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A Hard Day's Night: Cyanobacteria in Diel Cycles

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Abstract

Cyanobacteria are photosynthetic prokaryotes that are influential in global geochemistry and are promising candidates for industrial applications. Because the livelihood of cyanobacteria is directly dependent upon light, a comprehensive understanding of metabolism in these organisms requires taking into account the effects of day-night transitions and circadian regulation. These events synchronize intracellular processes with the solar day. Accordingly, metabolism is controlled and structured differently in cyanobacteria than in heterotrophic bacteria. Thus, the approaches applied to engineering heterotrophic bacteria will need to be revised for cyanobacterial chassis. Here, we summarize important findings related to diurnal metabolism in cyanobacteria and present open questions in the field.

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An Introduction to Day-Night Cycles in Cyanobacteria

The daily fluctuation of light is a nearly universal evolutionary pressure for life on Earth. For cyanobacteria, microorganisms that rely almost exclusively on light for energy, the response to these day-night cycles is particularly wide-ranging and includes the redirection of central metabolism [1, 2] and sweeping changes in gene expression [3, 4]. As important primary producers and progenitors (via endosymbiosis) to the other oxygen-evolving photosynthetic organisms [5], cyanobacteria and their responses to light-dark cycles (LDCs) have broad implications for understanding photosynthesis in higher organisms and for characterizing a phylum that has tremendous ecological impact and biotechnological potential [6, 7]. For instance, natural diel cycles influence infection by viruses (see Box 1) and also carry significant economic consequences for industrial-scale growth (see Beyond Cyanobacteria section). However, due to practical experimental considerations, most research, and reviews to date, have focused on the unnaturally static condition of perpetual light. Recent work probing the physiology of cyanobacteria in LDCs has opened up a fresh perspective on the life cycle of this keystone bacterial phylum. In this review we consolidate current knowledge on cyanobacterial growth in LDCs by starting with the cellular functions that are important for the day and night states. Thereafter, we address the current understanding of regulatory processes that are required to coordinate the transitions between the two. Finally, we discuss how research on cyanobacterial biology in LDCs has revealed a paradigm for diurnal growth that generalizes beyond cyanobacteria.

Surviving the Day

Each day, a cyanobacterium faces the formidable task of turning inorganic carbon into the organic molecules of life via photosynthetic carbon dioxide assimilation. As the sun rises, the cell encounters numerous metabolic challenges. It must perform cellular division by binary fission while also storing energy reserves for the night, a period of photosynthetic quiescence. Daytime activities take place in the background of photosynthesis, a process vital to the cell and one that requires significant resources for efficient function. In the process, damaging reactive oxygen species (ROS) are generated as a byproduct [8]. As a consequence, cyanobacterial metabolism is carefully orchestrated in both space and time [4, 9, 10] (**Fig. 1, Key Figure**).

Central Carbon Metabolism. Much of cyanobacterial metabolism can be described as temporally partitioned, and generalized as anabolic during the day and catabolic at night. Daytime metabolism begins with shifting carbon flux from the oxidative pentose phosphate pathway (OPPP) to the Calvin-Benson-Bassham Cycle (CBBC), and is controlled via products of the photosynthetic light reactions [11-13]. One of the critical steps in this process is inactivation of CP12, a redox-sensitive protein that is a master regulator of the CBBC [14, 15]. During the night, oxidized CP12 structurally sequesters glyceraldehyde 3-phosphate dehydrogenase 2 (Gap2) and phosphoribulokinase (Prk) and inhibits the CBBC. This switch is mediated by the redox state of the cyanobacterial cell, which changes markedly depending on photosynthetic activity. At the onset of light, photosynthetic reducing equivalents are generated, reduced CP12 releases Gap2 and Prk, and CBBC activity resumes. Metabolomic analysis reveals that anabolic metabolism is upregulated during this phase of the day, including pathways related to

amino acid, nucleotide, and quinone biosynthesis [1]. Upregulation of amino acid and nucleotide synthesis agrees with physiological observations that protein synthesis and DNA replication occur to a much greater extent during the day [16, 17].

Energy Storage and Electron Sinks. A principal activity during the daytime is accumulation of excess photosynthate, which is stored as the glucose polymer glycogen. During growth in LDCs, glycogen accumulates during the day and serves two primary purposes: i) as an energy-storage polymer in preparation for night [1, 18-21], and ii) as a "regulatory valve" to assimilate excess reducing power produced under conditions of particularly high light intensity [8, 22-24]. Mutations that target the glycogen biosynthesis genes *glgA*, *glgC*, or *glgP* significantly hinder the ability of cells to grow and remain viable in LDCs, highlighting the importance of glycogen storage [25-27].

Because cyanobacteria cannot rapidly turn off photosynthetic activity, conditions that temporarily impair daytime cell growth can cause a dangerous buildup in membrane redox potential [8, 28, 29]. The role of glycogen as a photosynthetic electron sink has been highlighted by investigations into the cyanobacterial nitrogen-deprivation response [25, 30, 31]. Nitrogen deficiency causes a rapid accumulation of glycogen as the downstream utilization of carbon skeletons via diverse biosynthetic processes is inhibited [30, 32]. In strains unable to synthesize glycogen, nitrogen deprivation causes growth defects and oxidative damage at high-light intensities that otherwise do not affect wild-type (WT) cells [8, 23, 24]. Additionally, under nitrogen deprivation conditions, mutants unable to synthesize glycogen secrete pyruvate and tricarboxylic acid (TCA) pathway intermediates, possibly as an attempt to redirect photosynthetic

output [25, 30, 31, 33]. Overall, the buffering of cellular redox state through glycogen synthesis and degradation is an important aspect of regulating cellular physiology.

Surviving the Night

As the day ends and night begins, cyanobacteria face a drastic change of lifestyle. The past few decades of research have taught us a great deal about cyanobacterial processes that occur in the light, but little about cyanobacterial life in the dark. Although a cyanobacterium in darkness is typically viewed as being in a dormant state, the cell is not inactive and many processes still operate dynamically. Studies on transcription, translation, and metabolism have demonstrated specific adaptive responses to darkness in *Synechococcus elongatus* sp. PCC 7942 (for a historical synopsis of this model organism see Box 2). While overall rates of these processes may be lower than in the light, or even close to zero in the case of DNA replication [34, 35], they are coordinated such that the cell can conserve energy, ensuring its survival until light is available again. With photosynthesis unable to proceed in the dark, a suite of cell-wide changes occurs, ranging from shifts in ATP and reductant levels, to redirection in the flux of carbon compounds, to altered cell division activities.

Glycogen breakdown and the OPPP. The initiation of glycogen degradation is essential for nighttime survival in those cyanobacteria that are unable to utilize an external fixed carbon source [1, 26]. The majority of the released glucose is shunted directly into the OPPP rather than the glycolytic pathway favored by diverse heterotrophs [11, 13, 36]. The primary function of the OPPP at night is to generate

reducing power in the form of reduced nicotinamide adenine dinucleotide phosphate (NADPH) when the main production route during the day, photosynthesis, is not active [2, 26, 37]. This preference for the OPPP over glycolysis is functionally relevant in its production of NADPH over NADH. A number of enzymes in photosynthetic organisms have evolved a preference for NADPH over NADH as a reductant source, including some that are important for detoxifying ROS [38, 39]. Cyanobacteria possess a variety of antioxidant and redox-buffering systems, such as enzymatic defences involving superoxide dismutase and catalyases, and non-enzymatic strategies using glutathione, peroxiredoxin, and caroteniods. Of these ROS responses, reduced glutathione-mediated reactions are critical for protection from the multiple ROS species that cells encounter. Importantly, the reduction of the disulfide in glutathione is mediated by glutathione reductase, which is dependent on NADPH. It is therefore not suprising that NADPH produced through the OPPP appears to be vital to surviving LDCs; many mutations that cause LDC sensitivity result in high oxidative-stress buildup that is not cleared in the dark [2, 27, 40]. Thus, carbon flux through the OPPP is one of the most critical processes for nighttime survival, and inactivation of any of the three core OPPP genes *zwf*, *gap*, or *gnd* causes severely attenuated growth when cells are cultured in LDCs [27, 41-43]. In contrast, the OPPP genes are dispensable when cells are grown under continuous light where NADPH is generated by photosynthesis (Fig. 2). Detoxification of ROS using NADPH produced by the OPPP is a common theme in other higher organisms as well, such as in the hawk moth (see Beyond cyanobacteria).

Consistent with a paradigm of the OPPP as the primary catabolic route for stored carbon, a genome-wide transposon mutagenesis screen in *S. elongatus* showed that

enzymes of the regenerative phase of the canonical TCA cycle are not essential for viability under either continuous light or in LDC conditions [27]. Metabolic flux studies utilizing ^{13}C isotopic tracing in *Synechocystis* sp. PCC 6803 show that carbon primarily cycles within the OPPP even when that species grows heterotrophically [12, 44]. These data reveal a fundamental difference in the orchestration of carbon processing pathways between cyanobacteria and most heterotrophs. While many of the reactions that are usually part of a TCA cycle have been shown to be non-essential in *S. elongatus*, the first three steps leading to 2-oxoglutarate (2-OG) production are mediated by essential genes. It is likely that intermediates produced from other TCA-cycle precursor metabolites can be generated via alternative reactions, but 2-OG is the only known precursor for nitrogen assimilation into glutamine and glutamate in cyanobacteria. Production of 2-OG via the TCA reactions and subsequent nitrogen assimilation strongly influence NADPH reductant balance, because glutamine and glutamate biosynthesis require considerable reductant input via reactions that preferentially utilize NADPH over NADH [45]. Thus, nitrogen assimilation via 2-OG is inhibited in the dark, in part due to the induction of glutamine synthase inactivating factor (IF7) ([46]; also see **Supplemental Table S1)**.

Transcription and Translation.

Several specific enzymatic reactions important for LDCs have been discussed, but an additional layer of regulation should be taken into account: the transcription and translation of the genes that encode these enzymes, and many others, is dynamic across the day-night cycle. Generally, gene expression decreases in the dark, with a few exceptions [3, 47, 48]. Of the genes that are expressed upon dark exposure, some

158 can be classified as being induced by darkness independent of the time of day or
159 circadian phase [49], while others' expression profile in darkness relies on a functioning
160 circadian clock [3].

161 It is clear that circadian regulation provides a fitness benefit to cyanobacteria when cells
162 are in sync with the environmental LDC [50]. Yet, there is considerable overlap between
163 genes found to be induced during dark exposure at nighttime [3], those induced by dark
164 exposure during the day [49], and those induced by dim light during the late afternoon
165 [51] (**Supplemental Table S1)**. Although many of these genes encode either proteins of
166 unknown function or are annotated simply as *dig* for dark-induced gene, some gene
167 annotations provide clues to important functions during dark exposure. For example, a
168 protein with high sequence similarity to CP12 (*synpcc7942_0252)* [14], a regulator of
169 ribosomal status *hpf* (*lrtA; synpcc7942_2352*) [49], and a probable chaperone protein
170 (*hspA, synpcc7942-0241*) suggest that redox regulation and control of protein synthesis
171 and degradation are key processes in the dark.

172 Examination of the protein landscape tells a different, less dramatic story. Ansong et al.
173 [52] showed that only 4% of proteins in *Synechococcus* sp. PCC 7002 change in
174 abundance between light and dark. This trend is also seen in other cyanobacteria; for
175 example, few proteins were found to have >2 fold change across light and dark phases
176 in *Cyanothece*, a N_2-fixing cyanobacterium [53]. However, while the overall abundance
177 of protein is relatively constant, the rate of translation of proteins has been observed to
178 decrease in the dark [17, 49], and post-translational modifications and intracellular
179 localizations may act as strong regulatory components at the protein level in LDCs.

Orchestration of Cell Physiology Under Light-Dark Cycles

The many metabolic changes that occur during the day-night transition are managed through a complex network of interconnected regulatory processes. The majority of the genome in *S. elongatus* is differentially transcribed in LDCs. A number of factors drive both transcriptional and protein levels including: circadian clock output, chromosome topology, signaling nucleotides, and changing concentrations of metabolites, such as NADPH and ATP (**Fig. 3**).

Transcription Factors*.* While multiple transcription factors affect transcription in cyanobacteria, two with wide-ranging influence stand out. The response regulators RpaA and RpaB are master transcription factors in cyanobacteria that act as control hubs of LDC physiology. RpaA provides the key output mechanism to convey temporal information from the circadian clock, and is responsible for the clock-dependent regulation of hundreds of genes [54, 55].

The link between the circadian clock – whose oscillator comprises proteins KaiA, KaiB, and KaiC – and activity of the transcription factor RpaA lies with two histidine protein kinases, SasA and CikA, which engage with the oscillator complex at different times of day [56]. Association of SasA or CikA with the oscillator, stimulates an activity that either phosphorylates (SasA) or dephoshorylates RpaA (CikA) [57]. Phosphorylated RpaA (P-RpaA) activates genes important for nighttime metabolism, and in the absence of RpaA (or KaiA [27]) the clock is locked into a daytime transcriptional regime that leads to metabolic imbalance, increased oxidative stress, and death in LDCs [2, 27, 54,

58]. In contrast, a strain that is locked in a “nighttime” mode through elimination of KaiC experiences constitutive expression of the OPPP and other nighttime metabolic pathways. This situation is generally permissive for growth in LDCs, although the lack of a timing mechanism exacts a fitness cost that can be observed when WT and KaiC-null strains are grown together in competition [59].

Less investigated is the activity of RpaB. It acts as a light-responsive regulator of gene expression that is independent of the clock [60, 61]. Manipulating RpaB expression level or phosphorylation state affects growth in LDCs, and its output overlaps with that of RpaA in ways that are not yet understood [62]. While RpaA acts as the sole output signal of the clock, RpaB feeds in signals of environmental light status to the cell, and integration of both signals is important for fitness in LDCs.

Chromosome Topology. One striking cellular change in cyanobacteria that occurs over a daily cycle and is circadian-controlled is that of chromosome topology. The extent of chromosome or plasmid compaction in *S. elongatus* varies depending on the time of day, being compact and highly supercoiled at some times and relatively relaxed at others [9, 63-65]. When supercoiling is relaxed by addition of an inhibitor of DNA gyrase, changes in gene expression patterns are observed. Expression of genes that are normally expressed when the genome is in a highly supercoiled state decrease, and those normally expressed when the genome is relaxed increase, upon the addition of the inhibitor, consistent with expectations for the time-of-day peak expression of a given gene and the topological state. While mostly correlative, this relationship between DNA compaction and supercoiling with transcriptional outputs suggests another possible mechanism for global regulation. The details of how genome organization, compaction,

and accessibility to interacting proteins may impact gene expression, protein localization, and cell division [16, 66, 67] is an area ripe for further study.

Cellular Energy Levels Shifts in ATP/ADP and NADPH/NADP+ ratios unavoidably occur in LDCs due to temporal division of photosynthesis and catabolism. The dynamics of ATP changes in LDCs have been measured by many researchers over decades, but results vary. In *S. elongatus* ATP levels were reported to fall precipitously within the first 2 minutes after a shift to darkness and then recover to near pre-dark levels within 20 to 60 minutes [48, 68]. More recently, Rust et al. made similar measurements, but over a longer duration of dark exposure. They found that, despite this quick recovery, ATP levels gradually decrease overall during dark exposure, reaching ~50% of pre-dark level and remaining low until light is reintroduced, after which ATP concentration rapidly recovers [69]. The physiological implication of these changes are likely to be global for the cell. For instance, ATP concentration directly affects the status of the circadian oscillator and its stimulation of the RpaA kinase, SasA [69].

Cellular Redox. Cellular redox homeostasis is of critical importance for growth in LDCs [52, 70, 71]. Mutants that are unable to funnel carbon metabolites through the OPPP produce an insufficient amount of NADPH at night [2]. This deficit results in diminished ability to detoxify cellular ROS accumulated during the day, which requires NADPH reducing equivalents [2, 8, 72]. Thus, limiting nighttime NADPH production by compromising OPPP activity likely has severe redox consequences for broad metabolic and regulatory systems in photoautotrophic microorganisms.

One common theme between cyanobacteria and plant chloroplasts is the redox-dependent regulation of many proteins [73]. Although both photosynthetic reactions and the OPPP generate NADPH, reductant levels drop in the dark as the photosynthetic reactions cease [14, 68]. Compounding this redox change, NADH levels rise in the dark, leading to a further decrease in the NADPH / NADH ratio [14]. Overall, the concentrations of NADPH and $NADP^+$ vary to an even greater extent than that of ATP over the course of LDCs, and have been correlated with changes in the transcription of genes that encode enzymes of photosynthetic and metabolic homeostasis processes [71]. In addition, many metabolic enzymes are redox-modified. As LDCs drive the changes in oxidation state that control these modifications the subsequent enzymatic activities also follow suit [14, 52, 70, 73-76] (**Fig. 1**).

In the absence of notable changes in protein levels, redox modifications of metabolic enzymes likely play a major role in dictating metabolic flux when cells are in the dark. Indeed, many of the critical enzymes required for survival in darkness are redox modified, including Zwf, Gnd, GlgC, GlgA, GlgP, and enzymes that regulate nitrogen assimilation [70, 77, 78]. Redox regulation directly mediates the critical shift between CBBC and OPPP activity at light-to-dark transitions through the direct inhibition of the CBBC enzymes Gap2 and Prk by CP12 in a redox-controlled and light-dependent manner [14, 15]. Moreover, numerous redox-active proteins and small molecules – thioredoxins, ferredoxins, peroxiredoxins, and glutathione – can directly modify target protein thiols [77-81] and impact enzymatic activity [52, 70]. While many questions remain regarding the mechanisms of redox regulation during growth under LDCs, the

maintenance of redox homeostasis is unquestionably important for cyanobacterial metabolic processes at night.

Signaling nucleotides. Evidence is accumulating that signaling nucleotides act as intracellular messengers of LDCs. Levels of cAMP, c-di-AMP, c-di-GMP, and ppGpp are all light dependent in cyanobacteria [40, 49, 82, 83]. ppGpp in particular is a potent effector of transcription in *S. elongatus* that is synthesized after a light-to-dark transition and is critical for maintaining fitness during dark-induced stress [49]. Viability in cells unable to synthesize ppGpp is impaired after exposure to darkness, although the mechanisms behind this phenotype are not yet known.

c-di-AMP, a newly discovered signaling nucleotide in cyanobacteria [40, 84], is also important for survival of *S. elongatus* during darkness. Inactivation of its cyclase, *cdaA*, leads to increased oxidative stress and decreased survival of the night periods of LDCs [40]. c-di-AMP and ppGpp levels are linked in Firmicutes [85, 86], bringing up the possibility that their activity is coordinated in cyanobacteria grown in LDCs; however, this potential connection remains unexplored.

Beyond Cyanobacteria

The need for metabolic shifts as an adaptation to diel cycles is also a dominating force for plants and eukaryotic algae, and influences global biogeochemical cycles such as CO_2 balance. In plants, constant adjustments to physiology in response to changes in light quality, intensity, and duration are made through the use of photoreceptors [87]. Changes in the photoperiod of LDCs cue plants to undergo different phases of growth, development, and metabolism. In *Arabidopsis*, for example, darkness elicits the

291 expression of over 80 genes that code for functions involved in photosystem II inhibition,
292 starch degradation, chloroplastic translation inhibition, and redox regulation, similar to
293 what we observe in cyanobacteria [88].

294 The responses of plants to darkness and LDCs are also important from an economic
295 and agricultural point of view. Post-harvest storage of green leafy vegetables, such as
296 kale and cabbage, in LDCs results in significantly improved appearance and health
297 value of crops compared to constant-condition controls due to increased tissue integrity,
298 chlorophyll content, and levels of glucosinolates [89, 90].

299 Moreover, photosynthetic organisms are not alone in struggling with oxidative stress
300 during LDCs, and some of the preventative mechanisms they utilize may be conserved
301 in heterotrophs. For instance, hovering flight in nectarivores is an immensely energetic
302 endeavor that comes with high metabolic turnover that generates ROS. In hawkmoths,
303 like cyanobacteria, this oxidative stress is likely detoxified by activity of the OPPP during
304 rest, which by producing NADPH maintains sufficient quantities of reduced glutathione
305 to act as an antioxidant [91] (**Fig. 2**). This strategy for oxidative stress management
306 after intense exercise may be of importance in other animals as well [92].

307 **Concluding Remarks**

308 Lessons from the genetically tractable and evolutionarily ancient cyanobacteria can
309 educate us on the metabolic strategies that have evolved to enable organisms to deal
310 with LDC stress, a phenomenon that is difficult to study in many other phyla. Insights
311 from cyanobacteria can also aide in developing strategies to harness photosynthetic
312 organisms for real-world industrial, biotech, and agricultural applications.

In this review, we have attempted to condense much of the knowledge that now exists on the cyanobacterial response to LDCs. There remain, though, many areas for growth in this respect (see Outstanding Questions). Many variables such as protein and metabolite levels appear surprisingly constant in LDCs on average. However, this balance seems possible only in the context of large shifts in transcription, primary metabolism, and glycogen levels that occur during the day. These shifts, in turn, are caused by large alterations in ratios of electron carriers, redox poise, nucleotide signaling, and chromosome structure, all compelled by signals from the internal circadian clock and external environment. Thus, maintaining physiological balance in a world of potentially jarring LDCs is an exhaustive task that requires a vigilant sensing of external and internally generated signals, and appropriate cellular responses.

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Box 1 : Viral Infections and Light-Dark.

The ocean and freshwater lake ecosystems teem with cyanobacteria as well as viruses that infect them. The ocean is home to upwards of 10^{30} phage particles, and their interactions with marine life play a critical role in ecosystem dynamics [93] and biogeochemical cycles [94]. Viral particles infecting cyanobacterial cells co-opt and utilize ATP and NADPH produced by the cyanobacterium during photosynthesis. Light and photosynthesis influence the success of the phage infection, including the number of phage particles that are generated during infection and released upon lysis [95, 96]. For example, in *S. elongatus* light has a strong influence on infection by the contractile phage AS-1, and infection and light absorption are correlated, occurring in a diel pattern under LDCs [97].

Some phage carry metabolism genes that enhance host daytime metabolic flux. For instance, a phage-borne *psbA* gene, encoding the photosynthetic reaction center D1 protein, may help maintain host photosynthetic capacity during infection. Moreover, genes of the pentose phosphate cycle (*talC*, *gnd*, *zwf*, and even the *cp12* gene that encodes the inhibitory factor of the CBBC) have been found in phage and are preferentially expressed during infection in the light [98]. At night overall phage gene expression decreases 100-fold [99].

Box 2 : Brief history of *Synechococcus* sp. PCC 7942

Synechococcus elongatus sp. PCC 7942 is the official name of a cyanobacterium that was isolated prior to 1973 from a local freshwater source by students taught by K.W.

Floyd at California State University, San Francisco. Several samples were transferred to S.V. Shestakov of Moscow State University, whose lab demonstrated that one of the isolates, termed R-2, was transformable by chromosomal DNA from an antibiotic-resistant strain in their collection called *Anacystis nidulans* 602 [100]. The California isolate became known for many years as *A. nidulans* R2. In 1978 C.A.M.J.J. van den Hondel brought the strain from Moscow to the lab of G. van Arkel (University of Utrecht), where he was able to isolate mutants that carried the selectable transposon Tn*901* in the small endogenous plasmid of *A. nidulans* R2. This work began the era of recombinant DNA-based molecular genetics research in cyanobacteria [101]. Drs. van den Hondel and van Arkel deposited the strain in the Pasteur Culture Collection, where it was given the accession number PCC 7942. A re-evaluation of the taxonomic structure of the cyanobacteria in the mid-1980s resulted in a renaming of previous *Anacystis* strains to the genus *Synechococcus*. For a period of several years, publications regarding this organism referred to it as *Synechococcus* sp. strain PCC 7942 without a species designation. A second edition of Bergey's Manual of Systematic Bacteriology was published in 2001 which included a section on the classification of cyanobacteria. A chapter by M. Herdman, R. Castenholz, J. Waterbury, and R. Rippka described the *Synechococcus* clade Cluster 1.1, typified by PCC 6301, which is so closely related to PCC 7942 as to be members of the same species [102]. These authors proposed the binomial *Synechococcus elongatus*, which is a name in keeping with the Botanical Code of Nomenclature. Most papers published since that date refer to the former *A. nidulans* R2 as *S. elongatus* PCC 7942. Note that the name *Synechococcus elongatus* had been used previously with reference to thermophilic

cyanobacteria that are phylogenetically distant from PCC 6301 and 7942. The name *Thermosynechococcus elongatus* is now used for those thermophilic strains, but care is advisable in reading the literature to distinguish the *S. elongatus* that refers to PCC 7942 and PCC 6301, typically grown at 30 C, from the relatives of *T. elongatus*, typically grown at 45-50 C [103].

Figures

Figure 1. Shift work: snapshot of cellular activities across the day and night. ***A)*** A representation of an *S. elongatus* cell with an overview of the major metabolic pathways important for day-night physiology. ***B)*** Reactions of glycogen metabolism, TCA pathway, and central metabolism that are present in *S. elongatus* are provided in more detail. Green arrows in panel B indicate reactions where the respective enzyme has a detectable light/dark-dependent redox modification in *Synechocystis* sp. PCC 6803 [69]. Data about the peak expression time of circadian genes is indicated using data collected from *S. elongatus* PCC 7942 [9]. Genes colored in red peak in expression in the subjective morning, genes colored in blue peak in expression in the subjective evening, and genes colored in black have no detectable circadian rhythm in *S. elongatus*. Essential genes and genes that cause light-dark sensitive phenotypes when mutated are indicated by full yellow and half yellow-half dark grey circles, respectively. Abbreviations: PBS, phycobilisome; PSII, photosystem II; cyt b_6f, cytochrome b_6f; PSI, photosystem I; Fd(red), ferredoxin (reduced); Ru1,5P, ribulose-1,5-bisphosphate; 3PG, 3-phosphoglycerate; 1,3-BPG, 1,3-bisphosphoglycerate; GAP, glyceraldehyde-3-phosphate; F6P, fructose-6-phosphate; G6P, glucose-6-phosphate; G1P, glucose-1-phosphate; 6PGL, 6-phosphogluconolactone; 6PG, 6-phosphogluconate; Ru5P, ribulose-5-phosphate; ac-CoA, acetyl-CoA; aKG, a-ketoglutarate; Glu, glutamate; Gln, glutamine.

Figure 2. Detoxifying ROS in the diurnal world. High rates of photosynthetic metabolism in light generate damaging ROS. During the day NADPH produced via photosynthesis can aid in clearing such molecules. At night ROS production ceases, and remaining ROS is cleared by nighttime metabolism. Here, detoxification can be aided by NADPH produced through degradation of glycogen by the OPPP.

Figure 3. Getting the message: signaling pathways important for the day-night transition. The signaling pathways effective during the day-to-night transition consist of environmental sensing via RpaB and its cognate histidine protein kinase NblS, circadian status via RpaA, intracellular redox and energy status through changes in concentrations of NADPH and ATP and redox state of the plastoquinone (Pq) pools, chromosome compaction, and nucleotide signaling molecules such as ppGpp and cyclic-di-AMP (synthesized by RelA and CdaA, respectively).

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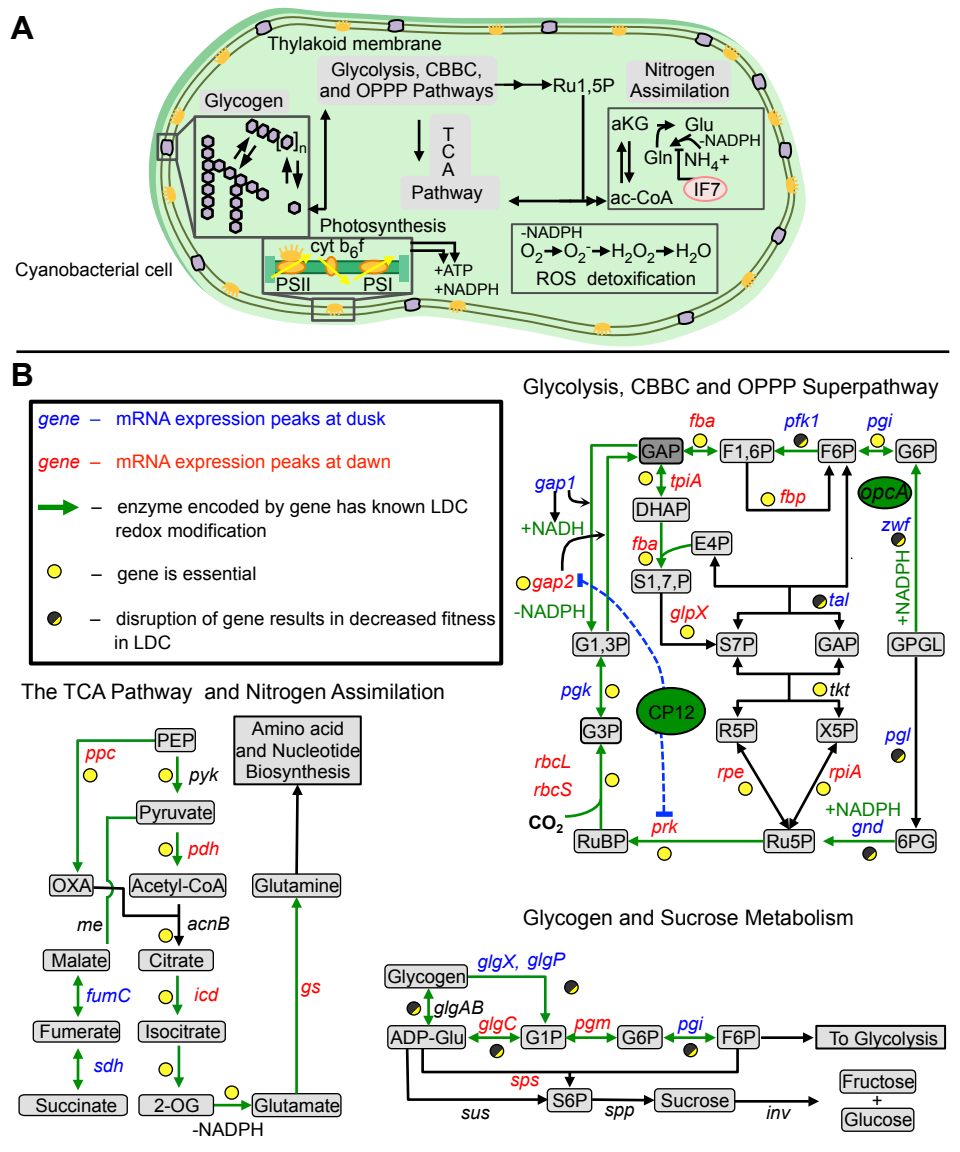
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Thylakoid membrane
Glycolysis, CBBC, and OPPP Pathways
Ru1,5P
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Gln
NH4+
ac-CoA
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Photosynthesis
cyt b6f
PSII
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+ATP
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-NADPH
O2→O2-→H2O2→H2O
ROS detoxification
Cyanobacterial cell
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gene – mRNA expression peaks at dusk
gene – mRNA expression peaks at dawn
– enzyme encoded by gene has known LDC redox modification
– gene is essential
– disruption of gene results in decreased fitness in LDC
Glycolysis, CBBC and OPPP Superpathway
fba
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pgi
GAP
F1,6P
F6P
G6P
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+NADH
zwf
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E4P
gap2
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S7P
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pgk
CP12
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G3P
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The TCA Pathway and Nitrogen Assimilation
Amino acid and Nucleotide Biosynthesis
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Isocitrate
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Succinate
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Glycogen and Sucrose Metabolism
glgX, glgP
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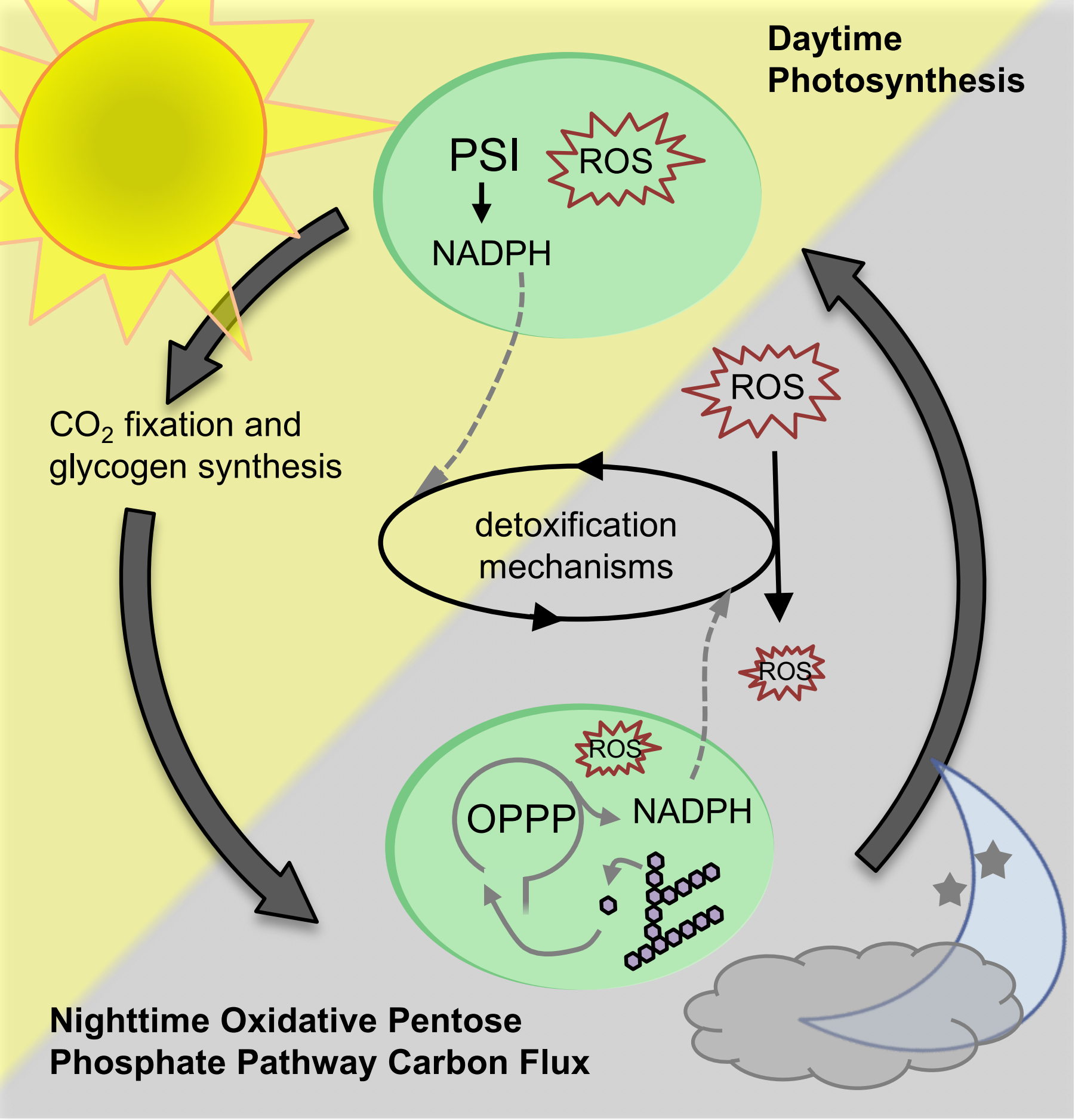
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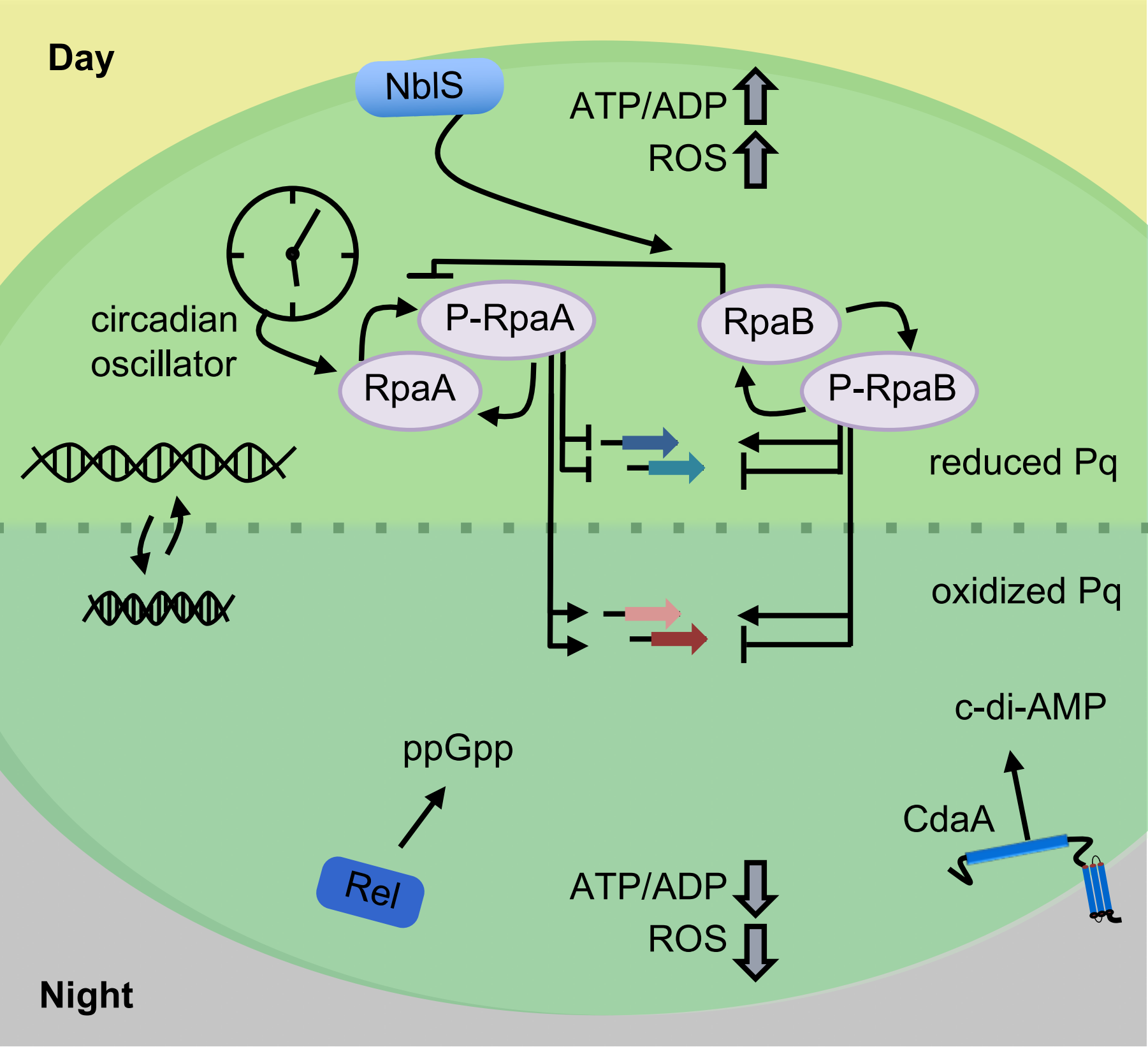
Day
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Night