

1 Pyruvate:ferredoxin oxidoreductase and low abundant ferredoxins support  
2 aerobic photomixotrophic growth in cyanobacteria

3 Yingying Wang<sup>a</sup>, Xi Chen<sup>a</sup>, Katharina Spengler<sup>a</sup>, Karoline Terberger<sup>a</sup>, Marko Boehm<sup>a,b</sup>, Jens Appel<sup>a,b</sup>,  
4 Thomas Barske<sup>c</sup>, Stefan Timm<sup>c</sup>, Natalia Battchikova<sup>d</sup>, Martin Hagemann<sup>c</sup>, Kirstin Gutekunst<sup>a,b</sup>

5 <sup>a</sup>Department of Biology, Botanical Institute, Christian-Albrechts-University, D-24118 Kiel,  
6 Germany; <sup>b</sup>Department of Molecular Plant Physiology, Bioenergetics in Photoautotrophs,  
7 University of Kassel, D-34132 Kassel, Germany, <sup>c</sup>Plant Physiology Department, University of  
8 Rostock, D-18059 Rostock, Germany, <sup>d</sup>Department of Biochemistry, Molecular Plant Biology,  
9 University of Turku, FI-20014 Turku, Finland

10 \*Kirstin Gutekunst

11 **Email:** [kirstin.gutekunst@uni-kassel.de](mailto:kirstin.gutekunst@uni-kassel.de)

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15 performed research, all authors analyzed data, YW and KG wrote the first draft of the paper, all authors  
16 contributed to the final version.

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19

20 **Abstract**

21 The decarboxylation of pyruvate is a central reaction in the carbon metabolism of all organisms.  
22 Both the pyruvate:ferredoxin oxidoreductase (PFOR) and the pyruvate dehydrogenase (PDH)  
23 complex catalyze this reaction. Whereas PFOR reduces ferredoxin, the PDH complex utilizes NAD<sup>+</sup>.  
24 Anaerobes rely on PFOR, which was replaced during evolution by the PDH complex found in  
25 aerobes. Cyanobacteria possess both. Our data challenge the view that PFOR is exclusively utilized  
26 for fermentation. Instead, we show, that the cyanobacterial PFOR is stable in the presence of  
27 oxygen *in vitro* and is required for optimal photomixotrophic growth under aerobic conditions  
28 while the PDH complex is inactivated under the same conditions. We found that cells rely on a  
29 general shift from utilizing NAD(H)-dependent to ferredoxin-dependent enzymes under these  
30 conditions.

31 The utilization of ferredoxins instead of NAD(H) saves a greater share of the Gibbs free energy,  
32 instead of wasting it as heat. This obviously simultaneously decelerates metabolic reactions as  
33 they operate closer to their thermodynamic equilibrium. It is common thought that during  
34 evolution, ferredoxins were replaced by NAD(P)H due to their higher stability in an oxidizing  
35 atmosphere. However, utilization of NAD(P)H could also have been favored due to a higher  
36 competitiveness because of an accelerated metabolism.

## 37 Introduction

### 38 *FeS clusters, pyruvate:ferredoxin oxidoreductase and ferredoxins*

39 Live evolved under anaerobic conditions in an environment that was reducing and replete with  
40 iron and sulfur. Later on, hydrogen escape to space irreversibly oxidized Earth (1, 2). Prebiotic  
41 redox reactions, that took place on the surfaces of FeS minerals, are at present mimicked by  
42 catalytic FeS clusters in a plethora of enzymes and redox carriers (3, 4). One example are  
43 ferredoxins, that are small, soluble proteins containing 4Fe4S, 3Fe4S or 2Fe2S clusters and shuttle  
44 electrons between redox reactions. They display a wide range of redox potentials between -240  
45 mV to -680 mV and are involved in a variety of metabolic pathways (5). Ferredoxins are among  
46 the earliest proteins on Earth and are accordingly present in all three kingdoms of life (6). FeS  
47 enzymes are especially widespread in anaerobes (7).

48 The advent of oxygenic photosynthesis necessitated adaptations, as especially 4Fe4S clusters are  
49 oxidized and degraded to 3Fe4S in the presence of oxygen resulting in inactivated enzymes (7-9).  
50 In aerobes, FeS enzymes are commonly replaced by FeS cluster free isoenzymes or alternative  
51 metabolic strategies (8). One well known example is the replacement of the FeS cluster containing  
52 pyruvate:ferredoxin oxidoreductase (PFOR), which catalyzes the decarboxylation of pyruvate  
53 during fermentation in anaerobes, by the pyruvate dehydrogenase (PDH) complex for respiration  
54 in aerobes (7, 10). Both enzymes catalyze the same reaction, whereat PFOR uses ferredoxin as  
55 redox partner and the PDH complex reduces NAD<sup>+</sup>. PFORs are evolutionary old enzymes. They are  
56 widespread in autotrophic and heterotrophic bacteria, in archaea, amitochondriate eukaryotic  
57 protists, hydrogenosomes as well as in cyanobacteria and algae (7). Depending on organism,  
58 metabolism and conditions, PFOR can be involved in the oxidation of pyruvate for heterotrophy  
59 or alternatively catalyze the reverse reaction by fixing CO<sub>2</sub> and forming pyruvate from acetyl CoA  
60 for an autotrophic lifestyle (11-13). The enzyme might have played a central role for the evolution  
61 of both autotrophic and heterotrophic processes from the very beginning (14). PFOR indeed  
62 participates as CO<sub>2</sub> fixing enzyme in four out of seven currently known and most ancient  
63 autotrophic pathways (reverse tricarboxylic acid (rTCA) cycle, reversed oxidative tricarboxylic acid  
64 (roTCA) cycle, reductive acetyl-CoA pathway, and dicarboxylate/hydroxybutyrate (DC/HB) cycle)  
65 (12, 15). PFORs contain one to three 4Fe4S clusters and get in general readily inactivated by  
66 oxygen upon purification. So far, there are only three reported exceptions to this rule: the PFORs  
67 of *Halobacterium halobium*, *Desulfovibrio africanus* and *Sulfolobus acidocaldarius* are stable *in vitro*  
68 in the presence of oxygen (11, 16-19). Even though all three enzymes are stable upon  
69 purification in the presence of oxygen, anaerobic conditions are required for *in vitro* maintenance  
70 of enzyme activities with the PFORs of *Desulfovibrio africanus* and *Sulfolobus acidocaldarius*. The  
71 enzyme of *Halobacterium halobium* is the only reported PFOR so far, which is active under aerobic  
72 conditions *in vitro* (19, 20). *In vivo* studies on these PFORs under aerobic conditions are missing.  
73 Ferredoxins that contain 4Fe4S clusters are likewise vulnerable to oxidative degradation. In the  
74 evolution from anoxygenic to oxygenic photosynthesis, the soluble 4Fe4S ferredoxin, which  
75 transfers electrons from FeS-type photosystems PSI to other enzymes in anoxygenic  
76 photosynthesis was replaced by an oxygen-tolerant 2Fe2S ferredoxin (9). In addition, ferredoxins  
77 have in general been complemented or replaced by NAD(P)H as alternative, oxygen-insensitive  
78 reducing agents in aerobes (10).

79

### 80 *The pyruvate dehydrogenase complex*

81 The PDH complex, which utilizes NAD<sup>+</sup> is composed of the three subunits: pyruvate  
82 dehydrogenase (E1), dihydrolipoyl transacetylase (E2) and dihydrolipoyl dehydrogenase (E3). It

83 catalyzes the irreversible decarboxylation of pyruvate. The PDH complex is active under oxic  
84 conditions but gets inactivated under anaerobic conditions in both prokaryotes and eukaryotes,  
85 albeit via distinct mechanisms. In the absence of oxygen NADH/NAD<sup>+</sup> ratios rise as respiration  
86 does no longer oxidize the NADH coming from the PDH complex and the subsequent reactions of  
87 the TCA cycle. In prokaryotes, as e.g. *E. coli*, NADH interacts with the dihydrolipoyl dehydrogenase  
88 (E3) subunit and thereby inhibits the PDH complex (21, 22). In eukaryotes, the PDH complex gets  
89 inactivated at high NADH/NAD<sup>+</sup> ratios via phosphorylation of highly conserved serine residues in  
90 the pyruvate dehydrogenase (E1) subunit (23).

91 *Synechocystis* sp. PCC 6803 is a cyanobacterium that performs oxygenic photosynthesis and lives  
92 photoautotrophically by fixing CO<sub>2</sub> via the Calvin-Benson-Bassham (CBB) cycle. In the presence of  
93 external carbohydrates these are metabolized additionally, resulting in a photomixotrophic  
94 lifestyle. In darkness *Synechocystis* switches to a heterotrophic or under anaerobic conditions to  
95 a fermentative lifestyle. As in many cyanobacteria, pyruvate can be either decarboxylated via  
96 PFOR or alternatively via the PDH complex in *Synechocystis*. PFOR is assumed to be involved in  
97 fermentation under anoxic conditions and the PDH complex in aerobic respiration. The  
98 observation that *pfor* is transcribed under photoautotrophic conditions in the presence of oxygen  
99 in the cyanobacteria *Synechococcus* sp. PCC 7942 and *Synechocystis* was therefore surprising but  
100 is well in line with the observation that other enzymes assigned to anaerobic metabolism in  
101 eukaryotes are expressed in the presence of oxygen as well (10, 24). *Synechoystis* possesses a  
102 network of up to 11 ferredoxins containing 2Fe2S, 3Fe4S and 4Fe4S clusters (25, 26). The 2Fe2S  
103 ferredoxin 1 (Ssl0020) is essential and by far the most abundant ferredoxin in *Synechocystis* and  
104 is the principal acceptor of photosynthetic electrons at PSI (27). Structures, redox potentials and  
105 distinct functions have been resolved for some of the alternative low abundant ferredoxins,  
106 however, the metabolic significance of the complete network is still far from being understood  
107 (25, 26, 28-31).

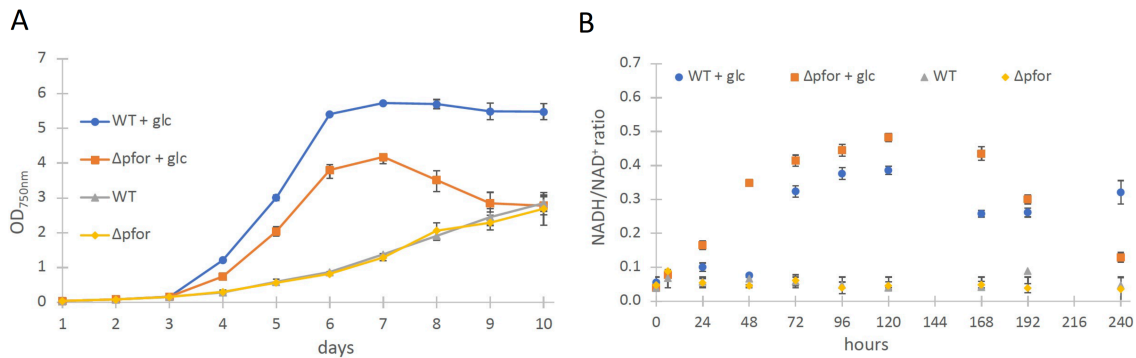
108 In this study we show that PFOR and low abundant ferredoxins are required for optimal  
109 photomixotrophic growth under oxic conditions. In line with this we found that the cyanobacterial  
110 PFOR is stable in the presence of oxygen *in vitro*. PFOR and ferredoxins can functionally replace  
111 the NAD<sup>+</sup> dependent PDH complex, which we found to get inactivated at high NADH/NAD<sup>+</sup> ratios.  
112 Likewise, the ferredoxin dependent F-GOGAT (glutamine oxoglutarate aminotransferase) is  
113 essential for photomixotrophic growth as well and cannot be functionally replaced by the NADH  
114 dependent N-GOGAT. The cells obviously switch in their utilization of isoenzymes and redox pools.  
115 However, the key factor for this switch is not oxygen but are the highly reducing conditions within  
116 the cells. Our data suggest that the pool of ferredoxins in *Synechocystis* functions as an overflow  
117 basin to shuttle electrons, when the NADH/NAD<sup>+</sup> pool is highly reduced.

118

## 119 Results

120 The roles of PDH complex and PFOR were studied in *Synechocystis* under different growth  
121 conditions. PDH could not be deleted from the genome indicating that this enzyme complex is  
122 essential, whereas *pfor* was knocked out in a previous study (28). In line with this we found that  
123 all fully sequenced cyanobacteria contain a PDH complex, which points out its significance and  
124 that 56 % thereof possess a PFOR in addition (Fig. 1S). We unexpectedly found that the  
125 *Synechocystis*  $\Delta pfor$  deletion mutant was impaired in its photomixotrophic growth under oxic  
126 conditions in continuous light. Growth impairment was typically visible starting around day three  
127 to six of the growth experiment (Fig. 1A and 3A). Under photoautotrophic conditions  $\Delta pfor$  grew  
128 just as the WT (Fig. 1A). The oxygen concentration in the photomixotrophic cultures was close to

129 saturation around 250  $\mu\text{Mol O}_2$  throughout the growth experiment (Fig. S2). Studies on the  
130 transcription of *pfor* and the alpha subunit of the pyruvate dehydrogenase (E1) of *pdhA* revealed  
131 that both genes are transcribed under photomixo- and photoautotrophic conditions (Fig. S3).  
132 These observations raised two questions: Why is the PDH complex, which catalyzes the same  
133 reaction as PFOR, not able to compensate for the loss of PFOR? And how can PFOR, which is  
134 assumed to be oxygen-sensitive, be of physiological relevance in the presence of oxygen?  
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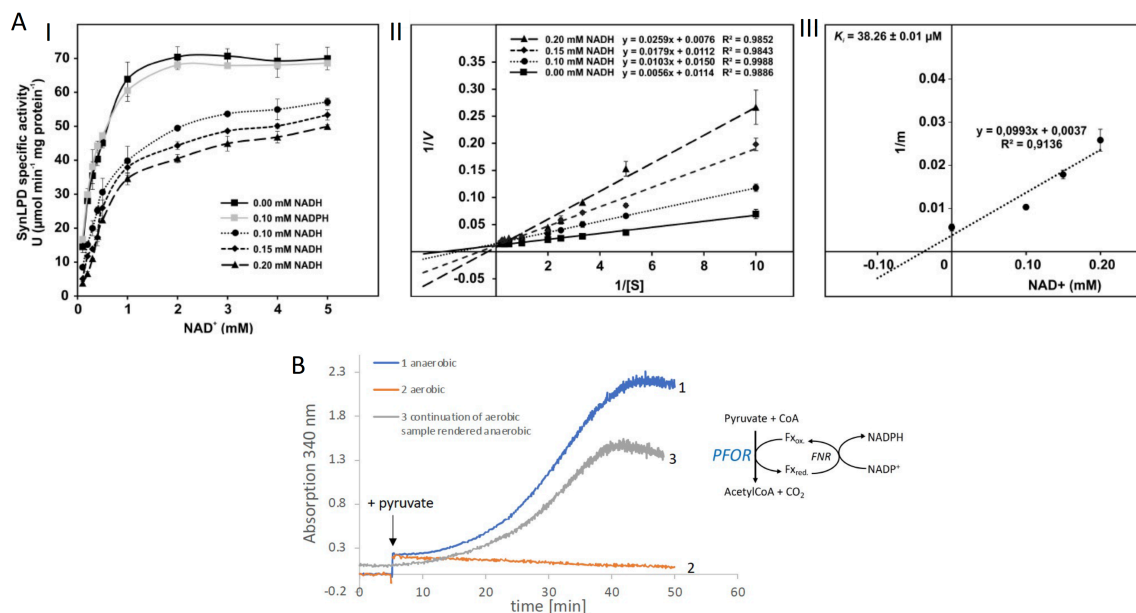


136  
137 Figure 1: (A) Growth and (B) NADH/NAD<sup>+</sup> ratios of wild type (WT) and  $\Delta pfor$  under photoautotrophic and  
138 photomixotrophic (+ glc) conditions in continuous light. Shown are mean values  $\pm$  SD from at least 3  
139 replicates.  
140

141 The most obvious assumption is that the PDH complex might get inactivated under  
142 photomixotrophic conditions. As the PDH complex gets inactivated at high NADH/NAD<sup>+</sup> ratios in  
143 prokaryotes and eukaryotes, we wondered if NADH/NAD<sup>+</sup> ratios might be increased under  
144 photomixotrophic conditions. Corresponding measurements confirmed this assumption.  
145 Whereas NADH/NAD<sup>+</sup> ratios were stable under photoautotrophic conditions in WT and  $\Delta pfor$  they  
146 raised three to fourfold in the first five days of photomixotrophic growth, exactly in that period in  
147 which the growth impairment of  $\Delta pfor$  in the presence of glucose was most apparent (Fig.1B).

148 In eukaryotes serine kinases phosphorylate three conserved serine residues of the pyruvate  
149 dehydrogenase (E1) at high NADH/NAD<sup>+</sup> ratios and thereby inhibit the PDH complex. In line with  
150 this, photomixotrophic growth of two out of ten serine/threonine protein kinase (spk) deletion  
151 mutants was affected, which indicates that phosphorylation of enzymes is relevant for optimal  
152 photomixotrophic growth in *Synechocystis* (Fig. S4).

153 In eukaryotes, phosphorylation of serine residues at sites 2 and 3 of the E1 subunit reduces  
154 enzyme activity moderately, whereas phosphorylation of the serine residue in site 1 alone  
155 completely inhibits the PDH complex (32-34). In order to check if the E1 subunit of *Synechocystis*  
156 contains these conserved serine residues as well, sequence alignments were performed and  
157 revealed that serine residues 2 and 3 are absent, whereas the serine residue 1 is present in  
158 *Synechocystis* and furthermore highly conserved in the E1 subunit of all 932 cyanobacterial PdhA  
159 sequences that were analyzed (Fig. S5 and S6). Immunoblot analyses indicate that the PdhA  
160 subunit of the PDH complex might either degrade or might get phosphohorylated at high  
161 NADH/NAD<sup>+</sup> ratios (Fig. S7 and S8). However, this could not be shown unambiguously as  
162 phosphorylation could not be confirmed by mass spectrometry (Table S3).  
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166 Figure 2: (A) Inhibition of the PDH complex in *Synechocystis* via inactivation of the dihydrolipoyl  
167 dehydrogenase (E3) subunit (SynLPD) by NADH. I: The rate of recombinant SynLPD activity (3 mM DL-  
168 dihydrolipoic acid) as a function of NAD<sup>+</sup> (0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4 and 5 mM) reduction in the presence  
169 of the indicated NADH concentrations (0, 0.1, 0.15 and 0.2 mM). NADPH (0.1 mM) was used as a control to  
170 demonstrate the specificity of NADH inhibition. Specific enzyme activity is expressed in  $\mu\text{mol NADH per min}^{-1}$   
171  $\text{mg protein}^{-1}$  at 25°C. II: Lineweaver-Burk plots of enzyme activities at four NADH concentrations. III: The  
172 inhibitor constant ( $K_i$ ) was estimated by linear regression of (I) the slopes of the three Lineweaver-Burk plots  
173 at the four NADH concentrations versus (II) the NADH concentration. Shown are mean values  $\pm$  SD from at  
174 least 3 technical replicates. (B) Enzyme activity of PFOR that was purified in the presence of oxygen. PFOR  
175 activity was measured in the presence of FNR, ferredoxin and NADP<sup>+</sup>. The reaction was started by addition  
176 of 10 mM pyruvate as indicated by the arrow. Assay 1 (blue line): The assay mixture was kept anaerobic  
177 with 40 mM glucose, 40 U glucose oxidase and 50 U catalase, showing that PFOR, which was purified in the  
178 presence of oxygen, is active. Assay 2 (red line): Assay 2 had the same composition as assay 1 but glucose,  
179 glucose oxidase and catalase were omitted, showing that anaerobic conditions are required for activity of  
180 PFOR *in vitro*. Assay 3 (grey line): This assay is the continuation of the measurement of assay 2 after addition  
181 of glucose, glucose oxidase and catalase. Representative traces of three replicates are shown.

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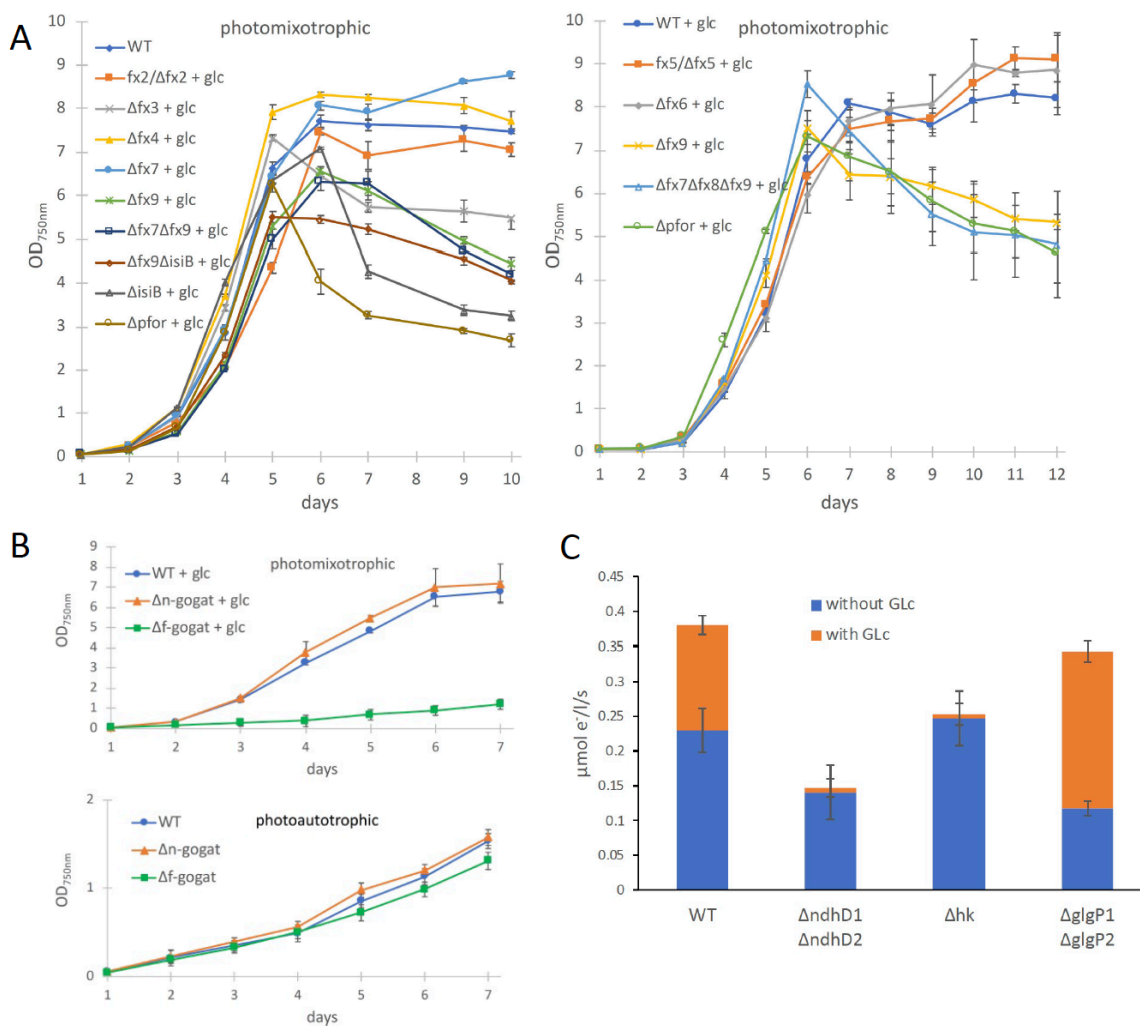
183 For prokaryotes it was shown that the PDH complex is inhibited by a distinct mechanism directly  
184 by NADH which binds to the dihydrolipoyl dehydrogenase (E3) subunit of the PDH complex.  
185 Therefore, the recombinant dihydrolipoyl dehydrogenase of *Synechocystis* (SynLPD) was tested in  
186 an *in vitro* assay with different NADH concentrations. The enzyme indeed loses activity at higher  
187 NADH/NAD<sup>+</sup> ratios, whereas NADPH has no effect (Fig. 2A). The SynLPD activity was completely  
188 inhibited by NADH with an estimated  $K_i$  of 38.3  $\mu\text{M}$  (Fig. 2A). Hence, the enzyme activity dropped  
189 to approximately 50% at a NADH/NAD<sup>+</sup> ratio of 0.1 (e.g. at 0.2 mM NADH in the presence of 2 mM  
190 NAD<sup>+</sup>). Please note, that much higher NADH/NAD<sup>+</sup> ratios (> 0.4) were measured in  
191 photomixotrophic cells of *Synechocystis* (see Fig. 1B). This points to an efficient inhibition of PDH  
192 activity via the highly decreased function of the E3 subunit (SynLPD). NADH/NAD<sup>+</sup> ratios above 0.1  
193 could not be tested in the enzyme assays due to the high background absorption of the added  
194 NADH, which prevented SynLPD activity detections. Taken together these measurements  
195 convincingly show that the PDH complex is most likely inhibited under photomixotrophic

196 conditions at high NADH/NAD<sup>+</sup> ratios, which provides evidence that pyruvate oxidation must be  
197 performed instead via PFOR and gives an explanation for the importance of PFOR under these  
198 conditions.

199 As the cyanobacterial PFOR is regarded as an oxygen sensitive enzyme that exclusively supports  
200 fermentation under anaerobic conditions, we overexpressed the enzyme and purified it in the  
201 presence of oxygen in order to check for its stability under aerobic conditions (Fig. S9, S10, S11C).  
202 Enzymatic tests revealed that PFOR from *Synechocystis* was indeed stable under aerobic  
203 conditions *in vitro*, which means that the enzyme was not degraded and kept its activity but  
204 required anoxic conditions for the decarboxylation of pyruvate (Fig. 2B) as reported for the oxygen  
205 stable PFORs of *Desulfovibrio africanus* and *Sulfolobus acidocaldarius* (11, 16).

206 In contrast to the PDH complex, PFOR transfers electrons from pyruvate to oxidized ferredoxin.  
207 In order to investigate if any of the low abundant ferredoxins (Fx) might be of importance for  
208 photomixotrophic growth, respective deletion mutants were generated (Table S1 and S2, Fig.  
209 S11A) and tested for their ability to grow under photoautotrophic and photomixotrophic  
210 conditions. To this end *fx3* (*slr1828*), *fx4* (*slr0150*), *fx6* (*ssl2559*), *fx7* (*sll0662*) and *fx9* (*slr2059*)  
211 could be completely deleted from the genome, whereas *fx2* (*sll1382*) and *fx5* (*slr0148*) kept some  
212 wild type copies of the genes. We did furthermore not succeed to delete *fx8* (*ssr3184*). Flavodoxin  
213 (*isiB*; *sll0284*), which replaces ferredoxins functionally under Fe-limitation was deleted as well. In  
214 addition, the double mutants  $\Delta fx7\Delta fx9$  and  $\Delta fx9\Delta isiB$  as well as the triple mutant  $\Delta fx7\Delta fx8\Delta fx9$   
215 were generated. Photoautotrophic growth of all these ferredoxin deletion mutants was similar to  
216 the WT (Fig. S12). However, under photomixotrophic conditions deletion of either *fx3*, *fx9* or  
217 flavodoxin (*isiB*) resulted in a growth behavior that was similar to  $\Delta pfor$  (Fig. 3A).

218 These results indicate that there might be a general shift to utilize the ferredoxin pool as soon as  
219 the NADH/NAD<sup>+</sup> pool is over reduced. Beside the PFOR/PDH complex couple, GOGAT (glutamine  
220 oxoglutarate aminotransferase) is as well present in form of two isoenzymes in *Synechocystis* that  
221 either utilizes reduced ferredoxin (F-GOGAT; *sll1499*) or NADH (N-GOGAT; *sll1502*). In line with  
222 our assumption that ferredoxin utilization is preferred in over reduced cells after glucose addition,  
223 we hypothesized that F-GOGAT might be required for optimal photomixotrophic growth.  
224 Respective deletion mutants were generated (Table S1 and S2, Fig. S11B) and revealed that  
225 neither  $\Delta f-gogat$  nor  $\Delta n-gogat$  were impaired in their growth under photoautotrophic conditions,  
226 whereas  $\Delta f-gogat$  displayed a strong growth impairment under photomixotrophic conditions in  
227 contrast to  $\Delta n-gogat$  and the WT (Fig. 3B). These data indicate that cells indeed rely on a general  
228 switch from utilizing NAD(H) to utilizing ferredoxins for optimal photomixotrophic growth. It was  
229 recently shown that photosynthetic complex I (NDH1) exclusively accepts electrons from reduced  
230 ferredoxin instead of NAD(P)H (35). Photosynthesis continues under photomixotrophic  
231 conditions. However, in addition to water oxidation at photosystem II (PSII), electrons from  
232 glucose oxidation can as well enter the respiratory/photosynthetic electron transport chain and  
233 eventually arrive at photosystem I (PSI) to support anoxygenic photosynthesis. Anoxygenic  
234 photosynthesis thus uses electrons from glucose oxidation that enter the  
235 respiratory/photosynthetic electron transport chain and are excited at PSI.  
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Figure 3: (A) Photomixotrophic growth of wild type (WT),  $\Delta pfor$ , ferredoxin (fx) and flavodoxin (isiB) deletion mutants as indicated. (B) Growth of WT,  $\Delta f-gogat$  and  $\Delta n-gogat$  under photoautotrophic and photomixotrophic conditions. (C) Electron transport with DCMU at PSI in the absence and presence of glucose in the WT,  $\Delta ndhD1\Delta ndhD2$ ,  $\Delta hk$  and  $\Delta glgP1\Delta glgP2$ . Shown are mean values  $\pm$  SD from at least 3 replicates.

Three entry points exist that can feed electrons from glucose oxidation into the plastoquinone (PQ) pool in the thylakoid membrane: the succinate dehydrogenase (SDH), which accepts electrons from the conversion of succinate to fumarate; NDH-2, which accepts electrons from NADH and photosynthetic complex I (NDH-1), which accepts electrons from reduced ferredoxin (see Fig. 4B). Based on the observed shift from utilizing ferredoxin instead of NAD(P)H, we thus wondered if photosynthetic complex I (NDH-1) might be required for anoxygenic photosynthesis under photomixotrophic conditions as an entry point for electrons coming from glucose oxidation. Cells were incubated with DCMU that blocks the electron transfer from PSII to the PQ-pool. Thereby, exclusively electron transfer from glycogen or glucose oxidation to PSI could be measured based on a recently developed protocol (36). According to this protocol electrons were counted that flow through PSI via DIRK<sub>PSI</sub> measurements by the KLAS/NIR instrument. The electron transport at PSI was then measured in the absence and in the presence of glucose. In addition to



256 the WT, several mutants were analyzed with deletions in entry points as well as glucose  
257 metabolizing enzymes. The mutant with a deleted photosynthetic complex I ( $\Delta ndhD1\Delta ndhD2$ )  
258 should no longer be able to feed electrons from reduced ferredoxin into the  
259 respiratory/photosynthetic electron transport chain, while the hexokinase mutant ( $\Delta hk$ ) should  
260 no longer be able to metabolize external glucose. The glycogen phosphorylase mutant  
261 ( $\Delta glgP1\Delta glgP2$ ) is unable to break down its internal glycogen reservoir (36-38). As expected and  
262 in parts shown recently (36), addition of glucose resulted in higher donations of electrons to PSI  
263 in the WT and  $\Delta glgP1\Delta glgP2$ , whereas neither  $\Delta ndhD1\Delta ndhD2$  nor  $\Delta hk$  were able to provide  
264 electrons from glucose oxidation to PSI (Fig. 3C). Anoxygenic photosynthesis using glucose  
265 oxidation and PSI thus relies on the ferredoxin dependent photosynthetic complex I. In line with  
266 this, it was shown earlier that  $\Delta ndhD1\Delta ndhD2$  is not able to grow in the presence of glucose and  
267 DCMU under photoheterotrophic conditions (39).

268 It should be noted in this context that there is no known glycolytic enzyme neither in the Emden-  
269 Meyerhoff-Parnass-, the Entner-Doudouhoff-, the phosphoketolase-, or the oxidative pentose  
270 phosphate pathway in *Synechocystis*, which utilizes ferredoxin as electron acceptor (38, 40, 41).  
271 PFOR is currently indeed the only known enzyme in the central carbon metabolism that reduces  
272 ferredoxin upon glucose oxidation (Fig. 4A). The second known source for reduced ferredoxin is  
273 PSI (Fig.4B). Further studies are required to elucidate the exact role of ferredoxins under  
274 photomixotrophic conditions.

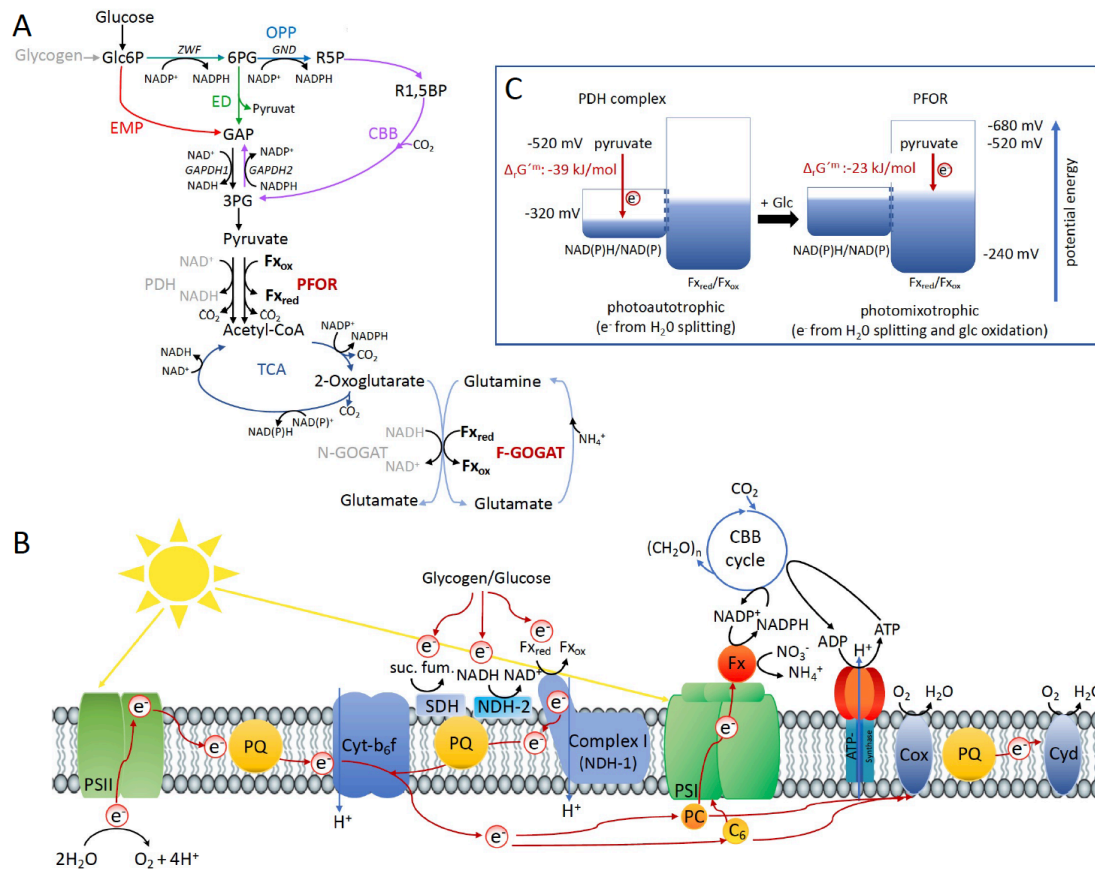
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## 276 Discussion

277 There is an irritating high number of reports in prokaryotes and eukaryotes on the presence and  
278 expression of enzymes under oxic conditions that are assigned to anaerobic metabolism (10, 24,  
279 42). One example is the production of hydrogen by the oxygen sensitive FeFe-hydrogenase in air-  
280 grown *Chlamydomonas reinhardtii* algae in a fully aerobic environment, which is enabled by  
281 microoxic niches within the thylakoid stroma (43). Another example is the constitutive expression  
282 of PFOR and the oxygen sensitive NiFe-hydrogenase under oxic conditions in cyanobacteria. By  
283 itself, the widespread presence of these enzymes in organisms that either live predominantly  
284 aerobically as e.g. cyanobacteria or are even obligate aerobes as e.g. *Sulfolobus acidocaldarius*,  
285 which possesses a PFOR, indicates a misconception and lack of understanding. The PFOR of  
286 *Sulfolobus acidocaldarius* could be isolated as stable enzyme in the presence of O<sub>2</sub>, however,  
287 enzyme activity measurements required the consumption of oxygen *in vitro* (11). Does this mean,  
288 that anaerobic micro-niches are required within this obligate aerobe to activate an enzyme of its  
289 central carbon metabolism? It might alternatively be that living cells have the ability to maintain  
290 reducing conditions in the presence of oxygen, which is a challenge in enzymatic *in vitro* assays.  
291 Conclusions on *in vivo* enzyme activities based on *in vitro* experiments therefore should be made  
292 with caution. Even though we could measure decarboxylation of pyruvate via PFOR only in the  
293 absence of oxygen *in vitro*, our data strongly indicate that this enzyme is active *in vivo* under  
294 aerobic and highly reducing conditions. We assume that either anaerobic micro-niches or  
295 alternatively mechanisms within the cell that are not understood yet, keep the enzyme active in  
296 an aerobic environment.

297 The replacement of FeS enzymes and ferredoxins by FeS free alternatives and NADPH in the  
298 course of evolution is in general discussed with regard to the oxygen sensitivity of FeS clusters in  
299 connection with the shift from anoxic to oxic conditions on Earth (8, 10). Oxygen is without any  
300 doubt one important factor. However, the shift from anoxic to oxic conditions went along with a  
301 shift from reducing to more oxidizing conditions. This shift was among others achieved by the

302 escape of hydrogen into space, which irreversibly withdrew electrons from Earth (2). The  
303 withdrawal of electrons and the establishment of oxidizing conditions might have been an  
304 additional important factor (independent of oxygen and the oxygen sensitivity of FeS clusters)  
305 that triggered these evolutionary changes by enabling reactions with higher driving forces. The  
306 idea is thus that PFOR and ferredoxins might have been replaced by the PDH complex and NADH  
307 due to their potential to release larger amounts of Gibbs free energy ( $\Delta G \ll 0$ ). When competing  
308 with other organisms for resources an accelerated metabolism can be highly beneficial. The  
309 decision to either utilize the PDH complex or alternatively PFOR and along this line, the  
310 replacement of PFOR by the PDH complex in the course of evolution might have been determined  
311 by the prioritization for high chemical driving forces. On that note, we were unable to delete the  
312 PDH complex in *Synechocystis*, which points to its essential role. PFOR is in contrast dispensable  
313 under photoautotrophic conditions and cells obviously prefer to decarboxylate pyruvate via the  
314 PDH complex under these conditions. By transferring electrons to  $\text{NAD}^+$  instead of ferredoxin less  
315 Gibbs free energy is stored. However, this comes along with a higher driving force that is visible  
316 when regarding the reaction Gibbs energies of  $\Delta_r G^m$  -39 kJ/mol for the reaction catalyzed by the  
317 PDH complex versus  $\Delta_r G^m$  -23 kJ/mol for the reaction catalyzed by PFOR (Fig. 4C) (44).  
318 Under photomixotrophic conditions, photosynthesis and glucose oxidation operate in parallel  
319 causing highly reducing conditions in the cells. As soon as the  $\text{NADH}/\text{NAD}^+$  pool is highly reduced,  
320 cells might be forced to switch to the ferredoxin pool, as shown by our data. Glucose is  
321 alternatively oxidized via four glycolytic routes. Flux analyzes have shown that glycolytic  
322 intermediates enter the CBB cycle, eventually lower glycolysis and finally provide pyruvate (45).  
323 Depending on the precise route taken, glucose oxidation yields distinct forms of reducing  
324 equivalents (38). Three enzymes are involved in oxidation steps: Glc6P dehydrogenase (Zwf) and  
325 6PG dehydrogenase (Gnd) yield NADPH, whereas GAP dehydrogenase (GAPDH) yields NADH.  
326 NAD(P)H is furthermore provided downstream in the TCA cycle. PFOR is thus the only known  
327 direct source for reduced ferredoxin in glucose oxidation (Fig. 4A). The wide network of low  
328 abundant ferredoxins in *Synechocystis* and the importance of these ferredoxins under  
329 photomixotrophic conditions on the one hand and the low number of known enzymes that  
330 directly reduce ferredoxins on the other hand unveils that our conception is not yet inherently  
331 consistent. An additional potential source of reduced ferredoxin could be the transfer of electrons  
332 from NAD(P)H. The transhydrogenase (PntAB), which is located in the thylakoid membrane utilizes  
333 proton translocation to transfer electrons from NADH to  $\text{NADP}^+$  (46). Electrons from NADPH could  
334 be further transferred to ferredoxin via ferredoxin-NADPH-oxidoreductase (FNR). Another  
335 potential turntable for the exchange of electrons is the diaphorase part of the NiFe-hydrogenase  
336 in *Synechocystis*, which was recently shown to shuttle electrons between NAD(P)H, flavodoxin  
337 and several ferredoxins *in vitro* (26).



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Figure 4: Optimal photomixotrophic growth requires low abundant ferredoxins, PFOR and F-GOGAT. Electrons from glucose oxidation that arrive at PSI require ferredoxin-dependent photosynthetic complex I (NDH-1). Cells shift from utilizing NAD(H) dependent to ferredoxin dependent enzymes when brought from photoautotrophic to photomixotrophic conditions. (A) Glycolytic routes, lower glycolysis and the TCA cycle yield NAD(P)H from glucose oxidation. The only known enzyme that produces reduced ferredoxin from glucose oxidation is PFOR. Both the decarboxylation of pyruvate as well as the synthesis from glutamate from 2-oxoglutarate and glutamine can be catalyzed by distinct enzymes that either utilize ferredoxin (PFOR, F-GOGAT) or NAD(H) (PDH-complex; N-GOGAT). (B) Photosynthetic complex I (NDH-1) accepts electrons from reduced ferredoxin. The complex is required for the input of electrons from glucose oxidation into anoxygenic photosynthesis in the presence of DCMU. (C) The  $\Delta_r G^{\circ\prime}$  of pyruvate decarboxylation via the PDH complex is more negative than via PFOR, which results in a higher driving force. Photomixotrophy results in reducing conditions. The redox potential of the NAD(P)H/NAD(P)<sup>+</sup> pool which is around -320 mV will turn more negative upon reduction. This could facilitate the transfer of electrons from NADH to ferredoxins. In addition, inactivation of NAD<sup>+</sup> dependent enzymes (such as the PDH complex) and their functional replacement by ferredoxin dependent enzymes (such as PFOR) support the suggested shift from the utilization of the NAD(H) to the ferredoxin pool.

In order to get a complete picture, it would be essential to know the redox potentials of all ferredoxins in *Synechocystis*. Currently, they have been determined for Fx1 (-412 mV), Fx2 (-243 mV), and Fx4 (-440 mV), whereas the value for Fx4 is based on measurements of a homologue in *Thermosynechococcus elongatus* (27, 29, 30). Fx1 to Fx6 in *Synechocystis* possess 2Fe2S clusters for which redox potentials between -240 to -440 mV are typical (5). For 3Fe4S clusters as present in Fx8 (containing one 3Fe4S and one 4Fe4S cluster) redox potentials between -120 to -430 mV

362 were determined and for 4Fe4S clusters as present in Fx7 (4FeFS) and Fx9 (containing two 4Fe4S  
363 clusters) redox potentials between -300 to -680 mV were found (5). Without yet knowing the  
364 exact values for all ferredoxins in *Synechocystis*, it is anyway likely that they span a wide range of  
365 redox potentials.

366 The redox potential of any given couple does not have a constant value but is influenced among  
367 others by the ratio of the redox partners. The redox potential of the NADH/NAD<sup>+</sup> pool will thus  
368 turn more negative upon reduction. Obviously, storing electrons as reducing equivalents with  
369 lower redox potential saves more of their potential energy. The driving force of a reaction is on  
370 the other hand higher if electrons are transferred across larger redox potential differences. This  
371 will slow down the back reaction and thereby speed up the forward reaction. The idea is thus that  
372 the NADH/NAD<sup>+</sup> pool gets reduced first prioritizing high driving forces. However, as the redox  
373 potential of the NADH/NAD<sup>+</sup> pool turns slowly more negative, it might reach levels that are  
374 characteristic for ferredoxin couples. This might provoke a metabolic shift to transfer electrons to  
375 oxidized ferredoxin instead of NAD<sup>+</sup> (Fig. 4C). This shift can be regulated on several levels. Among  
376 others, as shown in this study, high NADH/NAD<sup>+</sup> ratios can inactivate enzymes that rely on this  
377 couple and thereby support the action of isoenzymes that interact with the Fx<sub>red</sub>/Fx<sub>ox</sub> couple  
378 instead. In addition, electron turntables as the transhydrogenase, FNR and the diaphorase can  
379 support this shift (26, 46).

380 In the case of *Synechocystis*, it is especially beneficial to shift their reducing equivalent pools to  
381 ferredoxin, as Fx is able to donate electrons to the photosynthetic complex I (35). In contrast to  
382 SDH and NDH-2, the photosynthetic complex I is coupled to a proton gradient and thus yields a  
383 higher amount of ATP. By shifting their pools of reducing equivalents, cells are thus able to save  
384 a greater share of the potential energy of electrons instead of wasting it as heat. As a pay-off, this  
385 shift should obviously come along with a slowdown of metabolic reactions.

386

## 387 **Conclusion**

388 The cyanobacterium *Synechocystis* encounters highly reducing conditions under  
389 photomixotrophy in the presence of oxygen. The PDH complex gets inactivated under these  
390 conditions at high NADH/NAD<sup>+</sup> ratios and is functionally most likely replaced by PFOR. PFOR is  
391 stable in the presence of oxygen *in vitro* and reduces ferredoxin instead of NAD<sup>+</sup>. PFOR, low  
392 abundant ferredoxins and the ferredoxin-dependent GOGAT are required for optimal  
393 photomixotrophic growth. Electrons from the oxidation of external glucose furthermore rely upon  
394 the presence of photosynthetic complex I (which accepts electrons from ferredoxin) in order to  
395 reach PSI. These findings indicate that cells perform a general shift in the utilization of their  
396 reducing equivalent pools from NAD(H) to ferredoxin under photomixotrophic conditions.

397

## 398 **Materials and Methods**

### 399 *Growth conditions*

400 All strains were grown in 50 ml BG-11 (47) buffered with TES pH 8. WT,  $\Delta pfor$ ,  $\Delta f-gogat$ ,  $\Delta n-gogat$ ,  
401  $\Delta isiB$ , all ferredoxin deletion mutants,  $\Delta ndhD1\Delta ndhD2$ ,  $\Delta hk$ , and  $\Delta glgP1\Delta glgP2$  were and placed  
402 in 100 ml Erlenmeyer flasks on a rotary shaker at 28 °C, 50  $\mu\text{E m}^{-2} \text{s}^{-1}$  and 100 rpm. After several  
403 days of growth, the cells were inoculated into 200 ml BG-11 at an OD<sub>750</sub> of 0.05 and placed into  
404 glass tubes bubbled with air at 50  $\mu\text{E m}^{-2} \text{s}^{-1}$  at 28 °C and growth was monitored by measuring the  
405 optical density at 750 nm. In liquid cultures all the strains were grown without addition of  
406 antibiotics and for photomixotrophic conditions 10 mM glucose was added. In case of the mutants  
407 deficient in Serine/Threonine- and Tyrosine kinases all strains were first inoculated from agar

408 plates into 100 ml BG-11-Medium. The cells were pre-cultivated shaking Erlenmeyer flasks (140  
409 rpm) for 7 days under ambient air with  $35 \mu\text{E m}^{-2} \text{s}^{-1}$  and  $30^\circ\text{C}$ . Ahead of the growth experiment,  
410 cells were harvested from the cultures by centrifugation ( $5000 \text{ xg}$ ,  $20^\circ\text{C}$ , 5 min) and re-suspended  
411 in fresh BG11 medium. The cultures were adjusted to  $\text{OD}_{750}$  of 0.5 with BG-11 medium and  
412 subsequently split into two aliquots. One part of the cultures was supplemented with 10 mM  
413 Glucose and the remaining part served as a control without glucose. *Synechocystis* strains were  
414 grown under ambient air conditions with  $35 \mu\text{E m}^{-2} \text{s}^{-1}$  and  $30^\circ\text{C}$ . Growth was monitored by  
415 measuring the  $\text{OD}_{750}$  every 24 h until the cultures reached the stationary growth phase. Pictures  
416 displaying the phenotypes were taken at the end of the cultivation period.  
417 For mutant selection and segregation the cells were grown on BG-11-agar containing 50  $\mu\text{g}/\text{mL}$   
418 kanamycin, 20  $\mu\text{g}/\text{mL}$  spectinomycin, 25  $\mu\text{g}/\text{mL}$  erythromycin, 10  $\mu\text{g}/\text{mL}$  gentamycin, and 20  
419  $\mu\text{g}/\text{mL}$  chloramphenicol.

420

#### 421 *Construction of mutants*

422 All the primers used in this study are listed in table S1. All mutants are listed in table S2. Most  
423 mutants were constructed in the non-motile GT WT of *Synechocystis* sp. PCC 6803 while a few  
424 serine/threonine protein kinase mutants were constructed in the motile PCC-M WT strain of  
425 *Synechocystis* as indicated in detail in table S2 (48). The procedure to generate the constructs for  
426 deletion of *pfor*, *pdhA*, *isiB* and the different ferredoxin genes was described in Hoffmann et al.  
427 (2006) (49). In brief, the up- and downstream regions as well as the required antibiotic resistance  
428 cassette were amplified by PCR. Subsequently, the three fragments were combined by a PCR  
429 fusion including the outermost primers. The resulting product was inserted by TA-cloning into the  
430 pCR2.1 TOPO-vector (ThermoFisher, Waltham, MA, USA). Constructs for the deletion of the genes  
431 of the NADH-dependent and the ferredoxin-dependent GOGAT were generated by Gibson cloning  
432 (50) assembling three fragments into the pBluescript SK(+) in a single step. After examination by  
433 sequencing the plasmids were transformed into *Synechocystis* sp. PCC 6803 cells as described  
434 (51). Resulting transformants were either checked by PCR or Southern hybridization after several  
435 rounds of segregation (Fig. S11). The deletion strains of the serine/threonine kinase genes *spkA*,  
436 *spkB*, *spkD*, *spkG* and *spkL* carry mutations in their kinase domains and were generated  
437 accordingly. Their segregation was complete and will be described elsewhere (Barkse and  
438 Hagemann, in preparation). To generate a construct for overexpression of *pfor* (*sll0741*) including  
439 a His-tag a DNA fragment containing 212 bp up- and 212 bp downstream of the *sll0741* start  
440 codon, with a BamHI, XhoI and NdeI site in between and 20 bp sequences that overlap with the  
441 pBluescript SK(+) vector at the respective ends was synthesized by GeneScript (Piscataway  
442 Township, NJ, USA)(Fig S6A). Another DNA fragment containing a modified petE promoter,  
443 followed by His-tag, TEV cleavage recognition site and linker encoding sequences, various  
444 restriction sites and 20 bp sequences that overlap with the pBluescript SK(+) vector at the  
445 respective ends was also synthesized by GenScript (Fig S6B). These fragments were cloned into  
446 the pBluescript SK(+) vector by Gibson cloning, respectively. A kanamycin antibiotic resistance  
447 cassette was inserted into the EcoRV site of the plasmid containing the modified petE promoter.  
448 The resulting promoter-cassette plasmid and the PFOR plasmid were digested with BamHI and  
449 NdeI and the promoter cassette was ligated into the alkaline phosphatase treated PFOR plasmid  
450 to yield the final construct. This plasmid was sequenced, transformed into *Synechocystis* sp. PCC  
451 6803 and segregation was confirmed by PCR analysis (Fig S9C).

452

453

454 *Southern-Blotting*

455 200 ng genomic DNA was digested with Hind III and loaded on a 0.8 % agarose gel in TBE buffer.  
456 After blotting the DNA on a nylon membrane (Hybond N+, Merck, Darmstadt, Germany) it was  
457 cross-linked to the membrane in a Stratalinker (Stratagene, CA, USA). Detection of the respective  
458 bands was carried out by the Dig DNA labeling and detection kit (Roche, Penzberg, Germany)  
459 according to the manufacturers instructions.

460

461 *RT-PCR*

462 To a volume of 15 µl containing 1 µg of RNA 2 µl RNase-free DNase (10 U/µl, MBI Fermentas, St.  
463 Leon-Rot, Germany), 2 µl 10 x DNase buffer (MBI Fermentas, St. Leon-Rot, Germany) and 1 µl  
464 Riboblock RNase Inhibitor (40 U/µl, MBI Fermentas, St. Leon-Rot, Germany) were added before  
465 incubation at 37 °C for 2 hours. Subsequently the sample was quickly cooled on ice. 2 µl 50 mM  
466 EDTA was added and it was incubated at 65 °C for 10 min and again quickly cooled on ice to get  
467 rid of the DNase activity. To check the digestion efficiency, 1 µl of the sample was used as a  
468 template for PCR. 1 µl genomic DNA and 1 µl H<sub>2</sub>O were used as positive and negative controls,  
469 respectively. Reverse transcription PCR was performed with 9 µl of those samples free of DNA  
470 with the RT-PCR kit (Applied Biosystems, Karlsruhe, Germany) according to the manufacturer's  
471 instruction. 9 µl of the same sample was used in parallel as a negative control. The reaction  
472 mixture was incubated for 1 h at 37 °C including a gene-specific tag-1 primer. For the subsequent  
473 PCR a gene-specific tag-2 primer and the respective reverse primer (s. table S1) were used.

474

475 *Oxygen measurements*

476 To measure the concentration of dissolved oxygen in the cultures oxygen sensors from Unisense  
477 (Unisense, Aarhus, Denmark) were used. After a two point calibration of the sensor by using  
478 distilled water equilibrated with air and a solution with 0.1 M NaOH and 0.1 M ascorbate  
479 containing no oxygen it was placed in the respective culture and the measurement was started.

480

481 *Mass spectrometry*

482 Pieces of the gel corresponding to bands 1-4 in the Fig. 2A were excised, reduced and alkylated  
483 following by digestion with Trypsin Gold (Promega) and extraction of peptides as described (52).  
484 Peptides from the bands 2-4 were further enriched for phosphopeptides using TiO<sub>2</sub> as described  
485 (53). Next, the peptides were analyzed by LC-MS/MS using a Q Exactive Hybrid Quadrupole-  
486 Orbitrap mass spectrometer (Thermo Scientific) connected in-line to an Easy-nLC HPLC system  
487 (Thermo Scientific), as described (53). The raw data were processed with Protein Discoverer  
488 software (Thermo Fisher Scientific, Inc.). Database searches were performed using the in-house  
489 Mascot server (Matrix Science) against a database of *Synechocystis* 6803 proteins supplemented  
490 with sequences of common protein contaminants. The search criteria allowed for one  
491 miscleavage of trypsin, oxidation of methionine, acetylation of the protein N-termini and  
492 phosphorylation of S, T and Y residues.

493

494 *Determination of NAD<sup>+</sup>/NADH*

495 All the cultures used for NAD<sup>+</sup>/NADH determination experiment were grown autotrophically and  
496 mixotrophically in 250 ml BG-11 medium. 5 ml to 10 ml cells, equivalent to about 10<sup>9</sup> cells/ml (10  
497 ml cultures of OD<sub>750</sub> of 1) were sampled for the measurements. The cells were centrifuged at 3,500  
498 x g -9 °C for 10 min and the pellets were washed with 1 ml 20 mM cold PBS (20 mM KH<sub>2</sub>PO<sub>4</sub>, 20  
499 mM K<sub>2</sub>HPO<sub>4</sub>, and 150 mM NaCl). The suspension was transferred to a 2 ml reaction cup and was

500 centrifuged at 12,000 x g for 1 min at -9 °C. For all further steps the NAD<sup>+</sup>/NADH Quantification  
501 Colorimetric Kit (Biovision, CA, USA ) was used. The pellet was resuspended in 50 µl extraction  
502 buffer and precooled glass beads (Ø=0.18 mm) were added to about 1 mm to the surface of the  
503 liquid. The mixture was vortexed 4 times 1 min in the cold room (4 °C) and intermittently chilled  
504 on the ice for 1 min. 150 µl extraction buffer was added again and the mixture was centrifuged at  
505 3,500 xg for 10 min at -9 °C. The liquid phase was transferred as much as possible into a new  
506 reaction cup and centrifuged at maximum speed for 30 min at -9 °C. All further steps were  
507 conducted as described by the manufacturer. Finally, the samples were incubated for 1 to 4 hours  
508 in 96 well plates before measuring absorbance at 450 nm by TECAN GENios (TECAN Group Ltd.,  
509 Austria) along with a NADH standard curve.

510

#### 511 *Immunoblots*

512 Whole cell extracts were applied on 10 % SDS-polyacrylamide gels according to the protocol of  
513 Laemmli (1970). After separation of the proteins the gel was semi-dry blotted on a nitrocellulose  
514 membrane (Roti-NC, 0.2 µm Transfer membrane for protein analyses, Carl Roth, Karlsruhe,  
515 Germany). For blocking the membrane was incubated in 2.5 % BSA in TBS (20 mM Tris pH 7.5, 150  
516 mM NaCl). For the detection of phosphorylated Serine residues a TBS solution with a 1:100  
517 dilution of the Anti-Phospho-Serin Antibody (Qiagen, Hilden, Germany) was used. For detection  
518 of the PdhA subunit an antibody was raised against the peptide TKYRREVLKDDGYDQ (Fig. S7) in  
519 rabbits by Agrisera (Umeå, Sweden). On the membranes 1:1000 dilution of this antibody in TBS  
520 was used. As secondary antibody either an anti-mouse IgG-HRP conjugate or an anti-rabbit IgG-  
521 HRP conjugate was used at 1:10,000 dilution. For detection the membrane was immersed in a 1:1  
522 mixture of solution A (100 mM Tris/HCl pH = 8.5, 0.4 mM p-coumaric acid, 2.5 µM luminol) and  
523 solution B (100 mM Tris/HCl pH = 8.5, 100 mM H<sub>2</sub>O<sub>2</sub>) for 1 min and subsequently exposed to an  
524 X-ray film (Thermo Scientific CL-XPosure Film, Life Technologies GmbH, Germany).

525

#### 526 *Antibody against the PdhA subunit of the PDH complex*

527 In order to raise an antibody against the alpha subunit of PdhA from the PDH complex, the peptide  
528 TKYRREVLKDDGYDQ (Fig. S7) was used for immunization of rabbits (Agrisera, Umeå, Sweden).

529

#### 530 *Purification and activity measurement of dihydrolipoyl dehydrogenase (E3 subunit, SynLPD)*

531 The recombinant His-tagged SynLPD (Slr1096) was generated and purified essentially as described  
532 previously (54). Prior activity measurements, the elution fractions were desalted through PD10  
533 columns (GE healthcare, Solingen, Germany). The protein concentration was determined  
534 according to Bradford (55). SynLPD activity was determined in the forward direction. DL-  
535 dihydrolipoic acid served as the substrate at a final concentration of 3 mM. SynLPD activity was  
536 followed as reduction of NAD<sup>+</sup> (included in varying concentrations, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4  
537 and 5 mM) at 340 nm. The K<sub>i</sub> constant was estimated in the presence of four NADH concentrations  
538 (0, 0.1, 0.15 and 0.2 mM) as well as NADPH (0.1 mM) as control. Specific enzyme activity is  
539 expressed in µmol NADH per min<sup>-1</sup> mg protein<sup>-1</sup> at 25°C. Mean values and standard deviations  
540 were calculated from at least three technical replicates for all substrate/co-substrate  
541 combinations. All chemicals were purchased from Merck (Darmstadt, Germany).

542

#### 543 *Purification of pyruvate:ferredoxin oxidoreductase (PFOR)*

544 For the purification of PFOR from *Synechocystis* sp. PCC 6803 (Fig. S9, S10), three 6-L autotrophic  
545 cultures of the PFOR overexpression strain (PFOR:oe) were grown to an OD<sub>750</sub> of about 1. Cells

546 were harvested by centrifugation at 4.000 rpm in a JLA-8.1000 rotor for 20 min at 4°C. Initially,  
547 His-PFOR over-expression in the 6-L cultures was assessed by SDS PAGE analysis followed by  
548 immunoblotting with a His-tag specific antibody (GenScript; Fig S7). A specific band could be  
549 detected in the over-expression mutant, confirming expression and stable accumulation of the  
550 over-expressed and N-terminally His-tagged PFOR protein. For large-scale purification cells were  
551 resuspended in lysis buffer (50 mM NaPO<sub>4</sub> pH=7.0; 250 mM NaCl; 1 tablet complete protease  
552 inhibitor EDTA free (Roche, Basel, Switzerland) per 50 mL) and broken by passing them through a  
553 French Press cell at 1250 p.s.i. twice. Unbroken cells and membranes were pelleted in a Beckman  
554 ultracentrifuge using a 70 Ti rotor at 35.000 rpm for 45 min at 4°C. The decanted soluble extract  
555 was adjusted to a volume of 90 mL with lysis buffer and incubated with 10 mL TALON cobalt resin  
556 (Takara, Shiga, Japan) for 1 h at 4°C. The resin was then washed extensively with 200 mL lysis  
557 buffer and subsequently with 100 mL lysis buffer containing 5 mM imidazole. Bound proteins were  
558 eluted with 20 mL elution buffer (50 mM NaPO<sub>4</sub> pH=7.0; 250 mM NaCl; 500 mM imidazole). The  
559 protein was concentrated overnight to a volume of 2 mL in a Vivaspin 20 Ultrafiltration Unit (5  
560 kDa MWCO)(Merck, Darmstadt, Germany) and then loaded onto a HiLoad™ 26/60 Superdex™  
561 75 prep grade (GE Healthcare, Chicago, IL, USA) using 25 mM NaPO<sub>4</sub>, pH=7.0; 50 mM NaCl; 5%  
562 (v/v) glycerol as the running buffer. The run was monitored at 280 nm and fractions were collected  
563 (Fig. 8A).

564

#### 565 *Activity measurement of pyruvate:ferredoxin oxidoreductase (PFOR)*

566 The specific activity of the pyruvate:ferredoxin oxidoreductase was measured essentially as  
567 described (11). The activity assay contained in 1 ml 100 mM Tris-HCl (pH 8), 0.5 mM Coenzyme A,  
568 10 mM pyruvate, 5 mM thiamine pyrophosphate, 40 mM glucose, 40 U glucose oxidase, 50 U  
569 catalase, and 10 mM methyl viologen. Reduction of methylviologen was followed at 604 nm and  
570 an extinction coefficient of 13.6 mM<sup>-1</sup> cm<sup>-1</sup> was used. The reaction was started by adding 8.9 x 10<sup>-5</sup>  
571 M isolated PFOR.

572 We also tested ferredoxin reduction by the PFOR by a mixture containing the same substances as  
573 above except methyl viologen. To this mixture 1.6 mM ferredoxin 1 and 1.3 mM ferredoxin:NADP<sup>+</sup>  
574 reductase and 1 mM NADP<sup>+</sup> were added. In this case the reduction of NADP<sup>+</sup> was followed at 340  
575 nm. The same mixture without glucose, glucose oxidase and catalase were used to test if the  
576 enzyme also works in the presence of oxygen.

577

#### 578 *In-vivo electron flow through photosystem I*

579 The electron flux through photosystem I was measured by the Dual-KLAS/NIR (Walz GmbH,  
580 Effeltrich, Germany) by a newly developed method (36). In brief, cell suspensions were adjusted  
581 to 20 µg/mL chlorophyll and 20 µM DCMU was added. Electron flow through PSI was determined  
582 by dark-interval relaxation kinetics (DIRK) measurements at a light intensity of 168 µE/m<sup>2</sup>/s in the  
583 absence and presence of 10 mM glucose.

584

#### 585 *Determination of reaction Gibbs energies*

586 Δ<sub>r</sub>G<sup>m</sup> for the reaction catalyzed by the PDH complex and by PFOR were calculated using  
587 eQuilibrator (<http://ealibrator.weizmann.ac.il/>) according to (44). CO<sub>2</sub> (total) was considered as  
588 hydrated and dehydrated forms of CO<sub>2</sub> are considered to be in equilibrium in biochemical  
589 reactions. Ionic strength of 0.2M, pH of 7 and metabolite concentrations of 1 mM were assumed.  
590 In order to determine the redox potential of pyruvate we used the reactions Gibbs energy of -39  
591 kJ/mol for the PDH complex and -23 kJ/mol for PFOR. Assuming a redox potential of -320 mV for



592 NAD(P)H and -400 mV for ferredoxin the potential of pyruvate was determined according to  $\Delta G =$   
593  $-nF\Delta E$  to -520 mV.

594

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597 kinase (spk) deletion mutants is acknowledged.

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602

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## Supplementary Information

### Pyruvate:ferredoxin oxidoreductase and low abundant ferredoxins support aerobic photomixotrophic growth in cyanobacteria

Yingying Wang<sup>a</sup>, Xi Chen<sup>a</sup>, Katharina Spengler<sup>a</sup>, Karoline Terberger<sup>a</sup>, Marko Boehm<sup>a,b</sup>, Jens Appel<sup>a,b</sup>, Thomas Barske<sup>c</sup>, Stefan Timm<sup>c</sup>, Natalia Battchikova<sup>d</sup>, Martin Hagemann<sup>c</sup>, Kirstin Gutekunst<sup>a,b</sup>

kirstin.gutekunst@uni-kassel.de

<sup>a</sup>Department of Biology, Botanical Institute, Christian-Albrechts-University, D-24118 Kiel, Germany; <sup>b</sup>Department of Molecular Plant Physiology, Bioenergetics in Photoautotrophs, University of Kassel, D-34132 Kassel, Germany, <sup>c</sup>Plant Physiology Department, University of Rostock, D-18059 Rostock, Germany, <sup>d</sup>Department of Biochemistry, Molecular Plant Biology, University of Turku, FI-20014 Turku, Finland

S1: Bioinformatic analyses concerning the distribution of PDH complex and PFOR in cyanobacteria  
S2: Oxygen concentrations in photomixotrophic cultures of WT and  $\Delta pfor$   
S3: RT-PCR on *pfor* and *pdhA* in the WT under photoautotrophic and photomixotrophic conditions  
S4: Growth of serine/threonine protein kinase (*spk*) deletion mutants  
S5: Extract of the sequence alignment of PdhA subunit and sequence logo  
S6: Sequence alignment of 932 cyanobacterial PdhA sequences  
S7: Antibody against the PdhA subunit of the PDH complex  
S8: Immunoblot with an antibody against the E1 subunit of PdhA of the PDH complex  
S9: SDS PAGE analysis followed by immunoblotting of *Synechocystis* overexpressing PFOR  
S10: Large-scale PFOR purification  
S11: Examination of segregation of deletion mutants via PCR or Southern blot  
S12: Photoautotrophic growth of ferredoxin deletion mutants  
Table S1: List of primers used in this study to generate deletion strains and for RT-PCR  
Table S2: List of *Synechocystis* strains and mutants used in this study  
Table S3: Peptides of the alpha subunit of the pyruvate dehydrogenase (Slr1934) E1 component detected via MS/MS in band No. 1 of Fig. S8

diazotrophic (with N<sub>2</sub>ase)      non-diazotrophic (without N<sub>2</sub>ase)

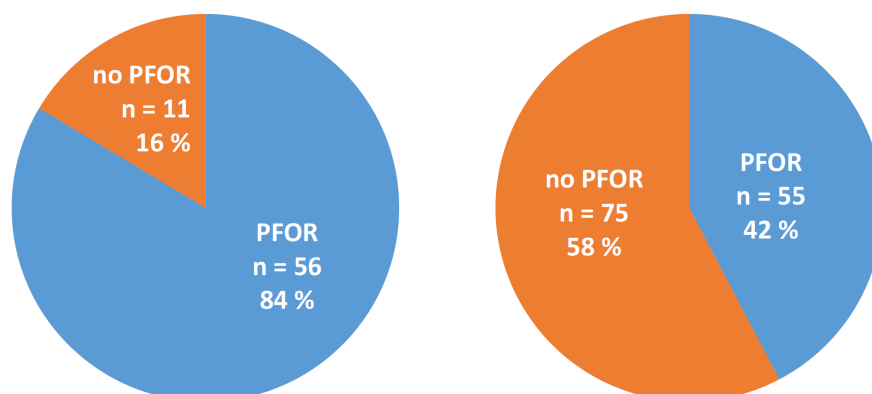


Figure S1: Bioinformatic analyses concerning the distribution of PDH complex and PFOR in diazotrophic and non-diazotrophic cyanobacteria. All shown genomes possess a PDH complex.

All completely sequenced cyanobacterial genomes were analyzed via *tblastn* for the presence of the PDH complex and PFOR. For this, in order to exclude symbionts, cyanobacterial genomes were in a first step searched for the *psbD* gene (PSII subunit). We used the *psbD* gene (*sl10849*) of *Synechcoystis* as bait. Only genomes containing *psaD* were used for all further analysis. 197 genomes remained and were searched by *tblastn* using the *pdhA* subunit (*slr1934*) from the PDH complex from *Synechcoystis* as bait. The largest expect value was  $2 \times 10^{-136}$ . *pdhA* was found in all genomes analyzed. 67 of these genomes contain *nifD* (highest e-value  $4 \times 10^{-104}$ ) and *nifK* (highest e-value  $1 \times 10^{-73}$ ), the two subunits of the nitrogenase for N<sub>2</sub>-fixation and a diazotrophic lifestyle. Diazotrophic and non-diazotrophic cyanobacteria were searched for the presence of PFOR by using *sl10741* from *Synechcoystis*. The highest e-value in this case was 0.

We found that all fully sequenced diazotrophic and non-diazotrophic cyanobacteria with PSII contain genes coding for a PDH complex and that 56 % thereof possess a PFOR as well. If we subtract from this group all diazotrophic cyanobacteria that contain a nitrogenase and might therefore utilize PFOR in the process of nitrogen fixation, 130 non-diazotrophic cyanobacteria remain. Within the group of non-diazotrophic cyanobacteria 42% possess a PFOR in addition to the PDH complex. This clearly shows that the property of holding both a PDH complex and a PFOR in cyanobacteria that live predominantly under oxic conditions is truly widespread. The analysis furthermore confirms our observation, that the PDH complex is preferred over the utilization of PFOR in cyanobacteria.

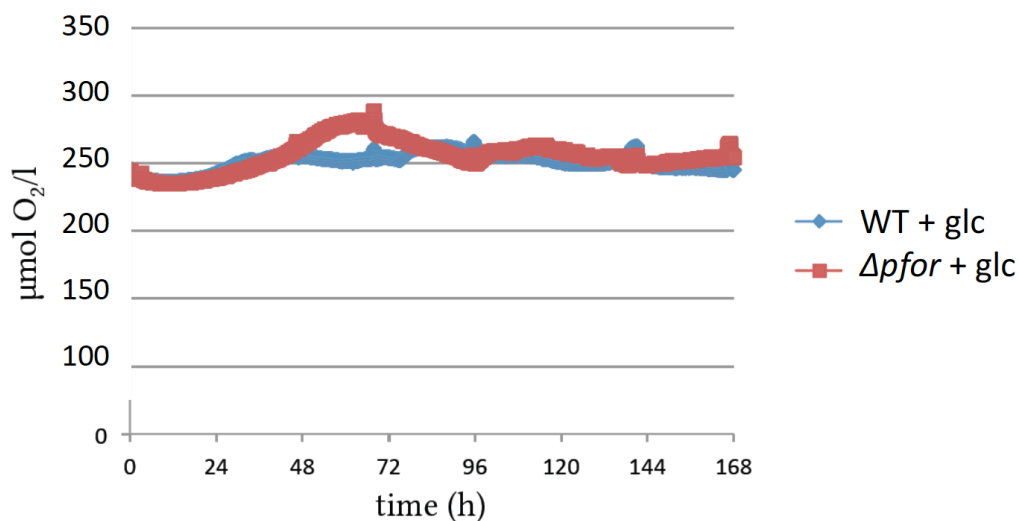


Figure S2: Oxygen concentrations in photomixotrophic cultures of wild type (WT) and  $\Delta pfor$  were close to oxygen saturation throughout the growth experiments. Original traces are shown.

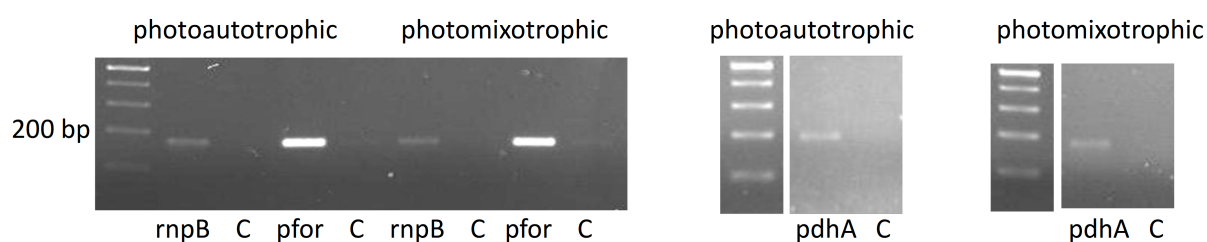


Figure S3: RT-PCR showing that *pfor* and *pdhA* are transcribed under photoautotrophic and photomixotrophic conditions in the wild type. Total RNA of wild type cells was reverse transcribed and subsequently subjected to PCRs with either primers specific for *rnpB*, *pfor* or *pdhA* (table S1). In the control reactions (C) reverse transcriptase was omitted.

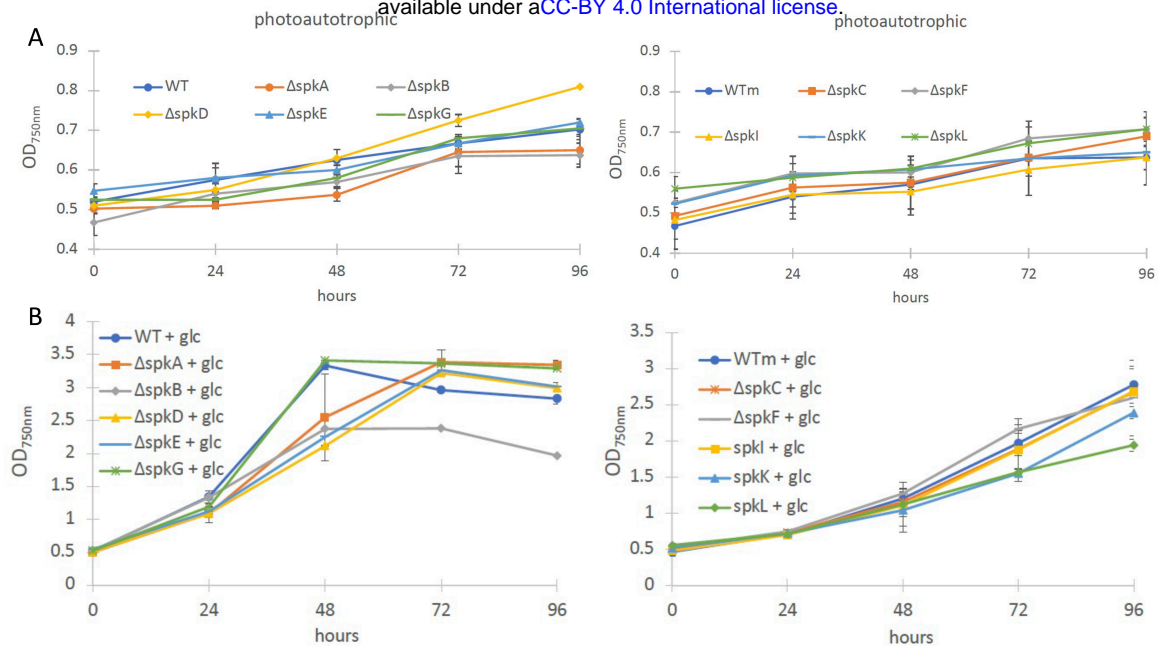


Figure S4: (A) Photoautotrophic and (B) photomixotrophic growth of serine/threonine protein kinase (*spk*) deletion mutants. The mutants were constructed in different *Synechocystis* WT backgrounds (table S2). *spkA*, *spkB*, *spkD*, *spkE* and *spkG* were deleted in the non-motile GT strain as all other mutants in this study with exception of *spkC*, *spkF*, *spkI*, *spkK*, and *spkL* that were deleted in the motile strain indicated as WTm. Shown are mean values  $\pm$  SD from at least 3 replicates.

Photoautotrophic and photomixotrophic growth of ten serine/threonine protein kinase (*spk*) deletion mutants was analyzed. They grew like the WT under photoautotrophic conditions (Fig. S4A) whereas the growth of  $\Delta$ *spkB* and  $\Delta$ *spkL* was affected under photomixotrophic conditions (Fig. S4B). This indicates that phosphorylation of enzymes is relevant for optimal photomixotrophic growth in *Synechocystis*.



A

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N7120   FRGHSLADP--DEMRSKAEKEFWFSRDPIKKLAALIEQNLADEAELKAIERKIQDVIDD
O6506   FRGHSLADP--DELRSKEEEKEYWFPRDPIKKLAADLTERNLATVEELKEIEQKIQALVDD
L8106   FRGHSLADP--DELRDQEEKDFWFSRDPIKKLANYLIEKNLASAEQLKEIDHKIQAVVDD
S7942   FRGHSLADP--DELRSKEEEKEFWLARDPIKRFAAHLTEFNLATHEELKAIDKKIEALVAE
S6803   FRGHSLADP--DELRSAEEKQFWAARDPIKKFAAFMTEHELASNEELKAIDKRIQEVIDD
Gviol   FRGHSLADP--DELRDPAEKEFWRKQDPIPRLAAFVREQELASAEELKAIDQEIRAEIDD
Btaurus YHGHSMSDPGVSYRTREEIQEVRSKSDPIMLLKDRMVNSNLASVEELKEIDVEVRKEIED
Rnorveg YHGHSMSDPGVSYRTREEIQEVRSKSDPIMLLKDRMVNSNLASVEELKEIDVEVRKEIED
Hsapiens YHGHSMSDPGVSYRTREEIQEVRSKRDPIILQDRMVNSKLATVEELKEIGAEVRKEIDD
      ::***::** .      ::      *** : : : ** :** * ... : :

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B



Figure S5: (A) Extract of the sequence alignment with the E1 subunits of the PDH complex. Shown are cyanobacterial sequences of *Nostoc* sp. PCC 7120 (N7120), *Oscillatoria* sp. PCC 6506 (O6506), *Lynbya* sp. PCC 8106 (L8106), *Synechococcus* sp. PCC 7942 (S7942), *Gloeobacter violaceus* (Gviol), and *Synechocystis* sp. PCC 6803 (S6803), and eukaryotic sequences of cattle (*Bos taurus* (Btaurus)), rat (*Rattus norvegicus* (Rnorveg)) and human (*Homo sapiens* (Hsapiens)). Serine residue 1 (S), is conserved in all PdhAs whereas residues 2 (S) and 3 (S), are only found in the eukaryotes. The first serine residue (S) was found in all 932 cyanobacterial PdhA sequences extracted from Genbank by a blast search as of January 11<sup>th</sup> 2021 (Fig. S5). (B) Sequence logo of 17 amino acids around serine residue 1 from 932 cyanobacterial *pdhA* sequences showing that this region is highly conserved. The logo was generated via <https://weblogo.berkeley.edu/logo.cgi>.

Figure S6: Sequence alignment by ClustalW of 932 cyanobacterial PdhA sequences extracted from Genbank by a blast search on January 11<sup>th</sup> 2021. The region containing the conserved serine residue (marked in red) is shown.

Alignment of cyanobacterial PdhA Sequences (only the part around the conserved serine residue (S) is shown)

```
NER82895.1      RTYRYKGHSMSDPKAYRTKEEVESYK-QRDPVEQVKATILKKK-----LASEAELAKID
MBC7866741.1   KTYRYKGHSMSDPQKYRTKEELEAYK-EKDPIEHVLKVLRTDY-----KVSDAEIEVMT
NET36155.1     RTYRYKGHSSDPARYRTKEEVQEQYK-DKDPVKMTEAKILKDK-----IATAEEIAAIK
WP_099077406.1 KTYRYRGHSMSDAQHYRTKEEVEEYR-KIDPIIQVLDI IKENN-----YATEAEIEAID
WP_110151329.1 KTYRYRGHSMSDPKAYRSRDEVQAVRDKSDPIEGLKR-ELEAA-----GVSEADLKTIE
WP_110154872.1 KTYRYRGHSMSDPKAYRTREEVQAMKDSDCIDHAKR-ELEAM-----GVSEDELKKID
WP_162547839.1 LTYRYRGHSMSDPKAYRSKEEVQKMRSEQDPIEQVRARLLEKG-----WATEDELKAID
WP_162544581.1 VTYRYRGHSMSDPKAYRSKEEVD RMRGEHDP IEQVRSRLLENG-----WATEDDLKGLD
WP_110150063.1 LTYRYRGHSMSDPKAYRTKDEVTKYRQERDPIEQVRARLLEAG-----VVTEDDLKKIE
WP_017290656.1 VTYRFRAHSMFDPPELYRDKAEEVEEWK-QRCP ISTLTQQLKAQG-----QITDADVERIE
WP_190651747.1 VTYRFRAHSMFDPPELYRDKAEEVEEWK-QRCP ISTLTQQLKAQG-----QITDADVERME
WP_190573087.1 TTYRFRAHSMFDAELYREKAEEVEQWK-QRCP IATLTQQLKEQE-----KISDADLEAME
WP_190936745.1 ITYRFRAHSMFDAELYRDKAEEVELWK-QRCP IETFAKRLQEQQ-----LLSDTEWEAME
BAZ39299.1     VTYRFRAHSMFDPPEFYREKTEVEEQWK-QRCP IEMLTTKL TEQG-----LLSGVELAAME
HFN00591.1     ITYRFRAHSMFDPPEFYREKAEEVEQWR-ERCP INTL FKT IQEKG-----WLSDTEWNQLN
HBC42436.1     RTYRFRAHSMFDAELYRDKKEVEEEWK-QRCP IATLTQQLQAQG-----LLSDQDLVTMK
WP_190401563.1 VTYRFRAHSMFDAELYRDKAEEVEEWK-QRCP IANLTQQLQAQG-----LLSDADLTAMQ
HBN08467.1     LTYRFRGHSMADPELYRNKAEEVEEWK-KRDP IPRFLEGCLANK-----LLSREDADRIS
HDW98853.1     ITYRFRGHSLADPDELRSP EEKEFWR-QRDP IKQLERYALEHN-----LMTEADFQAIH
WP_011431966.1 ITYRFRGHSLADPDELRSP EEKEFWR-QRDP IKQLERYALEHN-----LMTEADFQAIH
WP_099812446.1 LTYRFRGHSLADPDELRSP EEKEFWR-QRDP IKRLERYALEHN-----LMTEADFQAIQ
WP_011429423.1 ITYRFRGHSLADPDELRSP EEKEFWR-QRDP IKRLERYALEHN-----LMTEADFQAIQ
NJL98069.1     MTYRFRGHSLADPDELRDPQEKEFWR-KQDP IKQLERYGLEHN-----LTKADCQEIQ
NJK62068.1     ITYRFRGHSLADPDELRQPEDKEFWR-QRDP LKSLERYALEHA-----LVSEAEFQHIQ
WP_026101161.1 MTYRFRGHSLADPDELREVEEKEFWR-QQDP IKAFERYALEHE-----LMAQAELEDEIS
BAC89470.1     TTYRFRGHSLADPDELRDP AEKEFWR-KQDP I PRLAAFVREQE-----LASAEELKAID
WP_164928801.1 TTYRFRGHSLADPDELRDP AEKEFWR-KQDP I PRLAAFVREQE-----LASAEELKAID
WP_011142838.1 TTYRFRGHSLADPDELRDP AEKAHWR-KQDP L PRLRVWLEEQQ-----LASVEDLKRIE
WP_023173177.1 TTYRFRGHSLADPDELRDP AEKEFWR-QQDP I PRLAAFIAEQG-----FAGPDELKLID
HGZ85391.1     NTYRFRGHSLADPDELRDP AEKEFWR-KQDP I PKLASYIVSND-----LASEAELKIE
MBD1195191.1   LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LANAEELKID
WP_010310573.1 LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LATADELKID
WP_010315614.1 LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LATADELKID
PWL22038.1     LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LATADELKID
WP_185187231.1 LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEQN-----LATADELKID
GDx71957.1     LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LANADELKAID
NDF62096.1     LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLAAHLIEHN-----LANADELKAID
NBW63180.1     LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLGAQLIERG-----LATADDLKQID
NDG75008.1     LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLGAHLIEHN-----LATADELKID
WP_094588615.1 LTYRFRGHSLADPDELR AEAEKEFWA-QRDP IKRLGAHLIEQN-----LATADELKID
WP_094560219.1 LTYRFRGHSLADPDELR AEAEKEFWA-KRDP IKALAAHLIEQN-----LASGEELKID
WP_190389986.1 LTYRFRGHSLADPDELR AEAEKEFWA-KRDP IKALGSR LIEQN-----LATADELKID
WP_197153330.1 LTYRFRGHSLADPDELR AEAEKEFWA-KRDP IKALAVRLIEQN-----LASAEELKID
WP_106502205.1 LTYRFRGHSLADPDEL REEAEKEFWA-KRDP IKSLASRLIEQN-----LTTAEELKSIE
WP_186699049.1 LTYRYRGHSLADPDELR AEAEKAFWA-KRDP IKRLGAQLVEQQ-----LATADELKID
WP_193915991.1 LTYRYRGHSLADPDELR AEAEKAFWA-KRDP IKRLGGQLLEQQ-----LATADELKID
WP_193815924.1 LTYRYRGHSLADPDELR AEAEKAFWA-KRDP IKRLGGQLVEQQ-----LATADELKID
QNI69975.1     LTYRYRGHSLADPDELR AEAEKAFWA-KRDP IKRLGAQLVEQQ-----LATADELKID
WP_006909495.1 LTYRYRGHSLADPDELR AEAEKEFWA-KRDP IKRLAASLVEQQ-----LATADELKID
WP_087068638.1 LTYRYRGHSLADPDELR AEAEKEFWA-KRDP INRLAAHLVEQQ-----LASADELKAID
NDC35000.1     LTYRYRGHSLADPDELR AEAEKEFWA-KRDP IKRLAAQLVSQS-----LASAELEAID
NDC14028.1     LTYRFRGHSLADPDELR AEAEKEFWA-KRDP IKQLAAHLVAQN-----LATPEELKID
WP_048017862.1 LTYRYRGHSLADPDELR AQAEKDFWA-QRDP IKRLAAHLVEHG-----LVAAEELKID
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 WP\_168570583.1 LTYRFRGHSLADPDELSKKEEKDFWH-ARDPIARLGAHLLEHN-----LVRQEELDEIE  
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 KAA0213077.1 KTYRYYGHSMSDPQKYRSKDEVDQWK-SKDP IAAMAAYLMGE-----RGCLSEEQWQAME  
 \*\*\*: .\*: . \*

## PdhA

slr1934 pyruvate dehydrogenase E1 component, alpha subunit

MVSRILPELNTAEISLDRETALVLYEDMVLGRFFEDKCAEMYYRGKMFVHLYNGQEAVSSGIIKAMRQDEYV  
 CSTYRDHVHALSAGVPAREVMAELFGKETGCSRGRGSMHLFSSAHNLLGGFAFIGEGIPVALGAAFQTKYRREVL  
KDDGYDQVTACFFGDGTSNNGQFFECLNMAALWKLPILVVENNKWAIGMAHERATSQPEIYKASVFNMVG  
 EVDGMDVVAMHKVATEAVARARAGEGPTLIEALTYRFRGHSLADPDELSAEKQFWAARDPIKKFAAFMTEHEL  
 ASNEELKAIDKRIQEVDDALFAESSPEPNPEDLRKIYFAD

Figure S7: Amino sequence of the PdhA subunit of the PDH complex. The peptide that was used to raise an antibody is underlined. The conserved serine residue is shown in red and underlined as well.

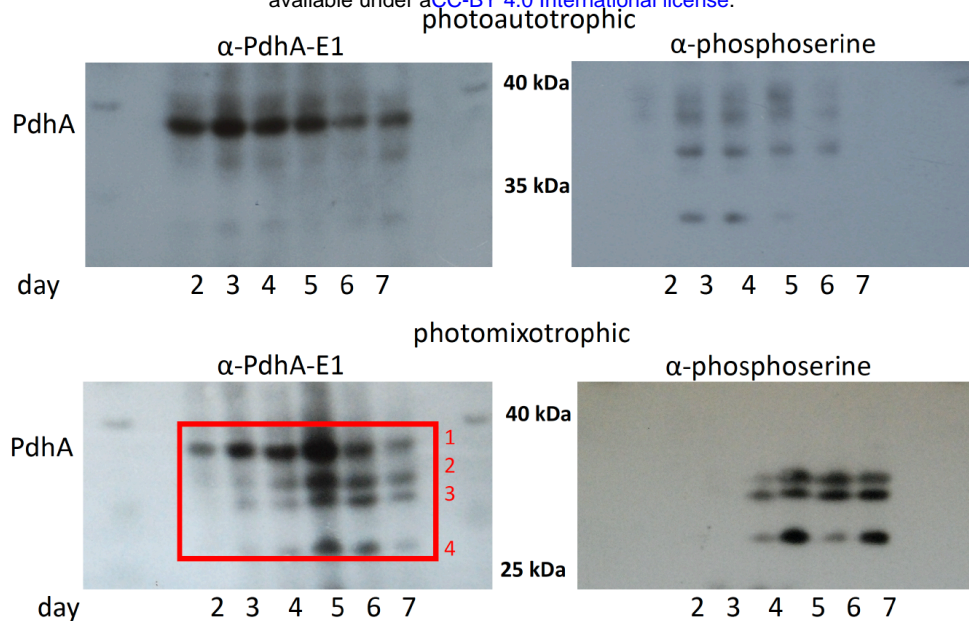


Figure S8: Immunoblots on protein extracts from days 2 to 4 of the wild type grown under photoautotrophic and photomixotrophic conditions. An antibody against the E1 subunit of PdhA of the PDH complex ( $\alpha$ -PdhA-E1) as well as an antibody that specifically detects phosphorylated serine residues ( $\alpha$ -phosphoserine) were utilized. Representative blots from more than three replicates are shown.

Phosphorylated proteins can be detected by immunoblots due to their modified electrophoretic mobility in contrast to unphosphorylated proteins. Therefore, immunoblots were carried out in order to check if the PDH complex of *Synechocystis* gets phosphorylated under photomixotrophic conditions. Protein extracts were obtained from cells taken from growth experiments on days 2 to 7 as the NADH/NAD<sup>+</sup> was especially high and as  $\Delta$ *pdfor* displayed its characteristic growth impairment in these days (see Fig. 1A and 1B). An antibody against the E1 subunit of PdhA ( $\alpha$ -PdhA-E1) (Fig. S7) and an antibody that binds specifically to phosphorylated serine residues ( $\alpha$ -phosphoserine) were used. As we were not able to delete *pdhA* of the PDH complex in *Synechocystis*, we unfortunately could not use a negative control for our immunoblot analyses. However, the expected molecular mass of the E1 subunit of the PDH complex is 38 kDa, and a corresponding strong signal of this size was detected under photoautotrophic and photomixotrophic conditions in the WT by  $\alpha$ -PdhA-E1 (Fig. S8).

In line with our hypothesis additional bands appeared on the blots from photomixotrophically grown cells on days 3 to 7 in the range between 26 to 36 kDa. The phosphorylation of a protein results in an additional negative charge which can result in a higher mobility in the SDS gel. All four bands were excised from the gel and analyzed via mass spectrometry. Many peptides which belong to PdhA were detected by MS/MS in the band 1 (red box in Fig. S8) confirming the reliability of the  $\alpha$ -PdhA-E1 antibody (Table S3). The MS/MS analyses of the bands 2-4 were aimed to discover the phosphopeptide GHpSLADPDELRL in the TiO<sub>2</sub>-enriched peptide fractions. Unfortunately, in contrast to the unmodified peptide, its phosphorylated form remained undetected. These forms were either below detection limits or not present. We subsequently subjected immunoblots as well to a specific antibody against phosphorylated serines ( $\alpha$ -phosphoserine). As expected, the phosphoserine antibody did not give a signal for band 1, (which we assumed as being the unphosphorylated form of PdhA) but precisely detected those bands 2-4 that appeared in addition on the blot from photomixotrophically grown cells (which we assumed as being the phosphorylated form of PdhA). Based on these results we cannot unambiguously establish if PdhA of the PDH complex in *Synechocystis* gets phosphorylated. It might as well be that the protein indeed gets phosphorylated and degraded thereupon, which would explain the additional bands that appear under photomixotrophic conditions. In this case the phosphorylation might have been lost in the degraded enzymes. The immunoblots thus give some convincing hints for



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either a phosphorylation and/or degradation of the PdnA protein in those days in which the NADH/NAD<sup>+</sup> ratios are high and PFOR gets important for optimal photomixotrophic growth.

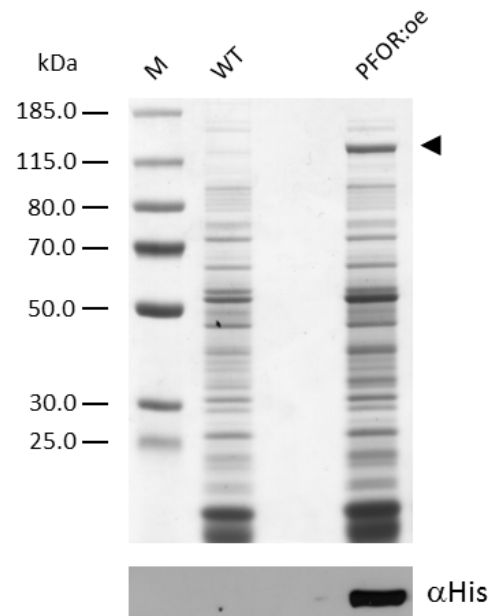


Figure S9: SDS PAGE analysis followed by immunoblotting of *Synechocystis* soluble extracts. Soluble extracts for the wild type (WT) and the mutant overexpressing PFOR (PFOR:oe) containing 15 µg of protein were loaded per lane. The arrowhead indicates the position of over-expressed PFOR.

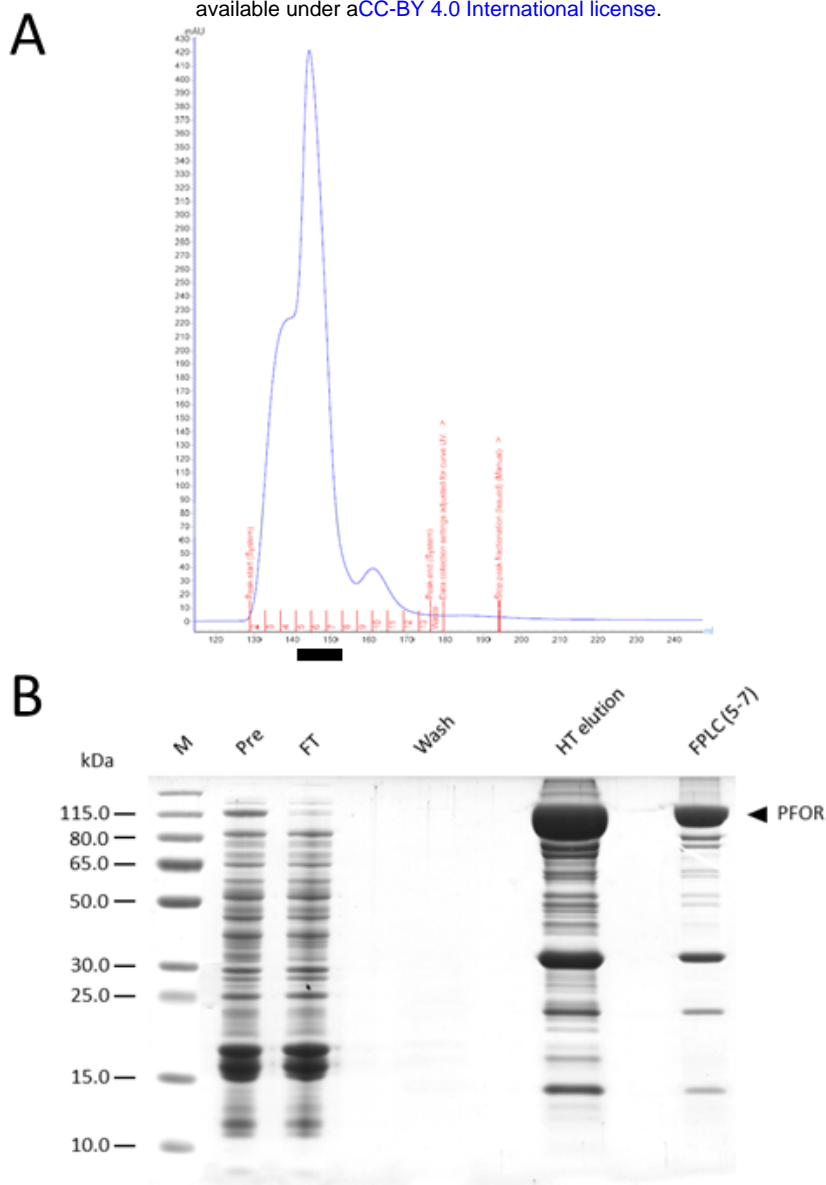


Figure S10: Large-scale PFOR purification. (A) The chromatogram of the FPLC size exclusion run. The collected fractions (5 to 7) are marked by the black bar underneath. (B) Various fractions from the purification procedure were analyzed by SDS PAGE. Soluble extracts before (Pre) and after (Post) the incubation with Talon Cobalt resin, a wash fraction, the His-tag elution and the pooled FPLC fraction (5 to 7) were loaded on the gel.

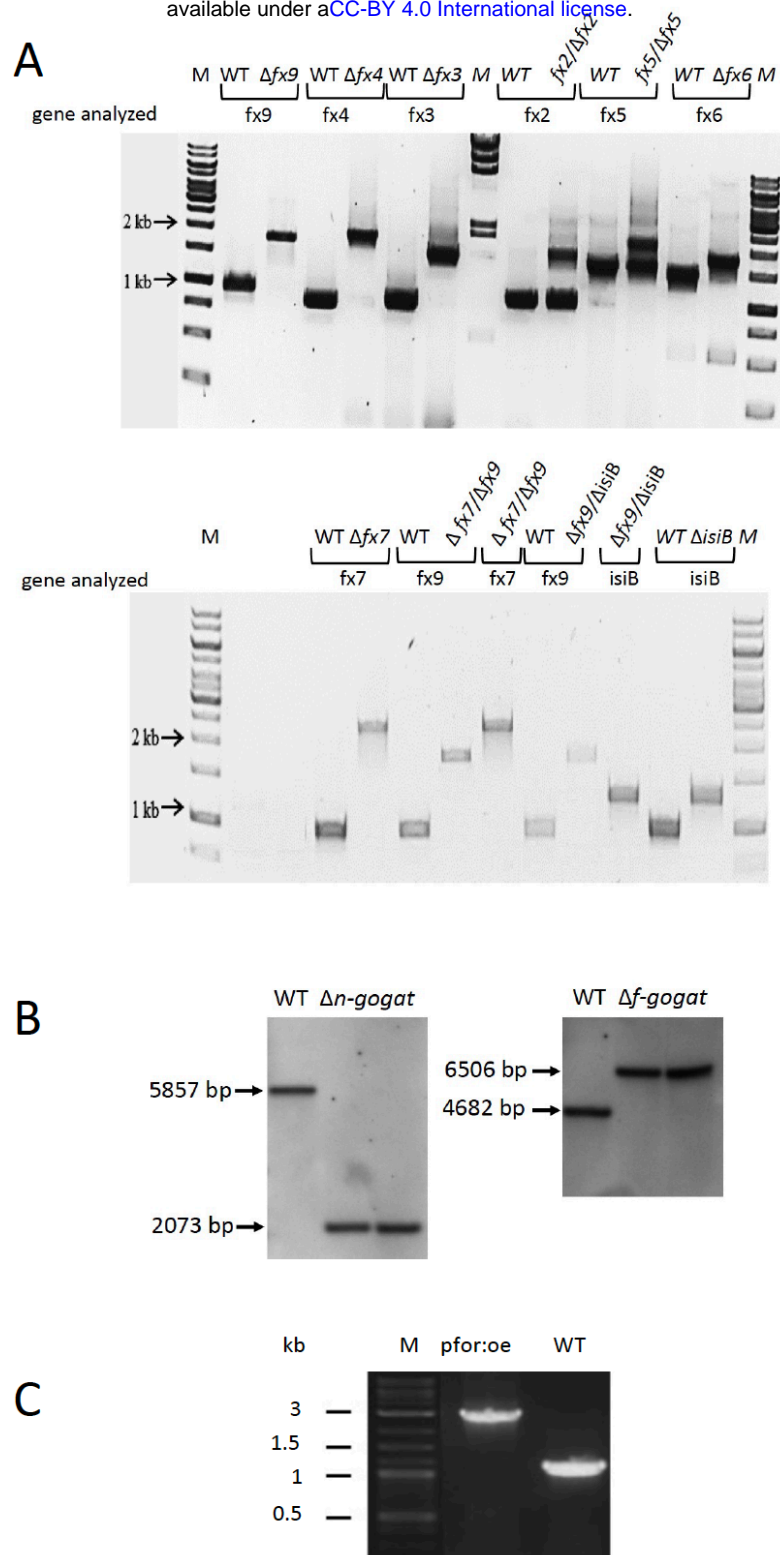


Figure S11: Examination of segregation of mutant strains. (A) PCR analysis of WT, ferredoxin (fx) and flavodoxin (isiB) mutants as indicated. (B) Southern blot of WT and  $\Delta n-gogat$  and  $\Delta f-gogat$  deletion mutants. WT DNA and DNA of two different mutant clones were applied after HindIII digestion. The sizes of the bands are indicated and correspond to those expected due to the mutation. (C) PCR analysis of PFOR overexpression (pfor:oe) mutant and WT.

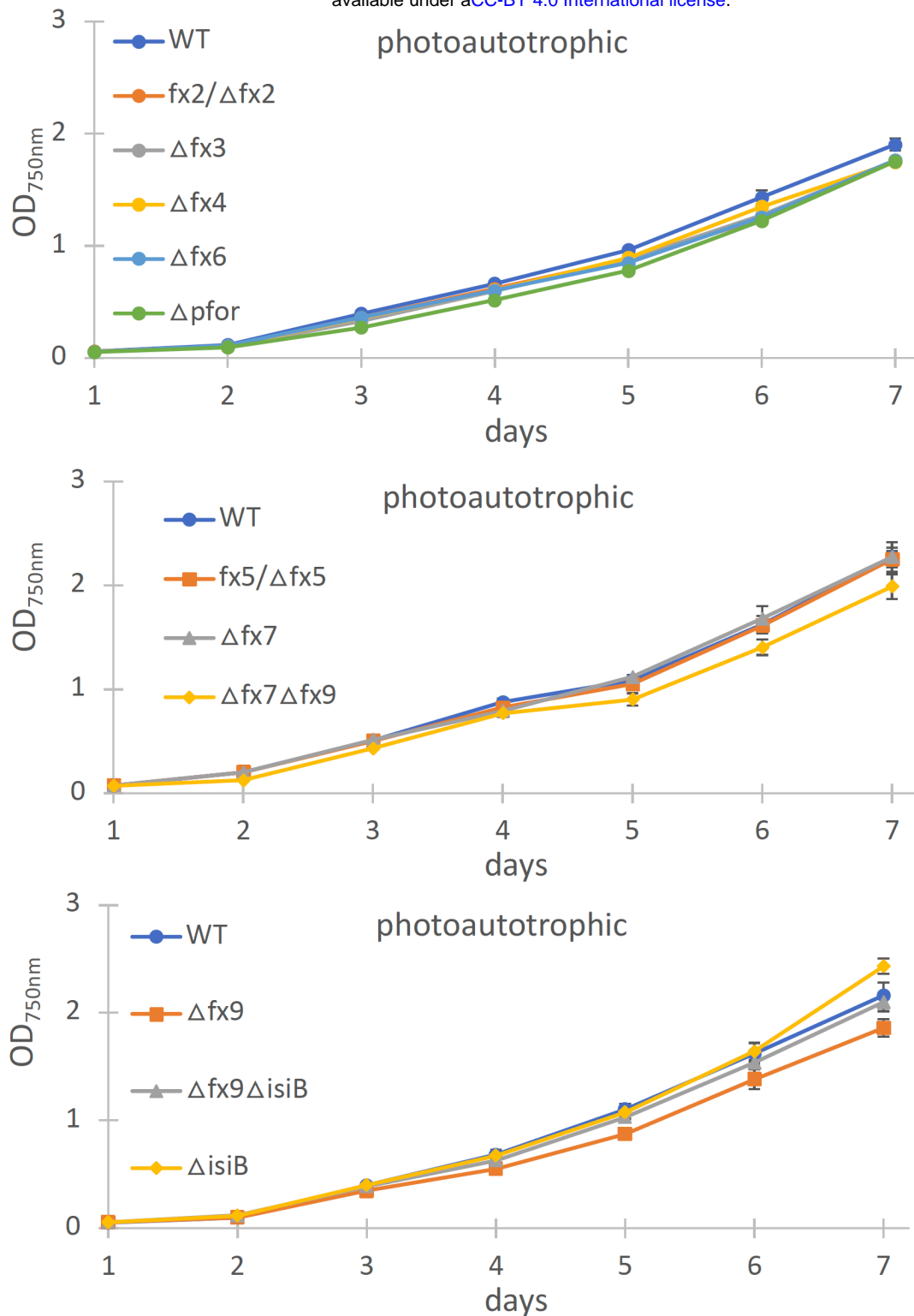


Figure S12: Photoautotrophic growth of different ferredoxin (fx) and the flavodoxin (isiB) deletion mutant as indicated in comparison to the wild type (WT). Shown are mean values  $\pm$  SD from at least 3 replicates.

Table S1: List of primers used in this study to generate deletion strains and for RT-PCR.

Primer name	Sequence	Fragment amplified	Construct
pfor-1	TGGGCTATCTCTTTCCCCGG	upstream recombination-site	Deletion of <i>pfor</i> ( <i>slI0741</i> )
pforin1	ATCTAATTTCTTTTTTCGTCGACAAGGGGTGATGGGATAAATGG		
Em1	GTCGACGAAAAAAGAAATTAGATAAA	Em-cassette	
Em2	GTCGACTTACTTATTAATAATTTATAGC		
pforin2	AATTATTTAATAAGTAAGTCGACGGTCTATTCGGAAAATCGCTTT	downstream recombination-site	
pfor-2	ATTTTTGGTATTCATCTGAGTG		
Fdx1.1	CCGGTCCTTAAAACCTCCCTT	upstream recombination site	Deletion of <i>fx1</i> ( <i>ssl0020</i> )
Fdx1in1	TTGGCACCCAGCCTGCGCGAACAGTAGAGAGATTGCCTCAT		
Sp-KG	TCGCGCAGGCTGGGTGCCAA	Sp-cassette	
Sp-rev	GCCCTCGCTAGATTTTAATGCGGAT		
Fdx1in2	ATCCGCATTAAAATCTAGCGAGGGCGGTAATAATGCTGGCCATGG	downstream recombination site	
Fdx1.2	TTAATCTACCTTCGTTTCCC		
Fdx2.1	CTCTCATATTCGACCTACC	upstream recombination site	Deletion of <i>fx2</i> ( <i>slI1382</i> )
Fdx2in1	ATCAGAGATTTTGAGACACAACGTGGTTATGGGCTGGTTGAATCCA		
Km1	CCACGTTGTGTCTCAAAATCTCTGAT	Km-cassette	
Km2	ATCGCCCCATCATCCAGCCAGAAAG		
Fdx2in2	CTTTCTGGCTGGATGATGGGGCGATGTAGGCTACAACCTG	downstream recombination site	
Fdx2.2	TCTGGGCAACGGCGTTTAAT		
Fdx3.1	CGTCTGCCGTAAGTGTAGAT	upstream recombination site	Deletion of <i>fx3</i> ( <i>slr1828</i> )
Fdx3in1	AGAGATTTATCTAATTTCTTTTTTCGTCGACCCATGGCAAAGCGGTAATAA		
Em1	GTCGACGAAAAAAGAAATTAGATAAA	Em-cassette	
Em2	GTCGACTTACTTATTAATAATTTATAGC		
Fdx3in2	GCTATAAATTATTTAATAAGTAAGTCGACTTCGGCTGGAATTCTCCCTT	downstream recombination site	
Fdx3.2	GCAAAGACTCAAAGGACTGG		
Fdx4.1	CAATTACAGCCATCCTGTTTG	upstream recombination site	Deletion of <i>fx4</i> ( <i>slr0150</i> )
Fdx4in1	TCAATAATATCGAATTCCTGCAGGAATGACCCAAACAATGGACT		
Cm1	CTGCAGGAATTCGATATTATTG	Cm-cassette	
Cm2	AAGCTTGATGGCGGCACCTCGCT		

Fdx4in2	AGCGAGGTGCCGCCATCAAGCTTAATGTTAGTCCAGCGGAGTT	downstream recombination site	Deletion of <i>fx5</i> ( <i>slr0148</i> )	
Fdx4.2	TTAGCAGGCAAGACCACACT			
Fdx5.1	CGATTCAGAACTCGGCATTG	upstream recombination site		
Fdx5in1	ATCAGAGATTTTTGAGACACAACGTGGCATAATGGTGGCATGGTCATG			
Km1	CCACGTTGTGTCTCAAATCTCTGAT	Km-cassette	Deletion of <i>fx6</i> ( <i>ss12559</i> )	
Km2	ATCGCCCCATCATCCAGCCAGAAAAG			
Fdx5in2	CTTTCTGGCTGGATGATGGGGCGATCGTTGACTCGTCTCACCATTG	downstream recombination site		Deletion of <i>fx7</i> ( <i>slI0662</i> )
Fdx5.2	TCAGTGCTGGTAACACCATGG			
Fdx6.1	TTCTCCACGCAGTTGGTGAC	upstream recombination site	Deletion of <i>fx8</i> ( <i>ssr3184</i> )	
Fdx6in1	GGTTCGTGCCTTCATCCGTCGACACCAGCATGGTATGGCGATC			
Gm1	GTCGACGGATGAAGGCACGAACC	Gm-cassette		Deletion of <i>fx9</i> ( <i>slr2059</i> )
Gm2	GTCGACCGAATTGTTAGGTGGCG			
Fdx6in2	CGCCACCTAACAATTCGGTCGACTTGTCGGATGGAACCTAAGC	downstream recombination site	Deletion of <i>fx9</i> ( <i>slr2059</i> )	
Fdx6.2	AAGCTCTGGACGCCATTACC			
Fdx7.1	CCGTACTTAATGAATCGGCC	upstream recombination site		Deletion of <i>fx9</i> ( <i>slr2059</i> )
Fdx7in1	TTGGCACCCAGCCTGCGCGACAGGCACTCCAGCGTTGCAC			
Sp-KG	TCGCGCAGGCTGGGTGCCAA	Sp-cassette	Deletion of <i>fx9</i> ( <i>slr2059</i> )	
Sp-rev	GCCCTCGCTAGATTTTAATGCGGAT			
Fdx7in2	ATCCGCATTAAAATCTAGCGAGGGCTTAATTGGGTGATGGAATCT	downstream recombination site		Deletion of <i>fx9</i> ( <i>slr2059</i> )
Fdx7.2	CTGAGTAGATTAATGTGGAC			
Fdx8.1	CGTTGGCTAGCATGTCACTG	upstream recombination site	Deletion of <i>fx9</i> ( <i>slr2059</i> )	
Fdx8in1	TCAATAATATCGAATTCCTGCAGTAAGGGTAGCGGACGTTCAA			
Cm1	CTGCAGGAATTCGATATTATTG	Cm-cassette		Deletion of <i>fx9</i> ( <i>slr2059</i> )
Cm2	AAGCTTGATGGCGGCACCTCGCT			
Fdx8in2	AGCGAGGTGCCGCCATCAAGCTTGGTTGGGAGGGGTCTAACTG	downstream recombination site	Deletion of <i>fx9</i> ( <i>slr2059</i> )	
Fdx8.2	CTCTGCCACTGTTAGGCTGC			
Fdx9.1	CGGAGGGGGAAACGGAAGAA	upstream recombination site		Deletion of <i>fx9</i> ( <i>slr2059</i> )
Fdx9in1	ATCAGAGATTTTTGAGACACAACGTGGGGCATTTCACCCGCACTACG			
Km1	CCACGTTGTGTCTCAAATCTCTGAT	Km-cassette	Deletion of <i>fx9</i> ( <i>slr2059</i> )	
Km2	ATCGCCCCATCATCCAGCCAGAAAAG			
Fdx9in2	CTTTCTGGCTGGATGATGGGGCGATCATCTTGCCGACTCCGCCA			

Fdx9.2	AATTCCAAAATAAATACCCC	downstream	
isiB1	ATGGATCATCCTCACACTTG	upstream recombination site	Deletion of flavodoxin ( <i>isiB</i> , <i>sII0284</i> )
isiBin1	GGTTCGTGCCTTCATCCGTCGACGATTACTGGAAAGTTACTAAGC		
Gm1	GTCGACGGATGAAGGCACGAACC	Gm-cassette	
Gm2	GTCGACCGAATTGTTAGGTGGCG		
isiBin2	CGCCACCTAACAATTCGGTCGACGCAATCCTAGGTAACCTAAG	downstream recombination site	
isiB2	CTGGTTTGTTCATGGTAGGAG		
pdhA1	CAGGCGATCGCGTAACCGTTG	upstream recombination site	Deletion of <i>pdhA</i> ( <i>sII1934</i> )
pdhAin1	TTGGCACCCAGCCTGCGCGATCTATGCGAAGTCGGTCAGC		
Sp-KG	TCGCGCAGGCTGGGTGCCAA	Sp-cassette	
Sp-rev	GCCCTCGCTAGATTTTAATGCGGAT		
pdhAin2	ATCCGCATTAATACTAGCGAGGGCACGTTACCGTTTGGGAGAA	downstream recombination site	
pdhA2	GACACCAACCGCTAATGGA		
NGOGATout1	CTATAGGGCGAATTGGGTACCCAAGTGAATTGCTTGGTGTGT	upstream recombination site	Deletion of NADH-dependent GOGAT ( <i>sII1502</i> )
NGOGATin1	GGTTCGTGCCTTCATCCGTCGACGACCTTCGTGGCAGGGCAT		
Gm1	GTCGACGGATGAAGGCACGAACC	Gm-cassette	
Gm2	GTCGACGAATTGTTAGGTGGCG		
NGOGATin2	CGCCACCTAACAATTCGGTCGACGCGGCGTTTGAGGAGAAT	downstream recombination site	
NGOGATout2	AGGGAACAAAAGCTGGAGCT ATAGGTTGCAAACCTCATTAGCTA		
FGOGATout1	CTATAGGGCGAATTGGGTAC ACCATCAGGCTGGGCAATTTGT	upstream recombination site	Deletion of ferredoxin-dependent GOGAT ( <i>sII1499</i> )
FGOGATin1	TTGGCACCCAGCCTGCGCGA GTGGCAACAGAGGAGTTTGCATA		
Sp-KG	TCGCGCAGGCTGGGTGCCAA	Sp-cassette	
Sp-rev	GCCCTCGCTAGATTTTAATGCGGAT		
FGOGATin2	ATCCGCATTAATACTAGCGAGGGC AGAAGACACTGACCTCTGTCTA	downstream recombination site	
FGOGATout2	AGGGAACAAAAGCTGGAGCT ACCGCAGGGACATTATGGGCTTA		
pfor-tag1	AGACCGTGTGCGAGCCAGCAAAGGGCCGATAGA	primer for RT-reaction	RT-PCR
pfor-tag2	AGACCGTGTGCGAGCCAGCAA	primers for PCR	
pfor-r	AACAATTTGGCCAGCTAACCGG		
pdhA-tag1	AGACCGTGTGCGACACGGGAATCCCTTCCCCAT	primer for RT-reaction	
pdhA-tag2	AGACCGTGTGCGACACGGGAAT	primers for PCR	
pdhA-rev	TTACGTTTGCAGTACCTATCGA		

rnpB-tag1	AGACCGTGTGCGACACCAATCATGGGGCAGGAA	primer for RT-reaction	
rnpB-tag2	AGACCGTGTGCGACACCAATCA	primers for PCR	
ndhD1out1	CTATAGGGCGAATTGGGTACGACTATCTGGGTAGTATGAACACTT	upstream recombination site	pD1 Deletion of <i>ndhD1</i> ( <i>slr0331</i> )
ndhD1in1	ATCAGAGATTTTGAGACACAACGTGGGGTGGTGATAAAACCGGTGAGAA		
Km1	CCACGTTGTGTCTCAAATCTCTGAT	Km-cassette	
Km2	ATCGCCCCATCATCCAGCCAGAAAG		
ndhD1in2	CTTTCTGGCTGGATGATGGGGCGATGACCCCCATTTATCTACTCTCCAT	downstream recombination site	
ndhD1out2	AGGGAACAAAAGCTGGAGCTTTCTTGGTCGACTTAAAAACCAAT		
ndhD2out1	CTATAGGGCGAATTGGGTACCAGGCGGCATAGTCTTCGAAAA	upstream recombination site	pD2 Deletion of <i>ndhD2</i> ( <i>slr1291</i> )
ndhD2in1	TCAATAATATCGAATTCCTGCAGAGTGTTCCAACATGGTAATAAGAA		
Cm1	CTGCAGGAATTCGATATTATTG	Cm-cassette	
Cm2	AAGCTTGATGGCGGCACCTCGCT		
ndhD2in2	AGCGAGGTGCCGCCATCAAGCTTTCAAAGTTCAACCCTAGTGATCTA	downstream recombination site	
ndhD2out2	AGGGAACAAAAGCTGGAGCTAACCGATGCCACACCGGTCTGATT		



Table S2: Liste of *Synechocystis* strains and mutants used in this study

Strain	Marker of genotype	<i>Synechocystis</i> WT background	Reference
WT		non-motile GT strain	Trautmann et al. 2012
WTm		motile PCC-M strain	Trautmann et al. 2012
$\Delta$ spkC	slI0599::km <sup>R</sup>	motile PCC-M strain	This study
$\Delta$ spkF	slr1225::km <sup>R</sup>	motile PCC-M strain	This study
$\Delta$ spkI	slI1770::km <sup>R</sup>	motile PCC-M strain	This study
$\Delta$ spkK	slr1919::km <sup>R</sup>	motile PCC-M strain	This study
$\Delta$ spkL	slI0095::km <sup>R</sup>	motile PCC-M strain	This study
$\Delta$ spkB	slr1697::km <sup>R</sup>	non-motile GT strain	France/ Bedu, Marseille, Rippka et al 1979
$\Delta$ spkD	slI0776::gm <sup>R</sup>	non-motile GT strain	France/ Bedu, Marseille, Rippka et al 1979
$\Delta$ spkE	slr1443::km <sup>R</sup>	non-motile GT strain	France/ Bedu, Marseille, Rippka et al 1979
$\Delta$ spkG	slr0152::spec <sup>R</sup> ::strep <sup>R</sup>	non-motile GT strain	France/ Bedu, Marseille, Rippka et al 1979
fx2/ $\Delta$ fx2	slI1382::km <sup>R</sup>	non-motile GT strain	Gutekunst et al. 2014
$\Delta$ fx3*	slr1828::em <sup>R</sup>	non-motile GT strain	Gutekunst et al. 2014
$\Delta$ fx4*	slr0150::cm <sup>R</sup>	non-motile GT strain	Gutekunst et al. 2014 *please note that the names of fx3 and fx4 are exchanged in Gutekunst et al. 2014
fx5 $\Delta$ fx5	slr0148::km <sup>R</sup>	non-motile GT strain	This study
$\Delta$ fx6	ssl2559::gm <sup>R</sup>	non-motile GT strain	This study
$\Delta$ fx7	slI0662::spec <sup>R</sup>	non-motile GT strain	This study
$\Delta$ fx9	slr2059::km <sup>R</sup>	non-motile GT strain	This study
$\Delta$ isiB	slI0284::gm <sup>R</sup>	non-motile GT strain	Gutekunst et al. 2014
$\Delta$ fx7 $\Delta$ fx9	slI0662::spec <sup>R</sup> , slr2059::km <sup>R</sup>	non-motile GT strain	This study
$\Delta$ fx7 $\Delta$ fx8 $\Delta$ fx9	slI0662::spec <sup>R</sup> , sss3184::cm <sup>R</sup> , slr2059::km <sup>R</sup>	non-motile GT strain	This study
$\Delta$ fx9 $\Delta$ isiB	slr2059::km <sup>R</sup> , slI0284::gm <sup>R</sup>	non-motile GT strain	This study
$\Delta$ n-gogat	slI1502::gm <sup>R</sup>	non-motile GT strain	This study

$\Delta$ f-gogat	<i>sll1499::spec<sup>R</sup></i>	non-motile GT strain	This study
$\Delta$ ndhD1 $\Delta$ ndhD2	<i>slr0331::km<sup>R</sup>, slr1291::cm<sup>R</sup></i>	non-motile GT strain	This study
$\Delta$ hk	<i>sll0593::spec<sup>R</sup></i>	non-motile GT strain	Theune et al. 2021
$\Delta$ glgP1 $\Delta$ glgP2	<i>sll1356::km<sup>R</sup>, slr1367::spec<sup>R</sup></i>	non-motile GT strain	Makowka et al. 2020

Table S3: Peptides of the alpha subunit of the pyruvate dehydrogenase (Slr1934) E1 component detected via MS/MS in band No. 1 (red box) of Fig. S8

Master	Accession	Description	Coverage [%]	# Peptides	# PSMs	# Unique Peptides	# AAs	MW [kDa]	calc. pI	Score Mascot: Mascot	# Peptides (by Search Engine): Mascot	Found in Sample: [S2] F2: Sample	# Protein Groups
Confidence	Annotated Sequence	Modifications	# Protein Groups	# Proteins	# PSMs	Master Protein Accessions	Positions in Master Proteins	Modifications in Master Proteins	# Missed Cleavages	Theo. MH+ [Da]	Found in Sample: [S2] F2: Sample	Confidence (by Search Engine): Mascot	Ions Score (by Search Engine): Mascot
slr1934	pyruvate dehydrogenase E1 component, alpha subunit	39	14	28	14	342	38,1	5.19	8.32	14	High	1	
High	[R].AGEGPTLIEALTYR.[F]		1	1	2	slr1934	slr1934 [248-261]		0	1490,785	High	High	80
High	[R].ATSQPEIYK.[K]		1	1	2	slr1934	slr1934 [207-215]		0	1036,531	High	High	28
High	[R].ATSQPEIYKK.[A]		1	1	4	slr1934	slr1934 [207-216]		1	1164,626	High	High	38
High	[K].CAEMYR.[G]	1xCarbamidomethyl [C1]; 1xOxidation [M4]	1	1	1	slr1934	slr1934 [39-45]		0	1008,391	High	High	32
High	[R].DHSVHALSAGVPAR.[E]		1	1	4	slr1934	slr1934 [82-94]		0	1329,702	High	High	64
High	[R].EVMAELFGK.[E]		1	1	1	slr1934	slr1934 [95-103]		0	1023,518	High	High	39
High	[R].EVMAELFGK.[E]	1xOxidation [M3]	1	1	2	slr1934	slr1934 [95-103]		0	1039,513	High	High	40
High	[K].FAAFMTEHELASNEELK.[A]	1xOxidation [M5]	1	1	1	slr1934	slr1934 [291-307]		0	1982,916	High	High	59
High	[R].FRGSLADPDEL.R.[S]		1	1	2	slr1934	slr1934 [262-274]		1	1512,755	High	High	44
High	[R].GHS LADPDEL.R.[S]		1	1	3	slr1934	slr1934 [264-274]		0	1209,586	High	High	61
High	[R].GHS LADPDELRS AEEK.[Q]		1	1	2	slr1934	slr1934 [264-279]		1	1753,835	High	High	44
High	[R].ILPELNTAEISLDR.[E]		1	1	1	slr1934	slr1934 [6-19]		0	1583,864	High	High	27
High	[K].LPILFVVENNK.[W]		1	1	1	slr1934	slr1934 [187-197]		0	1285,751	High	High	41
High	[R].QDEDYVCSTYR.[D]	1xCarbamidomethyl [C7]	1	1	1	slr1934	slr1934 [71-81]		0	1435,579	High	High	72
High	[K].VATEAVAR.[A]		1	1	1	slr1934	slr1934 [238-245]		0	816,4574	High	High	53