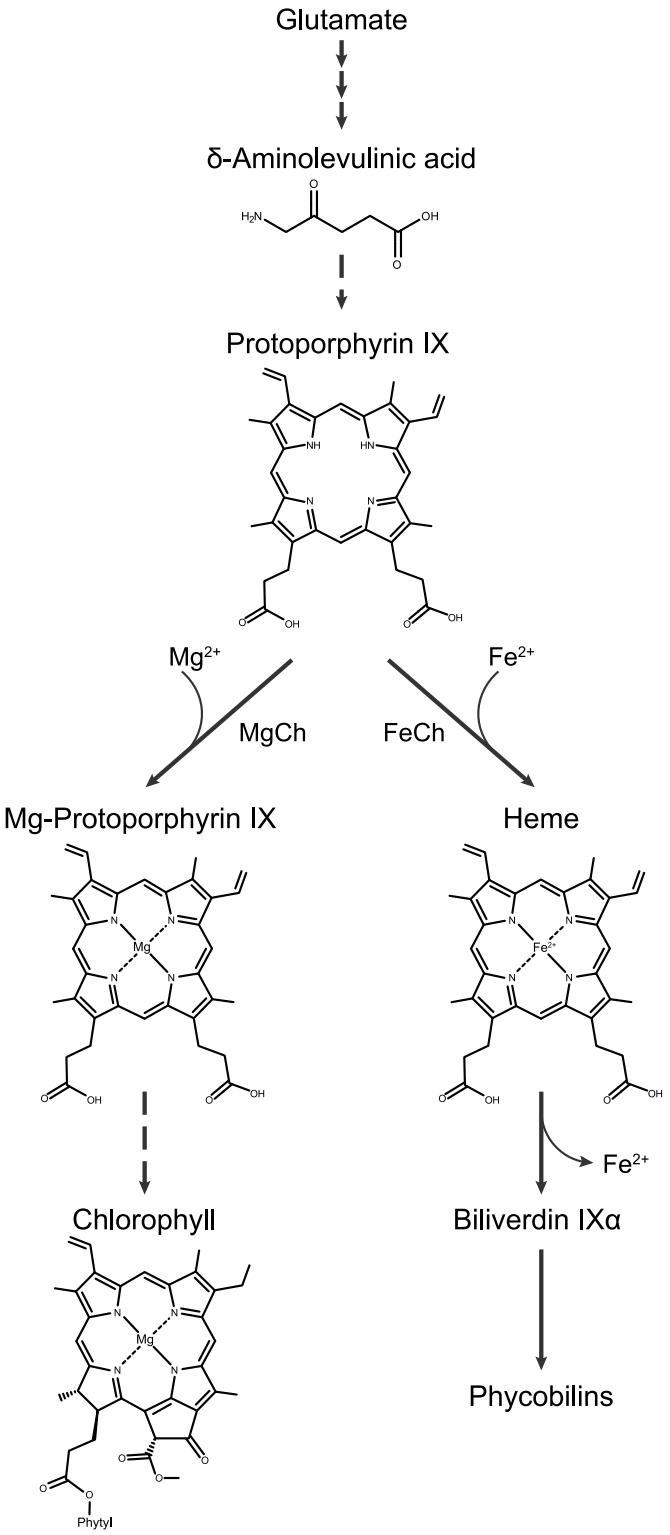

Fig. 1. Tetrapyrrole biosynthesis. Eight molecules of δ-aminolaevulinic acid (ð-ALA) form the tetrapyrrole ring. The cyclic tetrapyrrole protoporphyrin IX, a porphyrin, feeds into the magnesium-dependent (Mg^{2+}) chlorophyll or iron-dependent (Fe^{2+}) heme pathway. The chlorophylls are essential components in the photosystems, whereas the phycobilins serve in light-harvesting in the phycobilisome antennae [1].

Table 1
Enzymes, molecules and protein complexes involved in oxidative stress and/or oxidative stress responses in photosynthetic organisms.

Molecule	Class	Primary function	Molecule/cofactor/ligand	Role in oxidative stress	Reference(s)
Catalase	Enzyme	Decomposition of hydrogen peroxide	Heme	ROS detoxification	For review see [177]
Peroxidase	Enzyme	Decomposition of hydrogen peroxide	Heme	ROS detoxification	For review see [177]
Superoxide dismutase	Enzyme	Dismutation of superoxide radical into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2)	Iron	ROS detoxification	For review see [177]
Rubrerythrin	Enzyme	Hydrogen peroxide reduction	Iron	Oxidative stress defense	[111]
N/A[a]	Light-absorbing, photosensory	Cofactors, chromophores, etc.	Tetrapyrroles, porphyrins (e.g., heme, chlorophyll, protochlorophyll(ide))	Photosensitizers, antioxidants, oxidative stress signaling	[16,17]
N/A	Light-absorbing, photosensory	Light harvesting, photoprotection	Carotenoids	Energy dissipation, antioxidants	For review see [33]
Phytochromes (e.g. phyA, phyB) and phytochrome-like photoreceptors (e.g., BphP, RcaE)	Light-absorbing, photosensory	Light perception	Phycobilins	Regulation of oxidative stress response (including phytochrome-interacting factor [PIF]-dependent responses, regulation of tetrapyrrole and carotenoid biosynthesis, regulation of antioxidant accumulation)	[32,56,57,72,73,76–79]
Hemoproteins	Regulator, sensor	Diverse functions	Heme	Redox regulation/sensing, onset of oxidative stress response, heme export, heme sequestration	For review see [1–3]
Iron uptake regulator (Fur)	Regulator	Iron homeostasis	Heme/iron	Regulation of iron dependent ROS-detoxifying/responsive genes/enzymes	[122–124]
Iron responsive regulators (Irr)	Regulator	Iron homeostasis	Iron	Regulation of tetrapyrrole biosynthesis	[130]
DNA-binding protein (starvation or stationary-phase induced), Dps	Regulator	Hydrogen peroxide decomposition, DNA protection	Iron, heme	Regulation of oxidative stress defense	[112–115]
Ferritin	Iron/iron storage protein	Iron storage	Iron	Iron homeostasis, iron release	[104,120]
N/A	Metal, micronutrient	N/A	Iron (limitation or excess)	Oxidative stress induction	[32,33,107,108,178]
Phycobilisomes	Light-harvesting protein complex	Light harvesting	Phycobilins	Overexcitation can result in overreduction of photosystems and ROS formation	[23–25]
Photosystems	Light-harvesting protein complex	Light harvesting	Chlorophyll	Overexcitation can result in ROS formation	[9–12]
IsiA	Light-harvesting protein	light harvesting	Chlorophyll, carotenoid	Energy dissipation under iron-induced oxidative stress	[118]
Tryptophane-rich sensory protein (TSPO)	Protein of emerging function	Stress-related membrane protein	Tetrapyrroles, benzodiazepines, cholesterol	Tetrapyrrole homeostasis, fine-regulation of oxidative stress response	[90,159–164]

[a] N/A, not applicable to molecule being described.

Light- and phytochrome-based responses to oxidative stress

Light-induced oxidative stress primarily originates from the absorption of light energy by tetrapyrroles or tetrapyrrole-mediated electron transfer reactions. Energy transfer can occur from photosensitized chlorophyll to oxygen, resulting in the formation of highly reactive singlet oxygen [9,21]. In the Mehler reaction, oxygen is the electron acceptor instead of ferredoxin which results in the generation of superoxide anion radical [12]. In phycobilisome-containing cyanobacteria and algae, light-absorbing phycobilins (open-chain tetrapyrroles derived from heme) are highly abundant. Phycobilin-containing phycobilisomes can comprise up to 50% of the total soluble protein in the cell [22]. These molecules enable photosynthesis even under dim light. However, phycobilisomes can contribute to making cells more vulnerable to photoinhibition under higher light intensities where more light may be available than can be used effectively in the production of reduced carbon [23–25]. Additionally, photosensitized phycobiliproteins have been shown to promote the formation of reactive oxygen species [26,27]. Other factors contributing to photooxidative stress include the formation of singlet oxygen as a by-product of lipoxygenase activity, damage of catalase, UV-induced tissue damage, or electron transfer to oxygen from iron–sulfur clusters or ferredoxin (reviewed in [28]).

Light is a major factor in creating oxidative stress in photosynthetic organisms, although light-independent ROS formation has also been addressed [29,30]. Excessive light can result in oxidative stress by overreduction of the electron transport chain. Nutrient deprivation also can contribute to this affect primarily by impacting the ratios of photosynthetic proteins and/or electron transport capacity, as well as impacting levels and functions of micronutrient-dependent, oxidative stress-mitigating enzymes, as discussed in detail below [31,32]. Thus, either excessive light or nutrient deprivation can lead to ROS production [13,32,33]. Photosynthetic organisms employ different long- and short-term strategies to cope with light-induced oxidative stress (reviewed in [13,34]). Long-term signaling is achieved through light activation of photoreceptors resulting in a specific regulatory output, including photoreceptor-dependent induction of photoprotective mechanisms such as antioxidant, ROS detoxification and energy dissipation mechanisms (e.g., [32,35–39]). For example, phytochromes of plants and bacterial phytochrome-like photoreceptors (jointly referred to as phytochromes hereafter), a class of dimeric sensor kinases with a covalently attached open-chain tetrapyrrole chromophore, can sense light-intensity as well as light-quality changes resulting in a modulation of gene transcription, including readjustment of the photosynthetic apparatus to regulate and/or tune light absorption to match the external photoenvironment (reviewed in [7,40]). Induction of genes involved in photoprotection is also induced by temperature and nutrient starvation [32,41]. Short-term responses to light-induced oxidative stress include energy dissipation mechanisms, activation of antioxidant enzymes already present in the cell, and ROS-dependent signaling. In the latter case, ROS can act directly as a signal to activate ROS-mitigating mechanisms (reviewed in [42]).

ROS as developmental signals

The co-occurrence of excess light and aberrations in tetrapyrrole metabolism are one cause of ROS generation. ROS generation can also feedback to impact cellular tetrapyrrole homeostasis. For example, exposure of *Cucumis sativus* plants to high light resulted in an inhibition of ð-aminolevulinic acid (ALA) biosynthesis in plants that was attributed to ROS formation [43], which supports a negative effect of oxidative stress on tetrapyrrole biosynthesis. ROS formation is not only potentially harmful to cells, ROS can also provide an important developmental signal that is integrated with other signaling networks (reviewed in detail in [44,45]). Different types of ROS, e.g., singlet oxygen, superoxide, or hydrogen peroxide, can serve as signaling molecules and activate distinct signaling pathways, though crosstalk between these pathways also may occur [46]. Thus, ROS are involved in a diverse network of developmental signals and in signaling pathways in which they also can help limit oxidative damage [47–50].

A specific connection between singlet oxygen signaling and tetrapyrrole biosynthesis has been implicated. For example, protochlorophyllide accumulates in the dark in the plant *flu* mutant; upon illumination of the *flu* mutant, protochlorphyllide acts as a photosensitizer and results in elevated levels of singlet oxygen [17]. As singlet oxygen is highly reactive, its accumulation causes damage to cells. However, singlet oxygen also acts as a signaling molecule capable of triggering a stress response that results in growth inhibition and cell death. This is evident by the upregulation of stress response genes in the *flu* mutant after a dark/light shift [51]. The chloroplast-localized EXECUTER proteins are essential for initiating this singlet oxygen-triggered response [52,53]. Upregulation of stress-related genes in the *Arabidopsis* stn7, *tap38/pph1* and *npq4* mutants, including genes involved in the jasmonate hormone signaling pathway in plants, is likely mediated by elevated levels of singlet oxygen [47]. Similarly, the *Arabidopsis thaliana* npq1/lut2 double mutant that is deficient in two photoprotective xanthophylls accumulated higher levels of singlet oxygen compared to wild type under high light [54]. Transcript analysis of this mutant demonstrated a higher abundance of genes involved in protection against ROS suggesting a signaling function for singlet oxygen in nuclear gene expression and acclimation to stress [54]. Notably, tetrapyrrole synthesis was affected in both the *flu* mutant and the xanthophyll-deficient *npq1/lut2* mutant, providing specific evidence for a fine-tuning of tetrapyrrole biosynthesis through ROS [54,55].

Phytochrome-regulated oxidative stress response

Light affects ROS production and ROS-dependent signaling. The phytochrome photoreceptors phyA and phyB are specifically involved in regulation of ROS signaling by directly affecting the stability of phytochrome interacting factors (PIFs) [56,57]. Mutants of PIF1 and PIF3 are greening-deficient and accumulate protochlorophyllide and singlet oxygen after dark-grown seedlings were exposed to light, implicating PIFs in the prevention of singlet oxygen production during seedling etiolation. Genes with roles in ROS signaling, ROS responses and oxidative stress-induced genes were upregulated in *pif* mutants after light exposure [56]. Both PIF proteins were able to bind to the promoter sequences of the misregulated genes. PIF1 and PIF3, therefore, likely act directly as negative regulators of ROS-responsive genes [56,57]. PIFs accumulate in the dark whereas light-dependent PIF degradation is triggered by direct interaction of the proteins with phytochrome [57,58]. Notably, the same ROS-responsive genes impacted in the *pif* mutants were downregulated in phytochrome mutants, in which PIF1 and PIF3 proteins are stabilized [56]. Thus, ROS-responsive genes are downregulated in the dark through PIF1 and PIF3. With the onset of light, phytochrome absorbs red light, is activated, and mediates degradation of the PIFs, which in turn results in the derepression of ROS-responsive genes and contributes directly to the onset of oxidative stress-preventing mechanisms [56,58].

The tetrapyrrole biosynthesis pathway is regulated through tetrapyrroles primarily covalently attached to their cognate phytochrome sensors, although chromophore attachment has been infrequently reported as non-covalent. Any disturbances in the tetrapyrrole biosynthetic pathway can cause intermediates to

accumulate and, if unregulated or if the products are exposed to light, can result in an increase in cellular oxidative stress [59]. Therefore, control of tetrapyrrole biosynthesis prevents oxidative stress. Phytochrome-regulated PIF1 negatively regulates tetrapyrrole biosynthesis genes for protochlorophyllide oxidoreductase, ferrochelatase and heme oxygenase in the dark [60]. This finding suggests a role of phytochrome in preventing tetrapyrrole-induced oxidative stress by also contributing to PIF-dependent regulation of tetrapyrrole biosynthesis.

Changes in light quality and/or quantity regulate phytochrome-dependent induction of an oxidative stress response, while high light-induced ROS formation can also trigger a similar response through ROS as signaling molecules. Besides ROS- and phytochrome-mediated signaling, changes in the redox state, caused by light-induced changes in photosynthetic activity, affects tetrapyrrole synthesis [61–64].

Photoreceptor-regulation of energy-dissipation mechanisms

Carotenoids are accessory photosynthetic pigments that have essential functions in oxidative stress prevention through their role in energy dissipation and as non-enzymatic antioxidants (reviewed in [13]). In plants, carotenogenesis is regulated at the level of transcription by photoreceptors such as phototropin, cryptochrome and phytochrome, which impact expression of carotenoid biosynthetic or homeostasis genes [65,66]. Similar to the mechanism of the phytochrome-dependent transcriptional activation of ROS-responsive genes described above, transcription factor PIF1 binds to the promoter of the carotenoid biosynthesis gene *phytoene synthase* (*PSY*) and represses its expression in the dark [67,68]. This repression is reversed by degradation of PIF1, which is mediated by phytochrome-PIF interactions in the light [57]. Induction of *PSY* transcription through phyA, on the other hand, is achieved by light-dependent promotion of the interaction of transcription factor HY5 with light responsive elements in the *PSY* promoter region [69]. An involvement of phytochrome in upregulation of *PSY2* during seedling photoinduction also has been observed in maize [70]. However, a phytochrome-dependent increase in PSY activity under red light did not occur at a transcriptional level in tomato, but rather post-transcriptionally [71].

Photoreceptor regulation of carotenoid levels or regulation of light-associated stress is not limited to plants. In non-photosynthetic bacteria, the phytochrome-like photoreceptor BphP mediates induction of carotenoid biosynthesis [72,73]. BphP covalently binds the open chain tetrapyrrole biliverdin, and possibly phycocyanobilin [74]. The signaling cascade initiated by BphP induces accumulation of the carotenoid deinoxanthin in *Deinococcus radiodurans* to protect the organism from high irradiances of visible light [73]. Additionally, *bphP1* mutant in *Azospirillum brasilense* SP7 showed increased sensitivity to photooxidative stress [75]. Proteome analysis of the *bphP1* mutant implied that the photoreceptor triggers a cellular response that leads to the regeneration of proteins damaged by photodynamic stress [75].

Besides regulating carotenoid synthesis in some systems, phytochrome is also known to regulate synthesis and function of other non-enzymatic antioxidants. For example, phytochrome positively regulates key enzymes of the glutathione–ascorbate cycle that are involved in the detoxification of hydrogen peroxide, including glutathione reductase [76], glutathione-S-transferase [77] and ascorbate peroxidase [78]. Phytochrome-controlled genes encoding oxidative stress defense enzymes include a catalase-encoding gene (*CAT3*) of *Arabidopsis* that requires phytochrome and a blue light receptor for accumulation of the protein in the dark [79]. SOD accumulates in the light in plants. Although it is not clear if this effect is photoreceptor mediated in plants [80], photoreceptor control of SOD accumulation was established in a cyanobacterium [32].

Tetrapyrroles and tetrapyrrole-containing proteins can mediate the cellular detoxification of reactive oxygen species

Tetrapyrroles, including heme which is an excellent electron transfer molecule due to its central iron atom, are part of the electron transport chain or in the case of chlorophyll and phycobilins, funnel energy into the photosynthetic electron transport chain. Electron leakage can be associated with overreduction of the photosynthetic apparatus (phycobilisomes or photosystems; Table 1) or light absorption that exceeds the transfer capacity of the photosynthetic electron transport chain (described above) and also occurs during respiration. Thus, the major electron transport chains, i.e., the respiratory chain and the photosynthetic electron transport chain, are major generators of ROS, and thus are correlated with oxidative stress.

In addition to being associated with increased photooxidative stress, the cyclic tetrapyrrole heme has an essential role as a cofactor in sensor proteins [3,81]. Due to its central iron atom, protein-bound heme can act as a sensor of gases like carbon monoxide and oxygen, as well as the cellular redox state by means of a change in the reduction state of the central iron or by sensing of redox active molecules (reviewed in [2]). While the covalent attachment of heme to a protein implies redox or gas sensing, non-covalent binding of heme to a protein can be controlled by a thiol/disulfide redox switch, which can signal redox state either directly or indirectly (e.g., [82–85]).

Although some heme-bound proteins contribute to increased oxidative stress, heme can also have a role in mitigating ROS-related damage. Heme exhibits intrinsic peroxidase activity, which makes it an important cofactor in ROS-detoxifying enzymes, including catalases, superoxide dismutases and others (Table 1). In macrophages, heme suppresses oxidative stress [86]. Heme-containing cytochrome oxidases have the potential to serve as a sink for excess electrons from photosystem I (PSI) and minimize oxidative damage through oxygen consumption [87,88]. An involvement of cytochrome oxidase CtaDII, which complexes two heme molecules, in the oxidative stress response was implicated through observation of an upregulation of SOD in a *Synechococcus* sp. PCC 7002 mutant lacking CtaDII, which resulted in increased high-light resistance [89]. In plants, the universal stress response molecule and hormone abscisic acid (ABA) causes a transient elevation of heme levels, which was suggested to protect cells from damaging ROS by providing the heme cofactor for ROS-scavenging enzymes and ABA regulators [90]. In support of this protective role associated with heme, paraquat (methylviolgen)-induced oxidative stress was reduced in heme-treated plants [91].

Interconnection of oxidative stress, tetrapyrrole metabolism and nutrient availability

Photosynthetic protein levels are generally reduced when nutrients are deficient resulting in cells with a higher potential for overreduction of electron carriers, as well as reduced capacity for mitigation of photooxidative damage under nutrient-deficient conditions [31,32]. Accordingly, oxidative stress occurs as a result of nutrient deprivation across a range of organisms [32,92–95]. In response, energy dissipation mechanisms are induced and photosynthetic pigments are degraded to avoid excessive light absorption (reviewed in [96]). Upon nitrogen and sulfur starvation, degradation of light-harvesting antennae can also provide the cells with amino acids and carbon scaffolds [31,97–100]. One essential nutrient with a role in tetrapyrrole metabolism and which serves as a cofactor in electron transport chains is iron (reviewed in [101,102]). This makes iron of special significance in oxidative stress responses in photosynthetic organisms in which iron is a

key cofactor of the functional photosynthetic apparatus, generally resulting in a much higher iron requirement that for non-photosynthetic bacteria [103,104].

Iron-induced oxidative stress

Iron released from cellular enzymes can enhance oxidative stress. If the membrane-impenetrable, charged molecule superoxide anion is produced, it causes rapid oxidation of iron sulfur clusters, thereby releasing ferrous iron (reviewed in [105]). Ferrous iron then can act as a catalyst to generate hydroxyl radicals in the presence of hydrogen peroxide in the Fenton reaction [15]. During redox cycling, a release of stored iron from ferritin may also lead to ROS formation (reviewed by [106]). Therefore, iron is not only essential for detoxification of ROS, but in its free form or in iron-containing components can also lead to ROS formation (Table 1).

Iron in the oxidative stress response

Oxidative stress may be caused by iron starvation [32,33,107,108]. One explanation for this effect is the need for iron as a cofactor in ROS-detoxifying enzymes such as SOD and catalases. In cyanobacteria, iron-containing SOD is down-regulated under iron deficiency [32,109]. Iron-requiring heme is the prosthetic group of oxygen-binding catalases that catalyze the decomposition of hydrogen peroxide to water and oxygen (reviewed in [110]). Other iron-containing enzymes that are involved in oxidative stress defense mechanisms are rubrerythrin [111] and DNA-binding proteins from starved cells (Dps) [112–115], which prevent hydrogen peroxide-induced oxidative stress. The chlorophyll-binding protein CP43′ (IsiA), which is induced under iron starvation, is involved in energy dissipation [116–119]. IsiA is also induced under oxidative stress and it has been shown that its up-regulation is due to iron deficiency-induced oxidative stress [33]. Although implicated in enhancing oxidative stress through iron release under oxidative stress [106], ferritin also has an important role in the oxidative stress response in its function in coordinated storage and release of iron in iron homeostasis [104,120].

Besides the essential function of iron in heme biosynthesis, non-heme iron sensors exist that act as transcriptional regulators (reviewed in [121]). For example, the ferric iron uptake regulator (Fur), which also responds to interaction with heme through a decrease in DNA-binding activity, can bind ferrous iron ions and act as a repressor or activator of transcription in its iron-bound or apo-form, respectively [122–124]. In cyanobacteria, Fur protects cells from oxidative stress [124,125]. Fur from the filamentous cyanobacterium *Anabaena* was shown to negatively regulate expression of the gene for DNA-binding hemoprotein DpsA, which is involved in the oxidative stress response [126]. Overexpression of *fur* in *Anabaena* led to a decrease in SOD and catalase activity, whereas no increase in ROS levels was observed [123]. Fur is up-regulated in this organism in response to iron deprivation [122]. Fur overaccumulation in *Synechocystis* sp. PCC 6803 has been shown to impair IsiA accumulation [127]. Therefore, Fur appears to connect iron regulation with oxidative stress. Together, these examples show that mechanisms are in place that enable the cell to detoxify ROS formed in response to a high iron status of the cell.

The examples described show that incorporation and release of iron during tetrapyrrole biosynthesis (Fig. 1), and its role in oxidative stress responses, require tight co-regulation of iron homeostasis with tetrapyrrole homeostasis and oxidative stress responses. Failure to balance iron homeostasis with cellular tetrapyrrole status can have severe detrimental impacts on cellular fitness [122,128]. A large network of regulatory processes coordinating iron and tetrapyrrole homeostasis exists linking iron homeostasis to light regulation and photosynthetic pigment synthesis [32,63,122,128].

Iron-tetrapyrrole interconnection

Iron availability is integral to heme biosynthesis (Fig. 1). Porphobilinogen synthase is regulated by iron availability on a transcriptional level in bacteria [129]. This effect is mediated through the iron responsive transcriptional regulator iron response regulator (Irr), which is active only under iron-limitation, conditions under which it represses protoporphyrin synthesis [130]. Degradation of the Irr protein in the presence of iron is heme- [131] and ferrocheletase-dependent [132], resulting in a derepression of heme biosynthesis in replete conditions. The regulatory mechanism involving Irr also positively affects iron uptake [130]. Therefore, iron availability and transport is tightly co-regulated with heme biosynthesis. Relatedly, iron deficiency causes down-regulation of tetrapyrrole biosynthesis genes [109,122,128]. Together, these observations highlight the coordination between iron homeostasis and regulation of tetrapyrrole biosynthesis that occurs in cells.

A co-regulation of tetrapyrrole biosynthesis and iron acquisition was also observed in yeast where inhibition of ALA synthase results in down-regulation of iron-uptake genes [133]. When no iron is available, repression of heme biosynthesis prevents the accumulation of photosensitizing porphyrins that could lead to ROS formation. Another protective mechanism is based on the export of porphyrins out of the cell when disturbances in tetrapyrrole biosynthesis cause accumulation of intermediates [134], or through specialized heme scavengers like hemozoin in *Plasmodium* [135,136], or via the putative multistress regulator and potential heme scavenger TSPO in plants [90] binding tetrapyrroles such as heme.

Function of tetrapyrroles as signaling molecules and the oxidative stress response

Tetrapyrrole molecules indirectly regulate cellular processes like tetrapyrrole biosynthesis, redox control and many others through binding to proteins and subsequently changing the activities or binding affinities of these target proteins (see above). In plants, tetrapyrrole intermediates have been proposed to act as signals in retrograde signaling including oxidative stress signaling [137–142]. Mg-protoporphyrin IX accumulates in the cytosol during oxidative stress [143]. It was thought to act as a plastid-to-nucleus signaling molecule that serves as a primary mechanism by which plastid functional status is communicated to the nucleus, a theory that was later challenged [144,145]. Kindgren et al. [142] observed a high representation of proteins related to oxidative stress among proteins identified in interaction studies with Mg-protoporphyrin IX, supporting a signaling role for Mg-protoporphyrin IX in oxidative stress response. However, a more recent study provided evidence for tetrapyrrole-induced ROS accumulation leading to ROS-mediated retrograde signaling rather than tetrapyrroles acting directly as signaling molecules in the induction of photosynthesis-associated nuclear gene expression [146]. The identification of proteins that can scavenge and degrade tetrapyrroles [90,147–149] is consistent with the hypothesis that the tetrapyrrole state of the cell is sensed, which results in regulation of tetrapyrrole homeostasis to prevent overaccumulation of photosensitizing tetrapyrrole metabolites.

Recently it has been observed that *Synechocystis* cells lacking ChlR, which is a positive regulator of oxygen-independent tetrapyrrole biosynthesis enzymes, are unable to induce the greening process in the light under low-oxygen conditions [150]. When the

greening process is induced in the mutant under oxygen-sufficient conditions which allow oxygen-dependent tetrapyrrole biosynthesis needed for chlorophyll biosynthesis, the chlorophyll content increased concurrently with the other photosystem components [151]. These findings indicate that the levels of tetrapyrroles influence accumulation of the respective tetrapyrrole-requiring protein components to ensure that the complex components are only synthesized if a fully functional complex can be assembled. This observation is in accordance with the above-mentioned downregulation of tetrapyrrole synthesis due to a lack of iron in *Synechocystis* [109]. However, it is still possible that co-regulation of protein components can be achieved through mechanisms other than sensing of the tetrapyrrole status of the cell. Also, it was observed that expression of *psbA1*, which encodes the low-oxygen induced D1′ protein, is activated by ChlR [150]. The lack of *psbA1* on the other hand did not affect D1 levels, whereas D1 levels were decreased under low-oxygen conditions in mutants lacking either ChlR or the low-oxygen induced tetrapyrrole biosynthesis genes, indicating that the decrease of D1 under these latter conditions is caused by chlorophyll deficiency [150,151]. Other reports in planta implicated tetrapyrrole chromophore biosynthesis as positively correlated with holophytochrome synthesis [152]. It is likely that the cell has evolved mechanisms to 'measure' the state of each component of a functional complex to avoid 'energy sinkholes'. In this regard, phytochromes have been implicated in coordinating the synthesis of nuclear- and plastid-encoded components of photosynthesis complexes to ensure correct stoichiometry [152,153]. Similar tetrapyrrole-dependent coregulatory processes might exist for the tetrapyrrole-dependent oxidative stress response.

Recently Duanmu and coworkers found that biliverdin or phycocyanobilin impacts chlorophyll signaling in *Chlamydomonas* [154]. This is supported by data showing that the *hmox* mutant, which lacks open-chain tetrapyrroles biliverdin or phycocyanobilin, has reduced chlorophyll levels in light-grown cells. As the mutant is still capable of synthesizing heme, studies using an exogenous reductase to prevent heme buildup were used to show that the phenotype is associated with the absence of biliverdin or phycocyanobilin and not heme buildup leading to feedback inhibition [154]. Thus, there appears to be a signaling role of biliverdin or phycocyanobilin in the induction of greening in this system. This is also supported by the fact that biliverdin feeding rescues the *hmox* mutant phenotype. Notably, global transcriptomic analysis showed that genes that are induced by light and suppressed by biliverdin were enriched for genes encoding high light stress-related proteins. It was therefore suggested that a light-independent, biliverdin-driven signaling mechanism exists that targets a network that prevents or reduces oxidative stress. These findings could explain the presence of a phycocyanobilin synthase in this organism despite the lack of phycobilisomes and phytochromes, which are known to covalently attach phycocyanobilin as chromophore [154]. Among cyanobacteria, marine *Prochlorococci* lack phycobilisomes as well, but the phycobiliprotein phycoerythrin has been identified [155–157]. The chromophore of phycoerythrin is unlikely to function as a photoreceptor chromophore due to the lack of a 15,16-double bond needed for photoisomerization and as the light-harvesting capacity is low [158]. Thus, a function of the tetrapyrrole chromophore as signaling molecule is plausible.

We hypothesize that tetrapyrroles might act as a signal for oxidative stress and the tetrapyrrole status in cyanobacterial cells, analogous to what prior studies in plants and green algae imply. Potential sensors for tetrapyrroles in this context have not been described. We propose factors such as the outer membrane putative tryptophan-rich sensory protein TspO as possible sensors in cyanobacteria.

Tetrapyrroles, oxidative stress response and TspO

Homologs of TspO are found in a variety of organisms where the protein binds tetrapyrroles and has been implicated in the oxidative stress response (e.g., [90,159–164]). We also found a correlation between iron availability and *tspO* abundance at the transcriptional level in the cyanobacterium *Fremyella diplosiphon* [32]. Such a correlation is not surprising considering the crucial role of iron in tetrapyrrole metabolism (Fig. 1).

Tetrapyrrole binding to TspO has been shown in mammals, bacteria and plants [90,165–171]. We could also confirm this for a cyanobacterial homolog (Busch and Montgomery, unpublished data). If the binding of tetrapyrroles to TspO acts as a signal for the intracellular tetrapyrrole state, TspO could be involved in a signaling network which integrates iron availability, tetrapyrrole homeostasis under different light conditions and oxidative stress associated with iron and tetrapyrroles.

TspO influences tetrapyrrole and carotenoid levels in several organisms. For example, TspO in *Rhodobacter* functions as a negative regulator of bacteriochlorophyll and carotenoid biosynthesis [172]. In this organism, the tetrapyrrole pathway is targeted by TspO through a negative effect on coproporphyrinogen III oxidase activity [173]. In *Arabidopsis* on the other hand, TspO was itself regulated by tetrapyrrole metabolism [90]. Inducing cells to produce tetrapyrroles resulted in increased degradation of TspO protein [90].

TspO also has been implicated directly in the oxidative stress response. In the moss *Physcomitrella patens*, a mutant lacking TspO suffered from increased oxidative stress compared to wild type [159,164]. Often such a response is attributed to the ability of TspO to bind tetrapyrroles that can otherwise be harmful if free in the cell. However, ROS levels also were increased in *Arabidopsis* cells overexpressing *TSPO* [90]. Perhaps related to this observation, binding of photosensitizing porphyrins, including protoporphyrin IX, to mammalian TspO are correlated with photooxidative events connected to the mitochondrial permeability transition pore [174,175]. However, a role for TspO in regulation of the mitochondrial permeability transition pore in mice has been recently challenged [176]. Thus, the exact function of TspO in the oxidative stress response is far from clear. We propose that TspO plays a role in integrating tetrapyrrole homeostasis and stress signals and that the protein may serve to link these networks to achieve the necessary co-regulation for sustained cellular fitness.

Conclusions

Light is the main cause of oxidative stress in the photosynthetic cell, while other causes include imbalanced tetrapyrrole status and nutrient deprivation or excess, among others (Table 1). With light as the primary cause of oxidative stress, it is also the driver for the cellular response(s) to oxidative stress through ROS-dependent signaling and photoreceptor-mediated signaling (Fig. 2). Similarly, tetrapyrrole-light interactions are the primary cause of photooxidative stress but are also involved in oxidative stress-induced cellular responses to resist or mitigate oxidative stress. Widely accepted as important cofactors in light-sensing, light-harvesting and in various enzymatic reactions, the role of tetrapyrroles as direct signaling molecules is not as well established. We hypothesize a role of tetrapyrroles as signaling molecules in an integrated network that senses the tetrapyrrole status of the cell and results in a regulation of the oxidative stress-induced response and tetrapyrrole transport and metabolism. Through sensing of the iron-chelating tetrapyrrole heme, nutrient-adaptation processes could be initiated that would be integrated with the oxidative stress response known to be affected by nutrient availability.

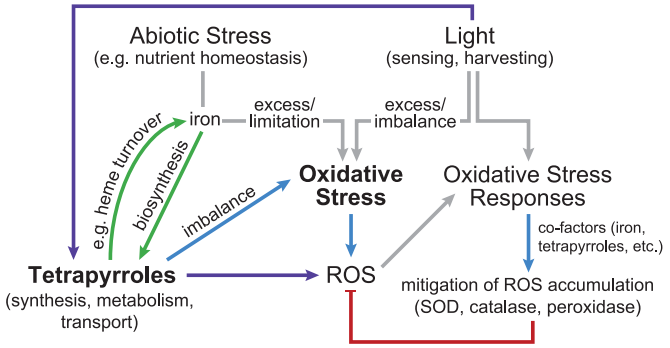

Fig. 2. Interconnection of tetrapyrroles, iron and oxidative stress. Oxidative stress can be caused by light-tetrapyrrole interactions and abiotic stresses, including nutrient deprivation. Iron depletion can serve as a cause of oxidative stress; however when present in excess in its free form, iron also can cause oxidative stress through the Fenton reaction. Iron is needed in tetrapyrrole biosynthesis and released during heme cleavage or turnover (green lines and see Fig. 1). Photoexcitation of free tetrapyrroles can result in the generation of reactive oxygen species (ROS; purple lines). The oxidative stress response is triggered through light via tetrapyrrole-binding phytochrome signaling transduction and ROS-dependent signaling. Tetrapyrroles, including heme, are involved in the oxidative stress response, or mitigation of ROS accumulation as cofactors in the antioxidant systems (red line).

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