Review

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Photorespiration: players, partners and origin

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Photorespiratory metabolism allows plants to thrive in a high-oxygen containing environment. This metabolic pathway recycles phosphoglycolate, a toxic compound, back to phosphoglycerate, when oxygen substitutes for carbon dioxide in the first reaction of photosynthetic carbon fixation. The recovery of phosphoglycerate is accompanied by considerable carbon and energy losses, making photorespiration a prime target for crop improvement. The genomics era has allowed the precise functional analysis of individual reaction steps of the photorespiratory cycle, and more links integrating photorespiration with cellular metabolism as a whole are becoming apparent. Here we review the evolutionary origins of photorespiration as well as new insights into the interaction with other metabolic processes such as nitrogen assimilation and mitochondrial respiration.

Photorespiration and photosynthesis

Photorespiration occurs in all oxygen (O_2)-producing photosynthetic organisms and is one of the major avenues of carbon metabolism in the biogeosphere. Biochemically, it begins with O_2 substituting for carbon dioxide (CO_2) in the first reaction of photosynthetic CO_2 fixation, which is catalysed by ribulose 1,5-bisphosphate (RubP) carboxylase-oxygenase (Rubisco). This substitution produces the toxic compound phosphoglycolate (2PG) [1], which becomes recycled to 3-phosphoglycerate (3PGA). Recycling requires a number of enzymatic steps, involving the photorespiratory C_2 cycle, in which one molecule of 3PGA is recovered from two molecules of 2PG and one out of four 2PG carbon atoms is lost as photorespiratory CO_2.

Functionally, the C_2 cycle is an ancillary metabolic process that is essential to allow photosynthesis to occur in O_2-containing environments, and it probably co-evolved with oxygenic photosynthesis in cyanobacteria that lived 3.8–2.5 billion years ago in the nearly O_2-free environment of the Precambrian ocean [2–4]. Later, about 1.5 billion years ago, the uptake of a cyanobacterium into a heterotrophic protist initiated the evolution of algae and higher plants [5]. Most plants are C_3 plants, i.e. CO_2 is directly fixed by Rubisco to produce the three-carbon compound 3PGA. Some scientists assume that the predecessors of present-day C_4 plants, in which CO_2 is initially fixed by an O_2-insensitive process into four-carbon compounds, channelled the high photorespiratory CO_2 fluxes to specific leaf cells, the bundle sheath, paving the way for the evolution of C_4 photosynthesis [6].

Quantitatively, if considered in terms of mass flow, photorespiration likely constitutes the second-most important process in the biogeosphere, exceeded only by photosynthesis itself. This is because cellular O_2 concentrations are typically much higher than those of CO_2. Therefore, although Rubisco strongly favours CO_2 over O_2, most land plants produce large amounts of 2PG during the day. Photorespiratory CO_2 losses are correspondingly high; they amount to about 20% of C_3 plant net-photosynthesis in moderate conditions [7] and can be even higher in warm and dry environments. Therefore, photorespiration has been a prime target for crop improvement [8,9] and even more so in recent years in which a steadily growing world population faces limited natural supplies and increasingly serious challenges from climate change.

This article will give an overview over the process and known components of photorespiration, review new insights into interactions with other metabolic processes such as nitrogen assimilation and mitochondrial respiration, and discuss the evolutionary origins of this important pathway.

Enzymes and pathways in plants

Photorespiration requires eight enzymes in the core photorespiratory C_2 cycle for the recycling of 2PG produced by Rubisco and several auxiliary enzymes. In higher plants, the individual reactions are distributed over the chloroplast, the peroxisome, the mitochondrion and the cytosol (Figure 1), and substrate flow requires many membrane passage steps. As yet, only two transporters of the photorespiratory nitrogen cycle have been identified [10,11] but none involved in the photorespiratory carbon cycle.

In the chloroplast

Absolute rates of 2PG production are determined by the amount and kinetic properties of Rubisco as well as by the concentrations of O_2, CO_2 and RubP. Within the chloroplast, a highly specific 2PG phosphatase (PGP) hydrolyzes 2PG to glycolate. Plants also have a cytosolic PGP, but only deletion of the plastidial enzyme results in a 'photorespiratory phenotype', i.e. such mutants die in normal air and require elevated CO_2 for normal growth [12]. Glycolate moves out of the chloroplast through a poorly characterised glycolate–glycerate antiporter and enters the peroxisome via porin-like channels [11].

In the peroxisome

Glycolate oxidase (GOX) is a flavinmononucleotide dependent peroxisomal enzyme that consumes glycolate and

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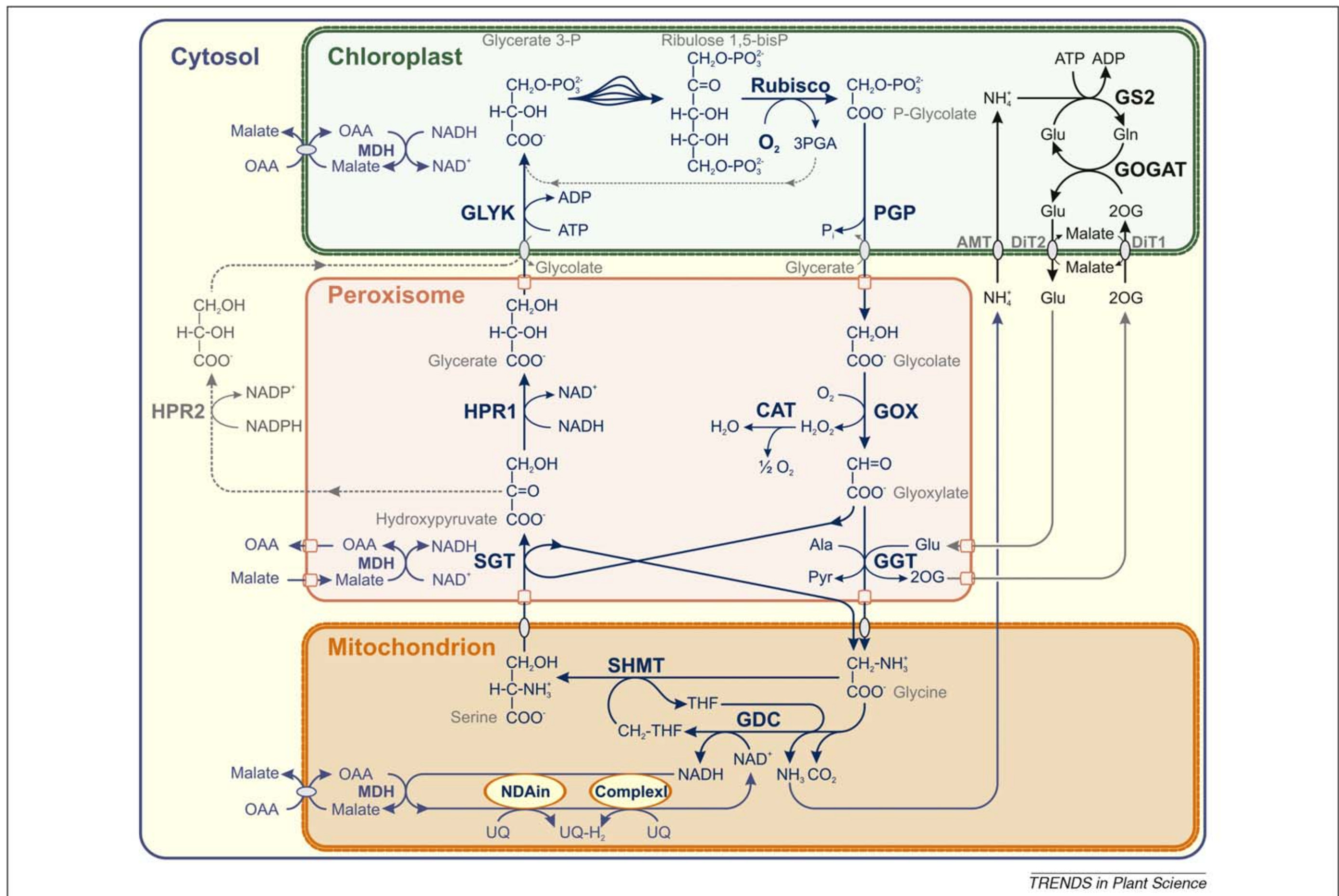

Figure 1. Multicompartmented photorespiratory carbon and nitrogen metabolism of plants. Flow-chart of reactions constituting the core of the C_2 cycle (blue), the photorespiratory nitrogen cycle (black), and several associated reactions (grey and light blue). This figure is modified from Bauwe [69]. The enzymes are CAT, catalase; ComplexI, NADH:ubiquinone reductase of the mitochondrial electron transport chain; GDC, glycine decarboxylase; GLYK, glycerate 3-kinase; GOGAT, ferredoxin-dependent glutamate synthase; GOX, glycolate oxidase; GGT, glutamate:glyoxylate aminotransferase; GS, glutamine synthetase; HPR1, peroxisomal hydroxypyruvate reductase; HPR2, cytosolic hydroxypyruvate reductase; MDH, malate dehydrogenase; NDAin, internal NADH:ubiquinone reductase; PGP, 2PG phosphatase; SGT, serine:glyoxylate aminotransferase; and SHMT, serine hydroxymethyltransferase. The multiple arrows from 3PGA to RubP symbolise Calvin-cycle reactions.

molecular O_2 to produce glyoxylate and H_2O_2 in an irreversible reaction. Similar to the photorespiratory phenotype observed in GOX antisense rice (*Oryza sativa*) plants [13], GOX-deficient maize (*Zea mays*) also requires elevated CO_2 for survival, finally providing clear evidence for the long disputed need of an intact photorespiratory metabolism in C_4 plants [14]. The generated H_2O_2 is decomposed by catalase (CAT). Three CAT isoforms exist in *Arabidopsis* (*Arabidopsis thaliana*), where they form part of a general ROS-scavenging network. One of these enzymes, CAT2, dominates in leaves, and its deletion causes a photorespiratory phenotype [15]. Instead of GOX, cyanobacteria and algae use glycolate dehydrogenase (GLD) to convert glycolate into glyoxylate using NAD^+ as an electron acceptor, which minimises generation of H_2O_2 in these non- or less-compartmented microorganisms. There are also indications for the simultaneous presence of GOX and GLD in green algae [16].

The next step involves two parallel reactions, serine:glyoxylate aminotransferase (SGT) and glutamate:glyoxylate aminotransferase (GGT), transaminating glyoxylate to glycine. SGT prefers serine as the amino donor and deletion of this enzyme leads to a photorespiratory phenotype [17]. GGT uses glutamate produced in the photorespiratory nitrogen cycle as the amino donor but can also use alanine. Two isoforms exist in *Arabidopsis*, where GGT1 represents the major form in leaves [18,19]. It is hypothesised that glyoxylate escaping these transamination reactions under stress conditions is scavenged by a pair of high-affinity glyoxylate reductases, the cytosolic GXR1 and the plastidial GXR2 [20].

In the mitochondrion...

In the mitochondrion, two molecules of glycine yield one molecule of serine by the combined action of glycine decarboxylase (GDC) and serine hydroxymethyltransferase (SHMT). The two enzymes are present in high concentration in the matrix of green leaf mitochondria [21], highly susceptible to oxidation *in vivo* [22], and likely targets for regulation by thioredoxin [23].

GDC is a multienzyme system comprising three enzymes (P-, T- and L-protein) that successively react with a shared lipoylated substrate protein (H-protein). The entire reaction cycle requires one molecule each of glycine, tetrahydrofolate (THF), and NAD^+ to produce one molecule of methylene THF (CH_2-THF). In addition, one molecule each of CO_2 and NH_3 is released (by P- and T-protein, respectively) and NADH is produced (by L-protein). CO_2 is possibly exported as bicarbonate via complex I-associated

γ-carbonic anhydrases [24,25]. Much of the generated NADH is recycled to NAD^+ within the mitochondrion, in a process that is largely uncoupled from ATP synthesis [26], and a likely smaller fraction is exported to the cytosol via the malate shuttle [27]. Notably, GDC null mutants do not survive even in a non-photorespiratory environment (1% CO_2), which is due to the essential role of GDC in one-carbon metabolism [28].

SHMT combines CH_2-THF with a second molecule of glycine to make serine and regenerate THF for GDC. In *Arabidopsis*, only SHMT1 contributes to photorespiratory metabolism [29]. The role of a second mitochondrial SHMT is not known, but similar to cytosolic and plastidial SHMTs it could serve to generate CH_2-THF from serine for biosynthetic purposes [30].

... back to the peroxisome

Serine goes back to the peroxisome where the amino group is transferred to glyoxylate by SGT and the hydroxypyruvate produced is reduced to glycerate by NADH-dependent hydroxypyruvate reductase (HPR1). NADH cannot permeate the peroxisomal membrane and must be generated by peroxisomal malate dehydrogenase (pMDH), consuming malate provided from the chloroplasts and the mitochondria. In contrast to the deleterious effect of interruptions in other C_2 cycle reactions, neither the deletion of HPR1 nor that of pMDH strongly impairs plant growth [31,32]. This is because hydroxypyruvate can move to the cytosol where it is reduced by NADPH-dependent hydroxypyruvate reductase (HPR2). While flux through HPR2 is typically low, this cytosolic bypass allows a redirection of photorespiratory carbon flux if peroxisomal NADH-generation is limiting [31].

Closing the circle

Finally, the plastidial enzyme glycerate 3-kinase (GLYK) completes the C_2 cycle by returning 3PGA, carrying three out of four 2PG carbon atoms back to the Calvin cycle in the chloroplast. GLYK is the only known 3PGA-producing glycerate kinase. Most bacteria and all animals use glycerate 2-kinases [33,34].

Interacting secondary pathways

In addition to the intimate and obligatory intertwining of photorespiration with photosynthesis, research over recent years has also provided evidence for the interaction of this pathway with several other metabolic processes [35–39]. Although a more comprehensive functional gene annotation of photosynthetically competent genomes is likely to provide further evidence for similar interactions, to date the four established interactions which we consider most important are (i) nitrogen assimilation, (ii) respiration, (iii) one-carbon metabolism and associated purine biosynthesis, and (iv) redox signalling. Since redox signalling has been extensively discussed recently [40], we confine ourselves here to the first three interactions.

Nitrogen assimilation

The C_2 cycle requires glutamate to produce glycine from glyoxylate and generates ammonia during CH_2-THF synthesis from glycine (Figure 1). These two processes and the refixation of photorespiratory ammonia form the photorespiratory nitrogen cycle [41], which is intertwined with, but much greater in magnitude than, primary nitrate assimilation [42]. Refixation consumes much energy and requires two chloroplast-localised enzymes, glutamine synthetase (GS2) and ferredoxin-dependent glutamate synthase (Fd-GOGAT). GS2 combines glutamate and ammonia to glutamine, which is used by Fd-GOGAT to provide glutamate from 2-oxoglutarate (2OG) for glycine synthesis and ammonia refixation.

Whilst this link has long been known, recent molecular genetic studies have clearly demonstrated its role in several plant species; however, some controversy remains. Specifically, a report suggesting dual targeting of *GLN2*-encoded GS2 to both chloroplasts and mitochondria [43], with the accumulation in mitochondria having a regulatory rather than enzymatic function, provoked the postulation of several functional modes of photorespiratory ammonia refixation [44]. However, so far GS2 has not been found in any mitochondrial proteomic studies [45].

Much more convincing was the recent demonstration that photorespiratory SHMT1 activity requires the mitochondrial accumulation of Fd-GOGAT [46]. Conversely, antisense reduction of SHMT activity resulted in a shift in the diurnal ammonia metabolism in potato (*Solanum tuberosum*) leaves indicating that internal accumulation of post-photorespiratory ammonia leads to nocturnal activation of GS2 and Fd-GOGAT [47]. The high interdependence of the processes of photorespiration and nitrate assimilation was yet further illustrated in the evaluation of transgenic tomato (*Solanum lycopersicum*) plants deficient in the expression of the mitochondrial isoforms of citrate synthase and isocitrate dehydrogenase, where both sets of plants displayed compromised nitrate assimilation and altered rates of photorespiration [48,49].

Respiration

With the exception of the above discussed interaction of photorespiration with photosynthesis and N-metabolism, knowledge of the interaction between photorespiration and mitochondrial respiration outstrips that of any other pathway. Indeed the relative carbon fluxes through each of these three pathways are, to a large extent, mutually dependent [36]. Two of these interactions are particularly well characterised whilst data is accumulating that indicates even more extensive crosstalk. The most established connections are those presented in Figure 2a and b, namely allosteric regulation of the tricarboxylic acid (TCA) cycle by immediate products of the reaction catalysed by GDC (or closely related derivatives thereof) and the essential NAD^+-regenerating interaction between the same enzyme and components of the mitochondrial electron transport chain. Genetic evidence has confirmed the allosteric regulation, supporting previous results obtained by classical *in vitro* biochemistry means [35], whilst the NAD^+-regenerating interaction provides a plausible role for the nonphosphorylating bypasses of the mitochondrial electron transport chain. In support of this suggestion, analysis of *Arabidopsis* lines in which the expression of the uncoupling protein UCP1 was knocked out revealed that this protein was also essential for efficient operation of photorespiration and hence photosynthesis

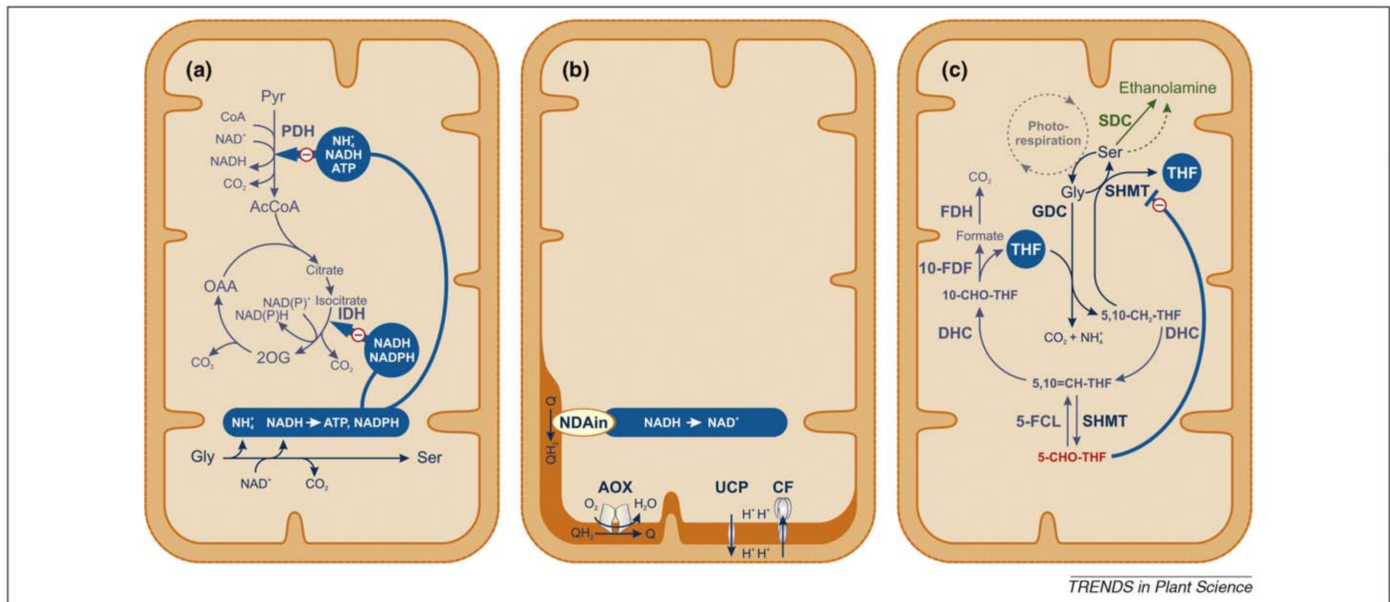

Figure 2. Metabolic interactions of photorespiration. **(a)** Allosteric inhibition of respiratory reactions in the mitochondria of illuminated leaves. Pyruvate dehydrogenase (PDH) and isocitrate dehydrogenase (IDH) activities are decreased. The products formed directly (NADH and ammonia) or indirectly (ATP and NADPH) by photorespiration and considered pivotal in this interaction are shaded in blue. This panel is modified from Bykova et al. [35]. **(b)** The oxidation of photorespiratory glycine in the mitochondrial matrix requires the recycling of NAD^+. This can be achieved by entry of electrons from NADH into the mitochondrial electron transport chain. These extra electrons may be accommodated by a non-proton-pumping pathway that consists of the internal NADH:ubiquinone reductase (NDAin) and alternative oxidase (AOX), such that electron flow is not restricted by the rate of ATP synthesis and would also support the considerable export of citrate required to sustain nitrogen assimilation. The mitochondrial uncoupling protein (UCP) bypasses ATP generation. This panel is modified from Fernie et al. [70]. **(c)** Interaction of photorespiration with mitochondrial one-carbon metabolism including production of ethanolamine and recycling of the inhibitor 5-CHO-THF to tetrahydrofolate (THF) in the THF cycle. THF itself is highlighted with a blue background to indicate its involvement in multiple places. This panel is modified from Collakova et al. [38]. Note that in all three instances a clear link between photorespiration and nitrogen assimilation is apparent. Abbreviations are 2OG, 2-oxoglutarate; 5-FCL, 5-formyl-THF cycloligase; 10-FDF, 10-formyl THF deformylase; AcCoA, acetyl CoA; AOX, alternative oxidase; DHC, 5,10-methylene-THF dehydrogenase/5,10-methenyl-THF cyclohydrolase; FDH, formate dehydrogenase; GDC, glycine decarboxylase; NDAin, internal NADH:ubiquinone reductase; Pyr, pyruvate; SHMT, serine hydroxymethyltransferase; SDC, serine decarboxylase; and THF, tetrahydrofolate.

[50]. That said, a study of the CMSI tobacco (*Nicotiana tabacum*) mutant, deficient in the expression of complex I of the mitochondrial electron transport chain, has also revealed it to be essential for photosynthesis under photorespiratory conditions [37]. In both cases it is believed that these proteins are required to ensure the subcellular redox conditions which potentiate efficient photosynthesis.

One-carbon metabolism

One-carbon metabolism is of great importance to plants supplying precursors for protein, nucleic acid and pantothenate synthesis as well as being incorporated into lignin, alkaloids and betaines [30,51]. Transfers of one-carbon units have long been documented to be intimately linked to the photorespiratory pathway at the mitochondrial glycine-to-serine conversion, catalysed by GDC and SHMT1. However, only recently the use of reverse genetics has begun to unlock the precise nature of the convergence of these pathways. Figure 2c combines knowledge from two recent studies illustrating the links between photorespiration and ethanolamine or THF metabolism, respectively. Recent functional evidence for interaction of photorespiration and ethanolamine was provided by the analysis of *Arabidopsis* plants in which expression of the *HPR1* and *HPR2* genes was knocked out [31]. As a result, these plants accumulated considerably higher amounts of ethanolamine. Although the exact metabolic route by which this occurred has yet to be clarified, it seems likely that it will involve the reaction catalysed by serine decarboxylase [52]. The link between photorespiration and THF metabolism was elegantly demonstrated by the evaluation of 10-formyl THF deformylase (10-FDF) knockout mutants of *Arabidopsis* [38]. In this study, double knockout of the two genes which encode 10-FDF resulted in dramatic accumulation of glycine and lethality in photorespiratory conditions. This demonstrates that the removal of 5-formyl THF, which is produced in a side-reaction of SHMT1 and a strong inhibitor of the SHMT reaction, and its recycling to THF are essential for the continued operation of the C_2 cycle. Despite the importance of these findings, many unanswered questions remain concerning the importance and metabolic prioritisation inherent to these interactions.

Photorespiration coevolved with oxygenic photosynthesis in cyanobacteria

During the last five years, the nucleotide sequences of about 50 cyanobacterial genomes became available, allowing the comprehensive analysis of 2PG metabolism in these organisms [4,53–55]. *In silico* analyses indicated the presence of two possible pathways, one similar to plant photorespiratory metabolism and a second similar to the bacterial glycerate pathway, in which glyoxylate is converted to glycerate via tartronic semialdehyde (Figure 3).

Most functional studies have focussed on the model strain *Synechocystis* sp. PCC 6803, in which mutants for almost all candidate genes were generated and the metabolic consequences of the respective knockouts studied [4,54,55]. Mutants deficient in single enzymes potentially contributing to 2PG metabolism did not show a photorespiratory phenotype, i.e. they could be selected and grown under ambient conditions (in cultures bubbled with normal air). Following this initial support of the *in silico* predictions, the

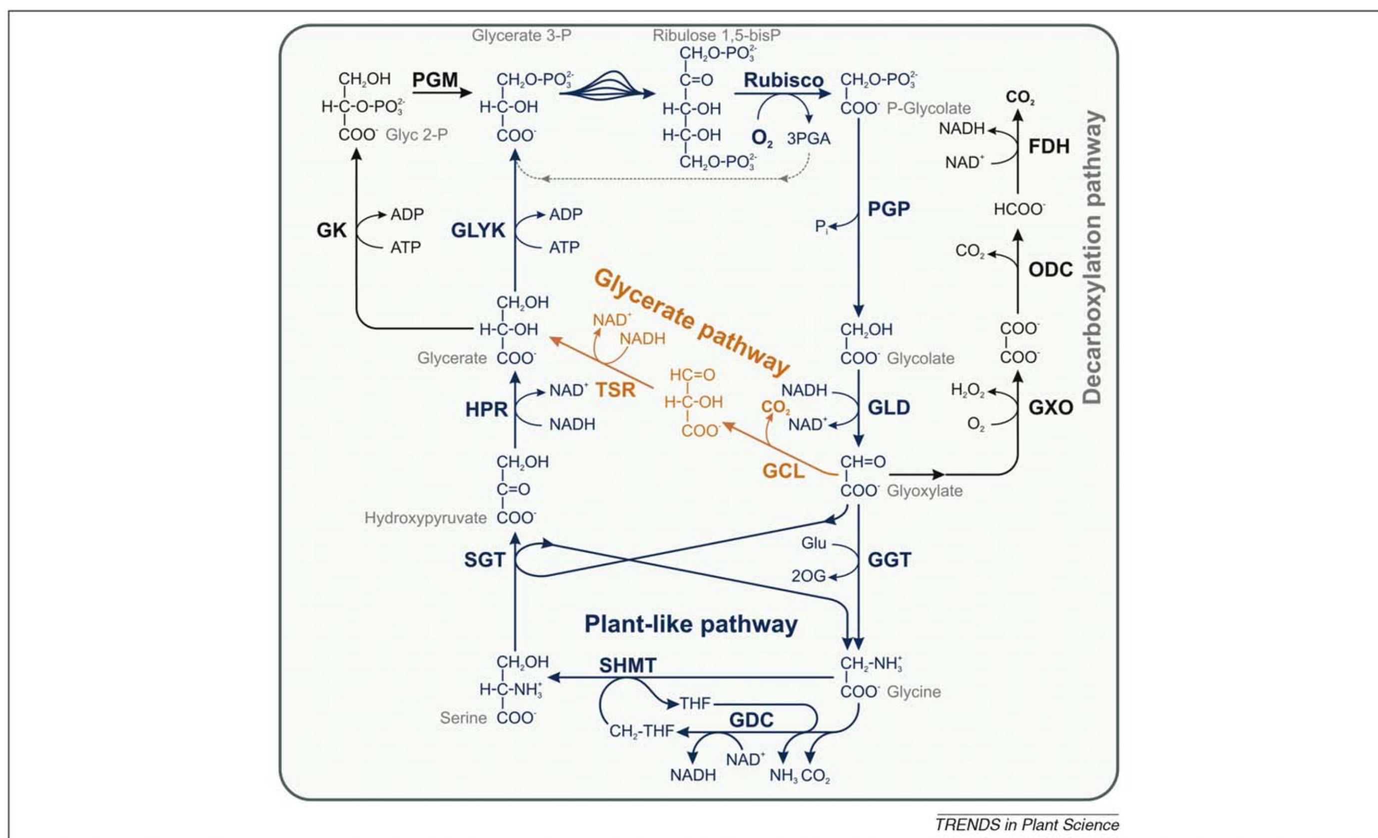

Figure 3. Cyanobacterial 2PG metabolism comprises overlapping plant-like (blue) and bacterial pathways (orange and black). Plant GOX-like enzymes are present in only a few cyanobacteria. In most cyanobacteria, glycolate dehydrogenases (GLD) produce glyoxylate, and 3PGA is formed by glycerate 3-kinase (GLYK), while the model strain *Synechocystis* 6803 uses 2PGA-forming glycerate 2-kinase (GK) in combination with phosphoglyceromutase (PGM). Cyanobacteria can circumvent the glycine-into-serine conversion by directly converting glyoxylate into hydroxypyruvate with glyoxylate carboligase (GCL) and tartronic semialdehyde reductase (TSR). Some species including *Synechocystis* are able to completely decompose glyoxylate to CO_2 via glyoxylate oxidase (GXO), oxalate decarboxylase (ODC) and formate dehydrogenase (FDH). The multiple arrows from 2PGA to RubP symbolise Calvin-cycle reactions.

presence of two partially overlapping photorespiratory pathways was verified by studies with double and triple mutants [4,55]. These experiments also revealed a third metabolic route for the complete oxidation of glyoxylate via oxalate and formate to CO_2 in this particular strain, but similar proteins are not encoded in the genomes of most other cyanobacteria [56]. Only *Synechocystis* triple mutants that were defective in all three pathways required high CO_2 for growth and bleached after transfer to ambient conditions, i.e. they showed a photorespiratory phenotype comparable to corresponding plant mutants. The same high-CO_2-requiring phenotype was caused by blocking the glycolate oxidation step, which directly precedes the branching into the three separate routes [4]. Other studies showed that an intact photorespiratory metabolism contributes to the protection of *Synechocystis* from photoinhibition [57], an effect that has also been shown in plants [58].

Cyanobacteria were the first prokaryotes that produced reducing equivalents for CO_2 assimilation by the oxidation of water, and hence were also the first organisms in which Rubisco was directly exposed to O_2. These ancient cyanobacteria probably lived in structures similar to present-day stromatolites, covered by thick layers of extracellular polysaccharides and inorganic sediments. In such containments, O_2 could have possibly accumulated to considerable levels and stimulated 2PG synthesis [59].

Extant cyanobacteria depend on CO_2 concentrating mechanisms (CCM) to assimilate inorganic carbon at the present-day high O_2 concentrations. The combination of high-affinity CO_2 and bicarbonate uptake with a sequestration of Rubisco in carboxysomes strongly favours RubP carboxylation and inhibits oxygenation in these microcompartments [60]. It was hence long thought that photorespiratory metabolism does not occur in cyanobacteria [61]; however, current hypotheses point to an evolution of CCMs only about 360–300 million years ago, during an intermittent drop in atmospheric CO_2 levels and a rise in O_2 levels to $> 30\%$ in the Carboniferous Period [60,62,63].

Detailed comparisons of cyanobacterial genomes point to the presence of a C_2 cycle as well as bacterial glycerate pathway enzymes in all cyanobacteria, suggesting that the respective metabolic routes evolved or already existed at the beginning of cyanobacterial history. Plants apparently lost the glycerate pathway enzymes. In contrast, many enzymes of the C_2 cycle have been conserved among cyanobacteria and plants [4]. It is remarkable that even the picoplanktonic *Prochlorococcus* and *Synechococcus* strains harbour a complete set of ‘photorespiratory’ genes. These cyanobacteria show a significant genome reduction because, due to the adaptation to the relatively constant oceanic environment, many genes for proteins involved in the acclimation to fluctuating environments were successively deleted [64]. The occurrence of not only one but two redundant 2PG-recycling routes in most cyanobacteria, the plant-like C_2 cycle and the glycerate pathway, suggests that 2PG might not be just a toxic metabolite but a valuable carbon resource.

On the other hand, cyanobacteria are very diverse and they also show much variation in 2PG metabolism. For example, the additional non-recycling decarboxylation pathway exists in only very few strains and likely evolved later under specific environmental selection, where the scavenging of photorespiratory carbon could have been less important than the dissipation of excess energy. Moreover, a plant-type 3PGA-forming GLYK is present in most cyanobacteria, whereas *Synechocystis* uses a bacterial-type 2PGA-forming glycerate kinase and requires phosphoglyceromutase to produce 3PGA [34]. In addition, cyanobacterial 2PG phosphatases are not related to the corresponding plant enzyme and glycolate is oxidised to glyoxylate by GLD in most cyanobacteria.

All this suggests that 2PG metabolism is essential for the viability of all organisms that perform oxygenic photosynthesis, regardless of whether they are prokaryotes, eukaryotic algae or plants. In C_3 plants, photorespiratory metabolism serves to (i) recycle the large amounts of 2PG generated during illumination back to 3PGA and (ii) prevent poisoning by noxious metabolites such as 2PG itself [1], glyoxylate [65] or glycine [66]. C_4 plants require an intact 2PG metabolism for survival in ambient air [14] but, due to the more efficient mechanism to deliver CO_2 to Rubisco by the C_4 photosynthetic cycle, produce much less 2PG than C_3 plants. This resembles the metabolic situation in extant cyanobacteria, which also concentrate CO_2 in the vicinity of Rubisco, and some data suggest that detoxification of 2PG and derived compounds could be more important than 2PG-recycling in these prokaryotes [4,66].

Future challenges

Photorespiration is an important multifaceted high-throughput process. It is also a determining factor of C_3 crop biomass production and closely related to the evolution of highly productive C_4 crops. Recent technological developments have addressed important questions concerning the photorespiratory pathway evolution and how it interacts with other cellular processes. Nevertheless, several important areas still need further investigation; for example, knowledge about participating membrane translocators is scarce and the regulation of photorespiration in the context of whole-cell metabolism and changing environments is still an open question.

Photorespiratory metabolism and its interaction with other cellular metabolisms show an unexpected complexity and the evaluation of transcript profiles has produced long lists of candidate plant genes which may functionally interact with photorespiration, potentially adding another level of complexity [40]. Subcellular inventories of protein location [67] as well as proteomic analysis of isolated organelles [68] may help to unravel this fascinating network. Future research will also need to analyse a larger diversity of photosynthetic organisms to achieve a better understanding of the evolution from cyanobacterial photorespiration to the highly compartmented photorespiratory metabolism of plants. Until now, the majority of these studies have been carried out with C_3 land plants with focus at a single molecular level such as transcripts, proteins or metabolites and as such do not provide a fully integrated view of photorespiration. Addressing this challenge will likely again lead to a myriad of complex interactions which are associated with this enigmatic pathway.

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