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Review

Calcium-dependent regulation of photosynthesis☆

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ABSTRACT

The understanding of calcium as a second messenger in plants has been growing intensively over the last decades. Recently, attention has been drawn to the organelles, especially the chloroplast but focused on the stromal Ca^{2+} transients in response to environmental stresses. Herein we will expand this view and discuss the role of Ca^{2+} in photosynthesis. Moreover we address of how Ca^{2+} is delivered to chloroplast stroma and thylakoids. Thereby, new light is shed on the regulation of photosynthetic electron flow and light-dependent metabolism by the interplay of Ca^{2+}, thylakoid acidification and redox status. This article is part of a Special Issue entitled: Chloroplast biogenesis.

1. Introduction

Calcium is an essential plant nutrient. It is required for structural roles in the cell wall and membranes, as counter-cation for inorganic and organic anions in the vacuole and plays an essential role as intracellular messenger in the cytosol [1]. The concentration of cytoplasmic calcium $[Ca^{2+}]_{cyt}$ in plant cells increases in response to various developmental conditions and environmental factors. It is considered that alterations in $[Ca^{2+}]_{cyt}$ are crucial for the physiological response of the plant. More than 30 distinct developmental processes or environmental challenges initiate perturbation in the $[Ca^{2+}]_{cyt}$ (for review see [2]). Such perturbation signals include plant hormones, light, stress factors, and pathogenic or symbiotic elicitors [3–10]. In the green alga *Chlamydomonas reinhardtii*, fast phototactic movements require both light-induced H^+ and Ca^{2+} signaling events that are associated with the eyespot region of *Chlamydomonas* and mediate the regulation of flagellar bending and appropriate swimming direction [11,12], thereby providing photoprotection by avoiding excess exposure to light.

The calcium signaling network consists of distinct modules responsible for i) the generation of the Ca^{2+} signature, i.e. an elevation of the $[Ca^{2+}]$ which is stimulus-specific in regard to its amplitude, frequency, and shape, in response to a signal, ii) recognition of the signature by Ca^{2+} sensors and iii) transduction of the Ca^{2+} signature message to targets that mediate signal-specific responses [9,13–15]. Molecular and bioinformatic analyses of *Arabidopsis* genes and genome revealed the presence of about 80 polypeptides at the level of Ca^{2+} signature, about 400 sensors and about 200 target proteins, indicating an intricate Ca^{2+} signaling network [14]. Herein a central question is: how do plants decode and distinctively transmit perturbations in cytosolic Ca^{2+} signatures to downstream targets? Two principle types of Ca^{2+}-decoding signaling components are known in plants. Type I components are "sensor-responder" proteins that possess both Ca^{2+}-binding and enzymatic "effector" domains. Important examples are the Calcium-Dependent Protein Kinases (CDPKs) [16–18] and the Calcium–Calmodulin-Dependent Kinases (CCaMKs) [19]. Type II components are "sensor-relay" proteins, such as calmodulin (CaM), which have a Ca^{2+}-binding domain but do not exhibit an enzymatic activity [20]. When Ca^{2+} is bound, these proteins are turned on to interact with respective target proteins and to alter their biological activity. Another example for type II components are Calcineurin B-like calcium sensor proteins (CBLs) from *Arabidopsis* [21], which specifically interact with a family of protein kinases designated as CBL-Interacting Protein Kinases (CIPKs) [22]. A prime example for such a type of regulation is the phosphorylation of the K^+ channel AKT1 via CIPK23 and up-regulation of its activity under limiting K^+-supply conditions [23,24].

Dark-induced increases of chloroplast stromal Ca^{2+} levels precede the generation of cytosolic Ca^{2+} transients in tobacco leaf cells [25], suggesting that the chloroplast represents an element of the cellular Ca^{2+} network and contributes to the cytosolic Ca^{2+} signaling [26–31]. Commonly, it has been described that Ca^{2+} uptake into the chloroplast occurs in the light while Ca^{2+} is released into the cytosol in the dark (as reviewed in [30]). Furthermore, there is emerging evidence that chloroplasts may contribute to cytosolic Ca^{2+} signaling via the chloroplast localized calcium sensor protein (CAS) [32–34]. While the exact mechanisms have not been resolved, cytosolic Ca^{2+} signals induced by

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external Ca^{2+} could not be generated in CAS knockout mutants [32,35]. Changes in chloroplast Ca^{2+} might influence enzymatic functions of Ca^{2+}-binding proteins in the organelle and might regulate oxygen-evolving capacity of PSII and properties of photosynthetic electron transfer and photo-protection mechanism. This raises the question how is Ca^{2+} taken up and released from chloroplasts?

2. Organellar Ca^{2+} dynamics, transporters and signaling

Chloroplasts are plant organelles that possess a high concentration of Ca^{2+}. The predominant portion of the chloroplastic Ca^{2+} (~15 mM [68]) is bound to the negatively charged thylakoid membranes or to calcium-binding proteins [69] keeping the resting free $[Ca^{2+}]_{stroma}$ as low as 150 nM to avoid the precipitation of phosphates (Fig. 1A).

Since more than 40 years it has been known, that a light-dependent uptake of Ca^{2+} occurs in isolated chloroplasts [36,37,70]. However, the molecular mechanisms behind this process are still poorly understood (for recent reviews see [31,34]). Based on the work of Kreimer et al. [37,70], the Ca^{2+} influx is mediated by a uniport-type carrier and linked to photosynthetic electron transport via the membrane potential.

Furthermore, in 1995 Johnson et al. [71] observed a Ca^{2+} flux in the chloroplast upon the change from light to darkness (Fig. 1B). This dark-stimulated Ca^{2+} flux was shown to peak 20–30 min after the offset of light with a magnitude that was proportional to the previous duration of light exposure and it was not prevented by the inhibition of photosynthetic electron flow with DCMU [25]. They concluded that Ca^{2+} was taken up during illumination, sequestered in the thylakoid lumen or by Ca^{2+} storage proteins and released from these stores rather than imported from the cytosol after lights-off.

It should be noted, that specific Ca^{2+} signals can also be observed in the chloroplast in response to pathogen-associated molecular patterns (PAMPs) [34,72] as well as cold, high-salt and hyperosmotic stimuli [34].

2.1. Import of Ca^{2+} across the chloroplast envelope and thylakoid membrane

Despite the analysis of Ca^{2+} signals in the chloroplast and their importance, the identification of Ca^{2+} transporters in the chloroplast envelope and thylakoid membrane remains an unresolved challenge. For the import of Ca^{2+} through membrane potential-driven Ca^{2+} transporters [73] two potential chloroplast envelope membrane Ca^{2+}-ATPases have been proposed (Fig. 1A). In the first place, the autoinhibited Ca^{2+}-ATPase AtACA1 was identified by Huang et al. in the *Arabidopsis* chloroplast envelope but its higher abundance in roots, the lack of Ca^{2+}-ATPase activity at the envelope [39] as well as the proteomic assignment of AtACA1 to the ER and plasma membrane [74,75] question the role of AtACA1 in chloroplastidial Ca^{2+} import. Secondly, the heavy metal P-type ATPase AtHMA1 was identified in the chloroplast envelope by a proteomic approach by Ferro et al. [40] and its localization was confirmed by GFP fusion [41]. However, conflicting studies concerning its transport of Ca^{2+} [76] and/or heavy ions like Cu^{2+} and Zn^{2+} [41,77] exist.

The family of mechanosensitive channel of small conductance-like (MSL) proteins exhibits two members in the chloroplast envelope of *Arabidopsis thaliana*: MSL2 and MSL3 [44,45]. They have been shown to regulate the plastid size, shape [44] and division [78]. However, Ca^{2+}-permeability can be only inferred from their bacterial homolog MscS [79].

Furthermore, the glutamate receptor AtGLR3.4 was localized to the chloroplast as well as the plasma membrane [42]. GLRs can form non-selective cation channels and have putative roles in Ca^{2+} signaling [43]. Interestingly, GLRs as well as cyclic nucleotide-gated channels (CNGCs) and two-pore channels (TPCs) were found in green algae, higher plants and animals. This is in contrast to the four-domain voltage-dependent Ca^{2+} channels (VDCCS), transient receptor potential channels (TRPs) and inositol (1,4,5)-trisphosphate receptors, which are absent from land plants (reviewed in [80]) but present in green algae such as *C. reinhardtii* [81].

The import of Ca^{2+} across the thylakoid membrane has been shown to be dependent on a light- or ATP-induced transthylakoid proton gradient [82]. Overexpression and knockdown of the thylakoid protein Post-Floral-specific gene 1 (PPF1) led to an increased and decreased calcium storage capacity of *Arabidopsis* guard cells, respectively [46]. Furthermore, its expression in human hepatoma cells led to inward Ca^{2+} currents. Therefore, PPF1 represents a candidate for the transport of Ca^{2+} into the thylakoid lumen.

2.2. Import of nuclear encoded proteins into the chloroplast

Ca^{2+} signals also regulate the import of proteins into the chloroplast via the TOC–TIC complex (translocon of the outer/inner envelope membrane of chloroplasts) (see review [51]). TIC20 and TIC110 have been proposed for the translocation of preproteins across the inner membrane [83,84] and recently the main components of the TIC20 complex have been identified: TIC56, TIC100, and TIC214 (YCF1) [85]. The import of proteins was shown to be affected by the CaM inhibitor Ophiobolin A as well as the calcium ionophores A23187 and Ionomycin [86]. Ca^{2+} influences the channel activity of TIC110 [83] and TIC32, an interaction partner of TIC110, was identified as a CaM-binding protein in vitro [87]. Interestingly, the interaction between TIC32 and TIC110 is inhibited in the presence of NADPH [87] providing a link between Ca^{2+} signaling and the redox status of the chloroplast.

2.3. Mitochondrial Ca^{2+} import

Mitochondria can sequester Ca^{2+} as well and mitochondrial Ca^{2+} signals not only regulate the rate of mitochondrial energy (ATP) production in animals [88] but are also a response to cold stress, hyperosmotic stress and mechanical stimuli in plants [89]. The search for mitochondrial Ca^{2+} import proteins took nearly 50 years and resulted in the identification of the Mitochondrial Calcium Uniporter (MCU) in 2011 [90,91], which is associated with several proteins (MICU1, MICU2, EMRE) in a uniporter complex [92–94]. MCU has a high-selectivity but low-affinity for Ca^{2+} [95] and interestingly, it is inhibited by ruthenium red, which was shown for the light-dependent Ca^{2+} influx in chloroplasts as well [37]. The identification of mitochondrial Ca^{2+} transporter in plants is missing so far. However, six potential MCU homologs have been identified in *A. thaliana*, one of which is predicted to be targeted not only to mitochondria but also to chloroplasts (At5g66650,) [30].

3. The impact of Ca^{2+} on chloroplast metabolism

The following section will introduce the importance of Ca^{2+} towards chloroplast metabolism and highlight on the reactions, which are closely linked to photosynthesis. These processes are illustrated in Fig. 1A and Table 1 summarizes the function of the involved proteins in regard to photosynthesis as well as their Ca^{2+} dependency. Besides the light-induced redox poise a low resting free $[Ca^{2+}]$ (~150 nM [71]) is needed for the activation of the photosynthetic carbon fixation. During light-to-dark transition, large Ca^{2+} fluxes into the stroma lead to the deactivation of carbon fixation (Fig. 1B) [25,82]. It is remarkable that the activation and deactivation of certain enzymes are regulated by the same signal molecule.

3.1. Light-independent reactions of photosynthesis

The light-independent reactions represent the known Calvin–Benson–Bassham (CBB) cycle which takes place in the stroma of chloroplasts and is the primary pathway of carbon fixation of C3 plants [119]. The CBB cycle proceeds in three main stages: carboxylation, reduction and regeneration. In the first stage, carbon dioxide is

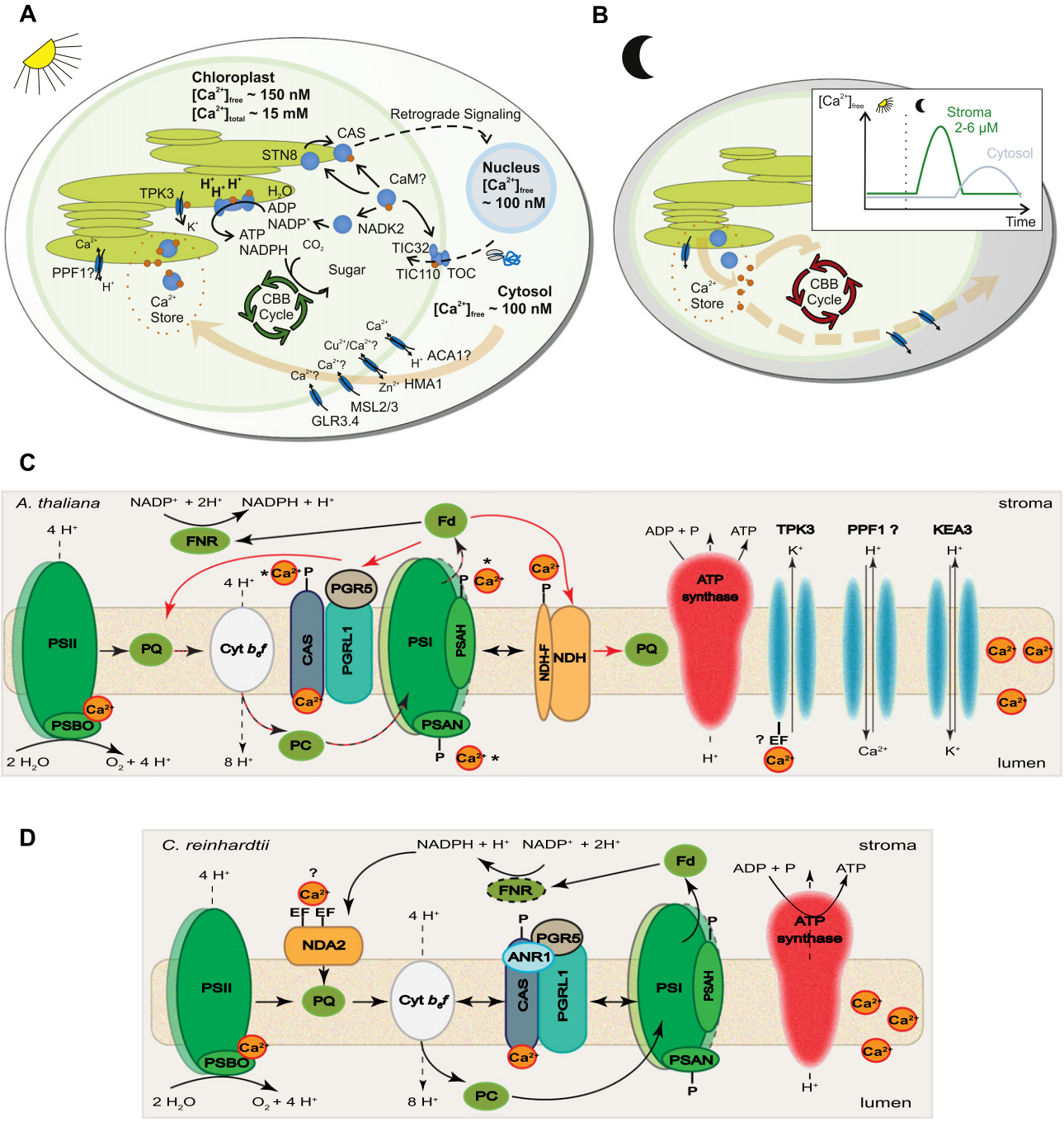

Fig. 1. Calcium dynamics and regulated processes in the chloroplast. (A) In the presence of light, Ca^{2+} (orange circles) is taken up from the cytosol [36–38] and stored in the thylakoid lumen and/or by Ca^{2+}-binding proteins. Candidates for the transport across the chloroplast envelope and the thylakoid membrane are ACA1, HMA1, GLR3.4, MSL2/3 and PPF1, respectively [39–46]. Although the presence of a CaM in the chloroplast has not been shown, there were different potential CaM-binding proteins identified in vitro [47]. CAS can bind Ca^{2+} as well as CaM and is phosphorylated by the CaM-binding kinase STN8 [48–50]. The CaM-dependent NADK2 [47] provides $NADP^+$, which is converted into NADPH by photosynthesis, which in turn is used in the active CBB cycle. Ca^{2+} is involved in retrograde signaling via CAS, possibly mediated by $^1O_2$ signaling [34] and affects the import of nuclear-encoded proteins at the TOC–TIC complex [51]. After lights-off (B), Ca^{2+} is released from its store, thereby increasing free $[Ca^{2+}]_{stroma}$ to 2–6 µM [52] (highlighted by orange arrows). This has an inhibitory effect on the enzymes of the CBB cycle [53–55]. The subsequent increase in free $[Ca^{2+}]_{cyt}$ indicates an export of Ca^{2+} into the cytosol in order to restore the free $[Ca^{2+}]_{stroma}$. The role of calcium in the photosynthetic machinery and the modulation of the proton motive force is depicted in (C) for *A. thaliana* and (D) for *C. reinhardtii*. During the LEF mode (black lines) electrons are transferred from water to form NADPH via PSII, PQ, Cytb_6f, PC, PSI, ferredoxin (Fd) and FNR. The electron transport chain is coupled to proton pumping (black dashed lines) building up a proton gradient, which is used by the ATP synthase to produce ATP and might be influenced by the ion channels TPK3 [56], PPF1 [46] and KEA3 [57,58]. CEF operates only around PSI [59] and is driven by two distinct pathways, (i) an NDH-dependent (vascular plants) [60,61] or NDA2-dependent (*C. reinhardtii*) [62] and (ii) the PGRL1/PGR5-dependent pathway [63]. Double-headed arrows indicate the ability to form a protein supercomplex in vascular plants (NDH–PSI supercomplex) [60] and *C. reinhardtii* (PSI–Cytb_6f–PGRL1–ANR1–CAS supercomplex) [64], respectively. Mobility of LHCII during state transitions as well as the possibility of FNR to associate with both supercomplexes is highlighted by dashed borders. The impact of calcium is illustrated by orange-colored Ca^{2+} ions, which can be bound to the thylakoid membrane or calcium-binding proteins. Proteins of the photosynthetic machinery which are known to directly bind Ca^{2+} are PSBO [65], CAS [66] and TPK3 [56]. NDA2 [62] possesses EF-hands, however Ca^{2+}-binding has not been shown. Proteins which are proposed to be phosphorylated in a calcium-dependent manner in *Arabidopsis* are PSAN [67], PSAH [67] and NDH-F [61]. In *Chlamydomonas* PSAN and PSAH phosphorylation has been observed (Bergner et al. 2015, submitted). Calcium was further shown to stimulate TPK3 activity in a positive manner and is possibly bound by a single EF-hand [56]. Asterisks indicate in vitro identified calcium-dependent phosphorylation of PSAN, PSAH and CAS. Please refer to text for abbreviations.

Table 1
Chloroplastidial proteins correlated to photosynthesis and calcium signaling.
Asterisks indicate in vitro identified Ca^{2+}-dependent phosphorylation and CaM-binding, respectively.

Protein	Function related to photosynthesis	Reference	Function related to calcium	Reference
Photosynthesis				
PSAN	Stabilization of LHCA2/LHCA3 and binding of PC to PSI	[96]	Ca^{2+}-dependent phosphorylation (*)	[67]
PSAH	PSI subunit important for state transitions	[97]	Ca^{2+}-dependent phosphorylation (*)	[67]
PSBO	Extrinsic PSII subunit important for oxygen evolution	[98,99]	Ca^{2+}-binding	[65]
CAS	Plant immunity; stomatal regulation; photoacclimation	[33,100]	Ca^{2+}-binding, CaM-binding (*), Ca^{2+}-dependent phosphorylation (*)	[49,66,67]
STN8	Phosphorylation of PSII core proteins and CAS	[50,101]	CaM-binding (*)	[49]
VAR1/FTSH5 VAR2/FTSH2	Degradation of photo-damaged D1 subunits	[102]	Ca^{2+}-dependent phosphorylation (*)	[67]
NDH-F	Cyclic electron flow in *A. thaliana*	[59,60]	Ca^{2+}-dependent phosphorylation	[61]
NDA2	Cyclic electron flow in *C. reinhardtii*	[62,103]	Ca^{2+}-binding via EF-hand motives (?)	[104]
Metabolism				
FBPase	Influence of photosynthetic activity and capacity of CO_2 fixation	[105,106]	Low Ca^{2+} activity ↑; high Ca^{2+} activity↓	[107,108]
SBPase	Influence of photosynthetic activity and capacity of CO_2 fixation	[106,109]	Low Ca^{2+} activity ↑; high Ca^{2+} activity↓	[53,55]
TKL	Regulation of carbon allocation between CBB and OPP	[110,111]	Ca^{2+}-dependent phosphorylation	[112]
CP12	Thioredoxin-mediated regulation of CBB	[113]	Ca^{2+}-binding	[114]
NADK2	De novo synthesis of $NADP^+$; chlorophyll synthesis; chloroplast protection against oxidative damage	[115–117]	CaM-binding (*)	[49,118]
Transporters and channels				
ACA1	–	–	Import of Ca^{2+} through chloroplast envelope (?)	[39]
HMA1	–	–	Import of Ca^{2+} through chloroplast envelope (?)	[40,41]
PPF1	–	–	H^+/Ca^{2+} antiport across thylakoid membrane (?)	[46]
GLR3.4	–	–	Ca^{2+} channel at the chloroplast envelope (?)	[42,43]
MSL2/3	–	–	Ca^{2+} channel at the chloroplast envelope (?)	[44,45]
TPK3	Enhancement of the proton gradient ΔpH	[56]	Ca^{2+}-binding via EF-hand motif	[56]
TIC110	Import of proteins into the chloroplast (?)	[51]	Ca^{2+} affects channel activity	[83,86]
TIC32	Regulation of protein import into the chloroplast	[51]	CaM-binding (*)	[87]

bound to its acceptor molecule ribulose 1,5-bisphosphate (RubP) by the enzyme ribulose 1,5-bisphosphate carboxylase/oxygenase (RubisCo), resulting in the formation of two 3-phosphoglycerate (3-PGA) molecules. In the reduction stage 3-PGA is phosphorylated and reduced by consumption of ATP and NADPH, products of the light-dependent reaction of photosynthesis, producing glyceraldehyde 3-phosphate (G3P). The here formed triose phosphates are either used in the final stage to regenerate RubP or enter the starch or sucrose biosynthesis pathway [120]. To maintain the balance between those competitive pathways the metabolic flux is highly regulated on the level of enzyme activity and content [121]. Calcium is believed to be important for the regulation of several key enzymes, including fructose 1,6-bisphosphatase (FBPase) and sedoheptulose 1,7-bisphosphatase (SBPase) of the reductive pentose phosphate cycle. FBPase catalyzes the breakdown of fructose 1,6-bisphosphate (F1,6BP) to fructose 6-phosphate (F6P) and inorganic phosphate (Pi). Regulation of this enzyme is influenced by the interplay of a wide variety of factors such as its substrate fructose 1,6-bisphosphate, stromal pH, magnesium ions, the reductive potential of the thioredoxin system and Ca^{2+} ions [107,122]. The activity of the FBPase is divided in two steps (hysteresis): a slow activation process accompanied by a structural change and a fast rate of catalysis [108,123]. Upon dark–light transition the enzyme gets activated by the redox potential of the ferredoxin–thioredoxin system (photo-reduced ferredoxin, thioredoxin and ferredoxin–thioredoxin reductase) [54,108,124]. Light further leads to an influx of Ca^{2+} from the cytosol into the chloroplast [36,37,125]. This increase in chloroplastic Ca^{2+} is probably not affecting the free $[Ca^{2+}]_{stroma}$, because Ca^{2+} is proposed to be transported into the thylakoid lumen and/or sequestered by Ca^{2+}-binding proteins [25]. Calcium was shown to have a dual function on the activity of FBPase. Pre-incubation of the enzyme with Ca^{2+} and F1,6BP was shown to have a positive effect towards its activation [52,123,126]. Therefore, a low resting free $[Ca^{2+}]_{stroma}$ is important to enable the activation of the CBB cycle enzymes. On the other hand, high concentrations of Ca^{2+}, which occur after light-to-dark transition by the release of the stored Ca^{2+}, lead to the deactivation of the FBPase [55,68,126].

SBPase is the second key enzyme, which functions at the intersection between the CBB cycle and the starch biosynthesis pathway. It catalyzes the removal of a phosphate group from sedoheptulose 1,7-bisphosphate (S1,7BP) to generate sedoheptulose 7-phosphate (S7P). The SBPase is regulated in a similar way to the FBPase. Oxidized SBPase becomes activated when reduced by dithiothreitol or reduced thioredoxin [53] and catalysis is inhibited at high Ca^{2+} concentrations [55]. Reduced or elevated expression level of these two CBB enzymes further was shown to have a direct impact on photosynthesis [105,109]. Reduction of SBPase [109] or FBPase [105] decreased photosynthetic capacity and reduced plant growth in potato or tobacco. The other way round, photosynthetic activity could be increased when expressing a cyanobacterial FBPase/SBPase in transgenic tobacco chloroplasts [106]. Thus, regulation of CBB cycle enzymes via Ca^{2+} will impact photosynthetic capacity.

Similar to the CBB cycle enzymes, calcium-dependent metabolic regulation appears to be present in the mitochondria as well. Several mitochondrial dehydrogenases such as pyruvate dehydrogenase (PDH) [127], NADH-isocitrate dehydrogenase (ICDH) [128], and a-ketoglutarate dehydrogenase (a-KGDH) [129], can be activated by increased Ca^{2+} concentration in the organelle.

Recent studies showed that the activity of the chloroplast transketolase (TKL), an enzyme involved both in the CBB cycle as well as the oxidative pentose phosphate pathway (OPP) [110], is modulated by calcium-dependent phosphorylation of a yet unknown kinase [112]. In the reduction stage of the CBB the transketolase catalyzes the reaction of F6P, S7P and G3P leading to the formation of xylulose 5-phosphate (X5P), erythrose 4-phosphate and ribose 5-phosphate (R5P) [111]. In the OPP pathway glucose 6-phosphate (G6P) is used to generate NADPH and the TKL catalyzes the same reactions as in the CBB cycle but in the opposite direction. Therefore a distinct control of these two pathways has to take place. Rocha et al. identified TKL as a new target of calcium-dependent phosphorylation using stromal protein fractions of *Arabidopsis* and *Pisum* in a phosphorylation assay in the presence of the chelator EGTA or Ca^{2+} [112]. They further could show that calcium-dependent phosphorylation of AtTKL1 occurs at a

conserved serine residue (Ser_{428}). In the presence of at least 25 μM calcium AtTKL1 gets phosphorylated whereas phosphorylation is strongly diminished in a mutant where the serine residue was replaced by an alanine residue. Enzyme activity measurements at stromal physiological pH 7.2 (dark) and pH 8 (light) suggest that the calcium-dependent phosphorylation event is not an on–off mechanism but rather a fine-tuned one to distribute carbons between CBB and OPP [112].

Besides its direct function on enzyme activity or catalysis Ca^{2+} is able to influence the carbon metabolism in a different manner. CP12, a redox-sensitive protein functioning in the formation of a supramolecular protein complex together with phosphoribulokinase (PRK) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [113], was shown to be able to bind calcium [114]. Radioactive calcium overlay assays of separated *A. thaliana* stroma proteins and mass spectrometry analysis led to the identification of CP12 as a novel chloroplast-localized calcium-binding protein. Calcium-binding of CP12 was confirmed with the recombinant protein although the exact calcium-binding mechanism is not known since CP12 does not contain typical EF-hand motives.

3.2. The CaM-dependent NAD kinase NADK2

One putative CaM target is a chloroplastic NAD kinase, which catalyzes the phosphorylation of NAD^+ into $NADP^+$ in the presence of ATP [118]. Currently only in vitro data substantiate protein–protein interaction between CaM and the chloroplast NAD kinase. Notably the $NADP^+$ produced in the chloroplast is the acceptor molecule for the photosynthetic electron transport in the light-dependent reaction of photosynthesis and provides electrons as NADPH for many metabolic processes [130].

Unlike in other organisms plants contain both CaM-independent and CaM-dependent NAD kinases. *Arabidopsis* contains three genes encoding NAD kinases: NADK1, NADK2 and NADK3. The chloroplast-localized NADK2 is the only putative CaM-dependent kinase, whereas the other ones are CaM-independent and localized in the cytosol [47,115,116,131,132]. Furthermore, NADK1 and NADK2 only phosphorylate NAD^+ while NADK3 phosphorylates both NAD^+ and NADH [131]. To date no CaM was found to be located in the chloroplast but several CaM-like proteins (CMLs) are predicted to be targeted to the chloroplast. Furthermore, CaM and NADK2 in vitro interaction was shown by Curien et al. using mass spectrometry, CaM-binding and fluorescence anisotropy assays [49].

The activity of CaM-dependent NAD kinase was shown to be changed during several stress conditions (e.g. pathogen attack, cold acclimation, oxidative stress) [133,134]. This could indicate a Ca^{2+}/CaM-dependent modulation of the NAD/NADP ratio which could be important for the activity of several metabolic enzymes requiring these cofactors [133,134].

Deletion of NADK2 in *Arabidopsis* (*nadk2*) reduced chlorophyll content and resulted in plants sensitive towards several environmental stresses (e.g. UVB, drought, heat shock and salinity). And therefore NADK2 seems to be essential for proper chlorophyll biosynthesis and protection against oxidative damage [116]. Takahashi et al. investigated the same mutant to understand the possible role of NADK2 in photosynthesis. Chlorophyll fluorescence analysis revealed that in comparison to wild type plants *nadk2* mutants showed decreased quantum yield of electron transport (ϕII) and open reaction centers of photosystem II (PSII) (Fv′/Fm′). However, non-photochemical quenching (NPQ) was increased fourfold in the mutant. They concluded that rather energy transduction within the antenna complexes than electron transport within the reaction center is affected and therefore analyzed possible effects in the xanthophyll cycle [117]. The xanthophyll cycle is part of the NPQ reaction and is important for the dissipation of excess light energy by the xanthophylls violaxanthin, antheraxanthin and zeaxanthin [135]. Quantification of xanthophyll content after high light treatment and dark adaptation showed that zeaxanthin accumulated even after prolonged dark adaptation and on account of this they concluded that lowered NADPH content of *nadk2* mutant failed to activate the zeaxanthin epoxidase [117].

Elevated NADP(H) production by NADK2 overexpression lines either in shade or sun plants showed pleiotropic effects on plant metabolism. While overexpression of NADK2 in *Arabidopsis* (shade plant) however has no visible effect on photosynthetic electron transport, overexpression of chloroplastic AtNADK2 in rice (NK2; sun plant) increased the rate of photosynthetic electron transport through PSII (ETR) [136]. In *Arabidopsis* on the one hand the carbon metabolism was changed due to the accumulation of CBB cycle metabolites together with increased RubisCo activity. On the other hand nitrogen assimilation was promoted shown by elevated levels of the amino acids glutamine and glutamate and up-regulated nitrate reductase (NIA) and nitrite reductase (NIR) genes [137]. In transgenic rice (NK2), the overexpression led to an enhanced tolerance towards oxidative stress caused by the production of reactive oxygen species (ROS) by methyl viologen (MV) [130].

The diverse effects on plants metabolism seen either in knockdown or overexpression NADK2 mutants reveal clearly that modulation of the $NADP^+$ content and NADP/NAD ratio is highly important for proper control of plant metabolism.

4. Ca^{2+} impact on photosynthetic electron transfer and photo-protection mechanism

Photosynthetic organisms must acclimate to their light environment to optimize photosynthesis and minimize photo-oxidative damage. Under low light conditions, excitation energy is collected to fuel photochemical work via the photosynthetic electron transfer machinery, while at higher excitation pressure excess photons have to be additionally quenched to avoid photodamage. The involvement of Ca^{2+} in the modulation of these processes is illustrated in Fig. 1C and D and discussed in the following section.

4.1. Calcium in photosystem II

Ca^{2+} is well known to be a structural component of photosystem II (PSII) and essential for efficient oxygen evolution. Oxidation of H_2O by PSII requires a metal cluster containing four mixed valence manganese ions, a calcium ion, and five oxo ligands (Mn_4CaO_5 cluster) [98,99,138]. Protein ligands to the metal cluster are almost exclusively stemming from the PSII core protein PSBA, with the exception that one manganese ligand is provided by PSBB [98,99,138]. PSBO, an extrinsic PSII subunit of the water splitting complex, is furthermore capable of binding calcium within the PSII protein complex [65,99] but does not provide any ligands to the binding of calcium or manganese in the Mn_4CaO_5 cluster [98,99,138]. Reversible release of Ca^{2+} can be triggered via acidification of PSII leading to an inactivation of oxygen evolution [139]. Recovery of PSII oxygen evolution capacity by replenishment of calcium is suppressed by addition of calcium channel blockers [139], suggesting that Ca^{2+} uptake into the intact PSII structure might be mediated via specific channel like structures. The functional role of Ca^{2+} in photosynthetic water-oxidation is discussed in detail elsewhere [140,141].

4.2. The versatile roles of CAS

Another Ca^{2+}-binding protein, localized to the thylakoid membrane, is the Calcium sensor protein CAS [66]. This plant-specific 42 kDa protein is encoded by a single-copy gene and is conserved in algae, mosses, ferns and seed plants. The moss *Physcomitrella patens* represents an exception, since it possesses three closely related CAS proteins [32,142]. CAS has initially been identified in the plasma membrane of *Arabidopsis* and has been described as extracellular Ca^{2+} sensor. It exhibits a low-affinity, but high-capacity for Ca^{2+}-binding, which occurs in the N-terminal region of the protein [66]. However, subsequently performed studies confirmed localization to the thylakoid membrane of the

chloroplast in *Arabidopsis* [32,35,100,143] and *Chlamydomonas* [144,145]. In the C-terminal region of the protein, a rhodanese-like domain was identified that might exhibit regulatory rather than enzymatic function. This hypothesis is based on the observation that the cysteine residue, which has a potential catalytic activity, is replaced by aspartic acid [32,146]. Additionally, the C-terminus of the protein contains a motif typical for interactions with 14–3–3 proteins and with proteins exhibiting a forkhead-associated (FHA) domain [100].

Ca^{2+} signaling has been shown to be crucial for regulating the stomatal aperture in *A. thaliana*, as closure of stomata is induced by an increase in the external Ca^{2+} concentration [147–149]. In the same line, previous studies using *cas* antisense or *cas* loss-of-function lines confirmed a role of CAS in stomatal closure upon application of external Ca^{2+} [32,66]. Usually, the closure of stomata via an increase of the external Ca^{2+} concentration is accompanied by transient and repetitive elevations in $[Ca^{2+}]_{cyt}$ [148]. However, such cytosolic Ca^{2+} transients were not detectable in the mutant strains, thus indicating a role of chloroplast-localized CAS for the regulation/generation of cytoplasmic Ca^{2+} signals [32]. Therefore, CAS function is crucial for proper stomatal regulation in response to elevations of external Ca^{2+} through the modulation of cytoplasmic Ca^{2+} dynamics [32,35]. Thereby, CAS is closely involved in the regulation of carbon dioxide availability and thus indirectly implicated in the modulation of the redox poise of the chloroplast stroma. Accordingly, CAS knockdown *Arabidopsis* plants were also shown to possess a lower CO_2 assimilation rate, likely due to less efficient photosynthetic electron transfer [150]. Moreover, Ca^{2+} and CAS appear to function in efficient de-etiolation in *A. thaliana* etiolated seedlings [48]. Colonization of Chinese cabbage by *Piriformospora indica* promoted CAS expression, correlating with a retardation of drought-induced decrease of photosynthetic efficiency and degradation of chloroplasts [151]. These data suggest that in vascular plants CAS is also involved in the regulation of photosynthetic efficiency, as demonstrated for *C. reinhardtii* as well (see below). In agreement with photosynthesis related functions, CAS expression is upregulated under high light conditions in vascular plants and *Chlamydomonas* [33,100,152] and potentially phosphorylated via the chloroplast kinase STN8/STL1 [100]. In *Arabidopsis*, STN8 is required for phosphorylation of PSII core proteins [50,101]. Interestingly, an in vitro CaM protein-binding assay had identified STN8 and CAS as potential targets, thereby suggesting that a common Ca^{2+}-dependent way of regulation may exist for both proteins [49]. In this way, STN8 could be involved in Ca^{2+}-dependent protein phosphorylation in the chloroplast as described recently for *Arabidopsis* [67]. Notably and in line, CAS has been identified as a substrate of Ca^{2+}-dependent protein phosphorylation [67]. In this regard, it is interesting that ATP-dependent peptidases VAR1/FTSH5 and VAR2/FTSH2 have been identified as targets of Ca^{2+}-dependent phosphorylation [67]. As these proteases have been implicated in degradation of photo-damaged PSII subunits [102], these data provide another link to the STN8 kinase.

Besides stomatal regulation, CAS is involved in the activation of plant immune signaling in *A. thaliana* [34], pointing to a function of chloroplast Ca^{2+} in retrograde signaling and regulation of nuclear gene expression. A similar conclusion was derived for CAS knockdown plants where amounts of transcripts for photosynthetic genes were decreased [150]. It has been proposed that the CAS-dependent retrograde signaling is mediated by $^1O_2$ signaling, since $^1O_2$-responsive genes were also affected in a PAMP-treated CAS knockout mutant [34]. Notably, the absence of CAS altered stromal Ca^{2+} signals, suggesting that CAS is crucial for Ca^{2+} transients within the chloroplast too [34]. In *Chlamydomonas*, the light-induced expression of nuclear-encoded Light-Harvesting Complex Stress-Related 3 (LHCSR3) is regulated via the thylakoid membrane protein CAS and Ca^{2+}, as revealed by the investigation of CAS knockdown mutant strains and calcium rescue experiments [33]. Screening a library of 20,000 insertional *Chlamydomonas* mutants resulted in the discovery of a CAS knockout mutant that was unable to grow at ambient CO_2, suggesting a possible role of CAS in CO_2 concentrating mechanism. However, the CO_2 phenotype of this mutant could not be rescued with hemagglutinin HA epitope-tagged CAS [153], implying that more work is required for establishing a link between CAS and CO_2 concentrating mechanism. Notably, LHCSR3 protein expression was also repressed by addition of the CaM antagonist W7 or the G-protein activator mastoparan in wildtype cells [33]. Moreover it was shown that the antagonist W7 blocks also transcription of the *lhcsr3* genes [154]. Thus, making another example, where changes in CAS expression altered regulation of nuclear gene expression.

In algae, LHCSR3 is required for the energy-dependent thermal dissipation (qE) of excess absorbed light energy [155]. qE is a constituent of NPQ and required for effective photo-protection. In vascular plants, the PSII protein PSBS is essential for qE [156], while the moss *P. patens* utilizes both types of regulatory proteins to operate qE [157]. *P. patens* possesses three *cas* genes, which were all found to be up-regulated in the absence of Proton Gradient Regulation Like 1 (PGRL1) [142]. PGRL1 was discovered in *Arabidopsis* [158] as a novel component for the Proton Gradient Regulation 5 (PGR5)/PGRL1-dependent cyclic electron flow pathway [63] operating in thylakoid membranes. The requirement of PGRL1 for efficient cyclic photosynthetic electron flow (CEF) has been also established for *Chlamydomonas* and *Physcomitrella* [142,159–161]. Protein–protein interactions between CAS and PGRL1 have been demonstrated in vivo for the *Chlamydomonas* proteins [145], suggesting a link between CAS and CEF.

4.3. Calcium in linear and cyclic electron flow

Besides linear photosynthetic electron flow (LEF), which provides ATP and NADPH, CEF delivers additionally required ATP for CO_2 fixation [162]. CEF is also important for the avoidance of over-reduction of the PSI acceptor side under stressful environmental conditions and is involved in re-adjustment of the ATP poise [163–166]. In microalgae and vascular plants, CEF is driven by two distinct pathways, (i) the NAD(P)H dehydrogenase (NDH)-dependent and/or (ii) PGRL1/PGR5-related pathway [59,63,159,160,167]. For both pathways, protein supercomplexes have been described (Fig. 1C and D). An NDH–PSI supercomplex has been identified in *Arabidopsis* [60], while for *C. reinhardtii*, Iwai et al. [64] isolated a protein supercomplex under state 2 conditions, composed of PSI–LHCI, LHCII, the cytochrome b_6/f complex, ferredoxin (Fd)–NADPH oxidoreductase (FNR), and PGRL1. Such a CEF-supercomplex has been isolated independently from cells under anoxia and found to be associated with the CAS and Anaerobic Response 1 (ANR1) [168]. As mentioned above, interactions between CAS and PGRL1, but also between CAS and ANR1 and ANR1 with PGRL1 were shown in vivo [168]. In line, knockdown of CAS and ANR1 expression by artificial microRNA expression in *C. reinhardtii* caused a strong inhibition of CEF under anoxia [168]. Importantly, CEF could be partially rescued by an increase in the extracellular Ca^{2+} concentration, concluding that CEF is Ca^{2+}-dependent [168]. These data establish a Ca^{2+}-dependent regulation of CEF via the combined function of ANR1, CAS, and PGRL1, associated with each other in a multiprotein complex. Moreover, these findings imply that CAS and Ca^{2+} are important factors in modulating qE and CEF. CEF and qE are interconnected as CEF participates in acidification of the thylakoid lumen, which is required for efficient qE. Recently this strong interdependence has been experimentally proven as the simultaneous knockout of LHCSR3 and PGRL1 had, in comparison to the single knockouts, a strong additive phenotype in *C. reinhardtii* [142]. Involvement of Ca^{2+} in the regulation of both components puts calcium in a prime role in regulating photo-protective mechanisms but also to integrate changes in chloroplast metabolism and/or responses to other environmental cues into the regulation of the photosynthetic functions.

Besides the PGRL1/PGR5-dependent, as outlined above, an NDH-dependent CEF pathway exists. From work in *Arabidopsis* it became obvious, that both CEF pathways are essential for photosynthesis as mutants defect in both pathways possessed significant stronger phenotypes as compared to single pathway mutants [59]. The NDH complex in

Arabidopsis forms together with PSI an NDH–PSI supercomplex that advances the in vivo function of the NDH complex [60]. Another modulation of NDH activity has been demonstrated to occur via phosphorylation of the NDH-F complex subunit [61]. It was further shown that the amount of phosphorylation closely correlated with the NDH complex activity [61]. The amount of NDH-F phosphorylation, on the other hand, was positively correlated with the presence of Ca^{2+} [61], thus indicating that a Ca^{2+}-dependent kinase is likely responsible for NDH-F phosphorylation and modulation of activity. In *C. reinhardtii*, the non-photochemical reduction of the plastoquinone (PQ) pool does not involve the NDH-1 complex, which is missing from the algal chloroplast, but instead a type II NADH dehydrogenase called NDA2 [62,103,104] functions as a PQ-reductase. Strikingly, NDA2 possesses two EF-hands, pointing to Ca^{2+}-binding capability and suggesting that NDA2 activity might also be modulated via Ca^{2+}. This would reveal that both CEF-pathways in *Chlamydomonas* are regulated by Ca^{2+}.

PSI has a central function in CEF but also in LEF. Two PSI subunits, PSAN and PSAH, have been recently described to be phosphorylated in a calcium-dependent manner [67]. This reasoning was based on in vitro assays; however, phosphorylation could not be confirmed by mass spectrometry. PSAH together with PSAL and PSAO is required for docking of phosphorylated Light-Harvesting Complex II (LHCII), which has been revealed via cross-linking experiments and RNA interference approaches [97,169,170]. In accordance, *Arabidopsis* plants lacking PSAH or PSAL are locked in state 1 [97], while plants lacking PSAO are reduced by 50% in state transitions [170]. The PSI crystal structure implies that PSAN is interacting with LHCA2/LHCA3 suggesting a role in their stabilization [96]. Moreover, PSAN plays a minor role in efficient binding of plastocyanin (PC) to PSI [171,172]. The fact that PSAH and PSAN interact with antenna proteins might indicate that their Ca^{2+}-dependent phosphorylation modulates excitation energy towards the reaction center. Phosphorylation of luminal PSAN might alter binding of negatively charged plastocyanin to PSI via charge repulsion, it might also help to orientate the positively charged N-terminal domain of PSAF which is crucial for the efficient binding of plastocyanin to PSI [172]. Further work will also be required to address whether a luminal Ca^{2+}-dependent protein kinase indeed exists, which is currently unknown. Another interconnection between PSI and Ca^{2+}-dependent regulation is the biosynthesis of $NADP^+$, the final electron acceptor of this complex. As outlined above, $NADP^+$, is generated from NAD^+ via NADK2 which is potentially regulated via a not yet identified CaM [118]. Yet, the depletion of NADK enforces NPQ [117], indicating that regulation of PSI acceptor side via availability of $NADP^+$ and NADK feedbacks into photo-protection, which is per se already closely linked to Ca^{2+}-dependent regulation.

4.4. TPK3 links Ca^{2+} to the acidification of the thylakoid lumen

Recently other ions such as potassium came into the focus as AtTPK3, a two-pore potassium channel, and AtKEA3, a K^+/H^+ exchanger, participate in the modulation of the proton motive force (Fig. 1C) [56–58]. Both proteins are localized to the thylakoid membrane. KEA3 likely functions in K^+/H^+ antiport, thereby driving K^+ uptake into the thylakoid lumen, particularly under conditions where a large proton motive force exists that would facilitate K^+ transport into the lumen. On the other hand, AtTPK3 has been described as a two-pore potassium channel that would drive K^+ transport out of the lumen into the stroma along the electrical potential gradient that is generated via active photosynthetic electron transfer. Down-regulation of *tpk3* expression is leading to a diminished capacity for building a ΔpH. At the same time *tpk3* knockdown plants exhibit a higher electric potential in light than in the wild type [56]. Thus Carraretto et al. [56] concluded that the TPK3-mediated K^+ efflux from the lumen is required for the regulation of the transmembrane electrical potential and for the enhancement of the pH gradient. These data also suggest that TPK3 and KEA3 are either differentially regulated and/or possess different capacities for potassium transport as the *tpk3* phenotype was recorded in the presence of functional KEA3, presumably. Here it is important to note that the regulation of AtTPK3 is Ca^{2+}-dependent [56]. In the absence of Ca^{2+} the channel is not active. Now it is tempting to speculate that Ca^{2+}-dependent regulation of CEF and AtTPK3 goes hand in hand and mediates appropriate acidification of the lumen allowing proper photosynthetic control and photoprotection. For further conclusions, Ca^{2+}-dependence of the AtTPK3 channel activity and regulation of CEF need to be determined in vivo. Here it has to be stated, that Ca^{2+}-dependent regulation of CEF via the PGRL1/PGR5-dependent pathway remains to be shown in vascular plants, although all player including CAS, PGRL1 and PGR5 also exist. However, Ca^{2+}-dependent regulation of CEF via the NAD(P)H dehydrogenase (NDH)-dependent CEF was already demonstrated (see above, [61]). Moreover, regulatory properties and in vivo potassium transport rates of KEA3 and TPK3 need to be determined to understand their impact and role in the regulation of photosynthetic electron transfer and photo-protection. Notably Ca^{2+} has been implicated in Ca^{2+} gated switching between localized and delocalized proton gradient energy coupling [173,174]. The concept of localized proton domains is controversially discussed in literature [175] and a detailed reflection is beyond the scope of this review. However, some of the described effects of calcium and potassium [173,174] on ATP formation should be re-visited in the light of TPK3 and KEA3. Moreover, the function of PPF1 that might transport Ca^{2+} into the thylakoid lumen at the expense of protons needs to be considered and further explored, as this will also contribute to modulation of the proton motive force.

5. Concluding remarks

Starting with the light-dependent import of Ca^{2+} into the chloroplast and a dark-stimulated stromal Ca^{2+} flux, it was shown that Ca^{2+} is closely linked to photosynthesis (Fig. 1). The regulatory function of Ca^{2+} includes processes like the CBB cycle, which are fueled by photosynthesis, as well as providing $NADP^+$ as the terminal electron acceptor for photosynthesis. But most remarkable is the pivotal role of Ca^{2+} in cyclic and linear electron flow. Although the molecular mechanisms are not completely understood, the impact of Ca^{2+} and Ca^{2+}-binding proteins such as CAS on CEF and photo-protective NPQ, indicates an interplay between the acidification of the thylakoid lumen and the regulation of CEF by Ca^{2+}, that could be described in a preliminary model.

During photosynthesis (Fig. 1C and D), a pH gradient across the thylakoid membrane is build up that is not only used for ATP production, but also for the import of Ca^{2+} into the lumen. The Ca^{2+} might be stored by binding to proteins or the thylakoid membrane, but probably also regulates CEF via CAS and PGRL1 in the PGRL1/PGR5-dependent pathway or Ca^{2+}-dependent phosphorylation of NDH-F in the NDH-dependent CEF. Furthermore it is needed for the TPK3-dependent enhancement of ΔpH. A high acidification could not only lead to the release of Ca^{2+} from PSII but also from the thylakoid membrane or Ca^{2+}-binding proteins. This might increase the concentration of free Ca^{2+} in the lumen. Export of Ca^{2+} from the lumen along the electrochemical gradient, as suggested for TPK3 dependent K^+ export, by a so far uncharacterized channel would further contribute to the regulation of ΔpH and $\Delta\Psi$ and might participate in control of photoprotective mechanisms such as the regulation of expression of LHCSR3.

For further exploration, the measurement of Ca^{2+} fluxes across the thylakoid membrane in dependency of LEF and CEF favoring conditions would be required to understand the regulatory role of Ca^{2+} in photosynthetic electron transfer. Furthermore, the identification and characterization of Ca^{2+} transporters and chloroplastidial CaMs or CMLs would broaden the understanding of these processes.

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