



Diel Infection of Cyanobacteria by Cyanophages

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Cyanobacteria exhibit biological rhythms as an adaptation to the daily light-dark (diel) cycle. Light is also crucial for bacteriophages (cyanophages) that infect cyanobacteria. As the first step of infection, the adsorption of some cyanophages to their host cells is light-dependent. Moreover, cyanophage replication is affected by light intensity and possibly the host cell cycle. Photosynthesis and carbon metabolism genes have been found in cyanophage genomes. With these genes, cyanophages may affect the host metabolic rhythm. Field studies suggest that cyanophage infection of cyanobacteria in aquatic environments is synchronized directly or indirectly to the light-dark cycle. These discoveries are beginning to reveal how the daily light-dark cycle shapes the interaction of cyanophages and cyanobacteria, which eventually influences matter and energy transformation in aquatic environments.

Keywords: cyanobacterium, *Prochlorococcus*, cyanophage, circadian rhythm, circadian clock

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INTRODUCTION

The cyanobacteria are a large and diverse group of microorganisms that are typically oxygenic photoautotrophs. This group comprises the unicellular cyanobacteria *Synechococcus* and *Prochlorococcus*, which are responsible for a vast majority of primary production in freshwater and oligotrophic marine ecosystems (Scanlan and West, 2002). Bacteriophages (cyanophages) that infect cyanobacteria are abundant in aquatic environments (Bergh et al., 1989; Proctor and Fuhrman, 1990; Suttle et al., 1990), and 15% of marine cyanobacteria are estimated to be infected by cyanophages at any given time (Proctor and Fuhrman, 1990). Three morphotypes of lytic cyanophages have been found to infect *Synechococcus* (Suttle and Chan, 1993; Waterbury and Valois, 1993; Wilson et al., 1993) and *Prochlorococcus* (Sullivan et al., 2003): T4-like myoviruses, T7-like podoviruses, and siphoviruses. They are all double-stranded DNA viruses. Similar to bacteriophages infecting heterotrophic bacteria, the life cycle of cyanophages consists of adsorption to a host cell and replication, formation, and eventually release of mature progeny phages after lysis of the infected host cells. Different from other bacteriophage groups, the life cycle of cyanophages is influenced by light, which might be an adaptation to their photosynthetic host cells. The importance of light to cyanophages was reviewed by Clokie and Mann (2006) 10 years ago, and here we review the progress in the past 10 years with a focus on cyanophage infection of *Synechococcus* and *Prochlorococcus* under daily light-dark (diel) cycles.

BIOLOGICAL RHYTHMS OF CYANOBACTERIA

Circadian rhythms are ~24 h cycles of physiological processes found in most living organisms as a fundamental adaptation to the Earth's daily fluctuation in light and temperature (Dunlap, 1999).

The endogenous circadian clock systems generate these ~24 h rhythms in constant conditions (continuous light). The freshwater cyanobacterium *Synechococcus elongatus* PCC 7942 has been used as a model system to study the circadian clock of prokaryotes (Kondo et al., 1994). The cyanobacterial circadian clock regulates many important cellular processes, including cell cycle, amino acid uptake, nitrogen fixation, photosynthesis, carbohydrate synthesis, and respiration (Golden et al., 1997). The molecular mechanism of cyanobacterial circadian clock has been reviewed extensively (Johnson and Egly, 2014; Cohen and Golden, 2015), and here we introduce its major components for reference. The circadian clock of *S. elongatus* PCC 7942 is composed of three proteins KaiA, KaiB, and KaiC (Ishiura et al., 1998). KaiC is an autokinase and also an autophosphatase. KaiA can stimulate KaiC phosphorylation, while KaiB can promote KaiC dephosphorylation by inactivating KaiA. Interactions of these three Kai proteins generate circadian oscillations in the phosphorylation state of KaiC (reviewed by Dong and Golden, 2008; Johnson et al., 2008; Dong et al., 2010a). The KaiABC circadian clock is synchronized with the light-dark cycle through the intracellular adenosine triphosphate (ATP) (Rust et al., 2011) and oxidized plastoquinone levels (Kim et al., 2012; **Figure 1A**) that reflect photosynthetic activity. This circadian clock is responsible for genome-wide transcriptional oscillations in *S. elongatus* (Liu et al., 1995; Ito et al., 2009), with one group of genes peaking at subjective dawn and the other group peaking at subjective dusk (Ito et al., 2009). The response regulator RpaA serves as the master transcriptional regulator of these clock outputs (Markson et al., 2013).

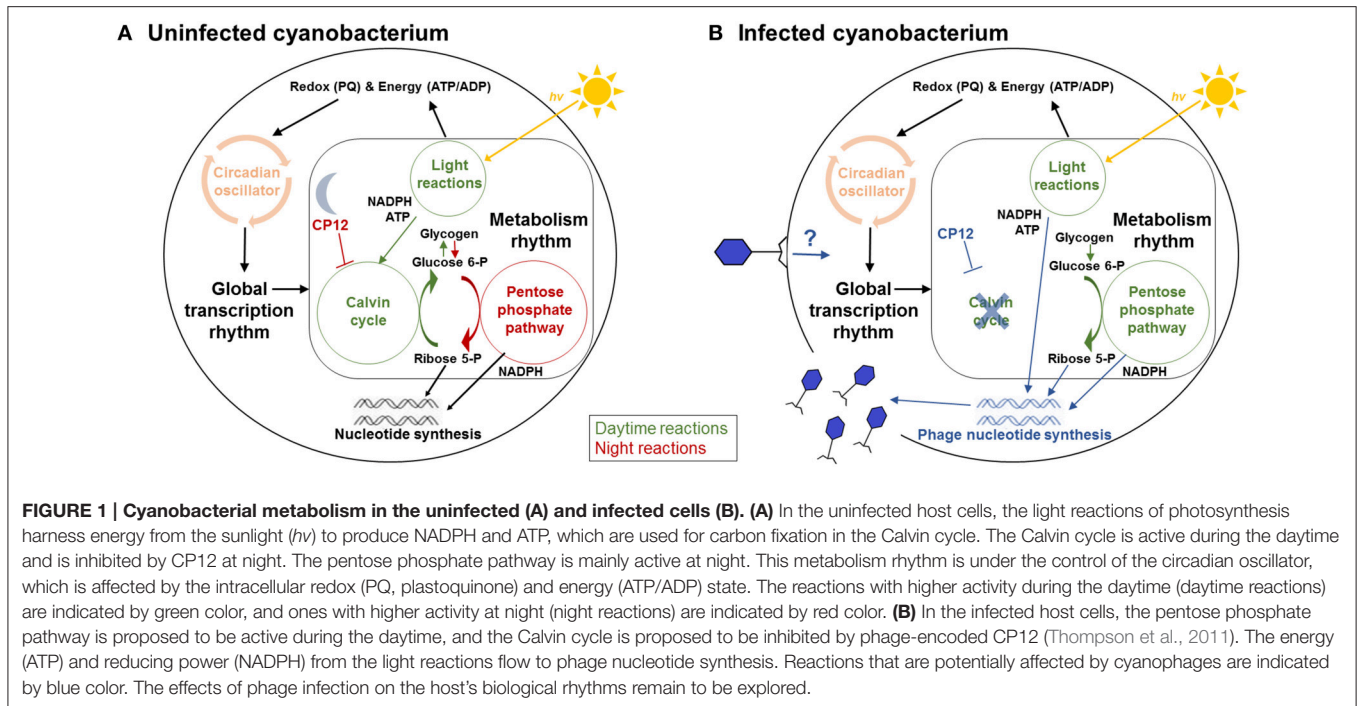
As the most abundant photosynthetic organism in the ocean, the unicellular cyanobacterium *Prochlorococcus* is responsible for almost 50% of the total primary production in oligotrophic regions (Partensky et al., 1999). Sequenced *Prochlorococcus* strains all encode *kaiB* and *kaiC*, but lack *kaiA* (Holtzendorff et al., 2008; Axmann et al., 2014), suggesting that their biological timing system is different from that of *S. elongatus* (Holtzendorff et al., 2008; Johnson and Egly, 2014). Indeed, synchronized *S. elongatus* cells are able to maintain periodic oscillations of cell cycle (Mori et al., 1996) and gene expression under continuous light (Liu et al., 1995), while *Prochlorococcus* lacks this ability (Holtzendorff et al., 2008). Therefore, *Prochlorococcus* maintains a diurnal rhythm rather than a circadian rhythm. Recombinant KaiC protein from *Prochlorococcus* MED4 is constitutively phosphorylated, and dephosphorylation of KaiC cannot be promoted by KaiB proteins from *Prochlorococcus* or *S. elongatus* (Axmann et al., 2009). These data suggest that *Prochlorococcus* may have lost the autonomous circadian clock, but retain an hourglass-like timing system that needs a daily resetting (Holtzendorff et al., 2008; Axmann et al., 2009).

When *Prochlorococcus* strain MED4 was grown under light-dark cycles, the expression of around 80% genes showed diel oscillations, with the majority of transcripts peaking at dawn or dusk (Zinser et al., 2009; Waldbauer et al., 2012). Photosystem I and II genes showed maximum expression at dawn, just in time to harvest energy from sunlight (Zinser et al., 2009). The Calvin cycle genes had maximum transcript abundances at dawn, and this was thought to be an anticipatory regulation for

the immediate increase of biomass when the light energy was captured (Zinser et al., 2009). On the other hand, the pentose phosphate pathway genes had maximum expression at dusk, which may prepare for glycogen catabolism at night (Zinser et al., 2009). Diel oscillations were also observed for nearly half of all *Prochlorococcus* population transcripts in the North Pacific Subtropical Gyre (Ottesen et al., 2014), which were similar to those of lab cultures (Zinser et al., 2009; Waldbauer et al., 2012). Moreover, the co-occurring heterotrophic bacterioplankton groups displayed diel periodicity in many transcripts as well, which is probably caused by the tight metabolic coupling between primary producers like *Prochlorococcus* and consumers living in the open ocean (Ottesen et al., 2014). Since microorganisms constitute more than 90% of the living biomass in the sea (Azam and Malfatti, 2007), biological rhythms of marine cyanobacteria are likely to influence matter and energy transformation in the world's oceans.

LIGHT-DEPENDENT AND LIGHT-INDEPENDENT ADSORPTION OF CYANOPHAGES ONTO THEIR HOST CELLS

Phage adsorption to a host cell is the first step of infection. During adsorption, phage tails recognize specific receptors on the host cell, such as lipopolysaccharide, membrane proteins, pili, or flagella (Labrie et al., 2010). Cyanophages infecting freshwater (Cséke and Farkas, 1979; Kao et al., 2005) and marine *Synechococcus* (Jia et al., 2010) have been used to study the effect of light on cyanophage adsorption onto their host cells. Cyanophage AS-1 is a myovirus that infects closely related freshwater *S. elongatus* strains PCC 6301 and PCC 7942. When *S. elongatus* PCC 6301 was grown under continuous light, 70% of cyanophage AS-1 were adsorbed within 15 min, and a maximum adsorption of 80% was reached after 20 min (Cséke and Farkas, 1979). When the PCC 6301 culture was moved to the dark after infection, only 40% of cyanophage AS-1 were adsorbed after 20 min (Cséke and Farkas, 1979). The adsorption of cyanophage AS-1 to *S. elongatus* PCC 7942 was also lower in the dark than that in the light (Kao et al., 2005). Jia et al. studied the adsorption of nine different cyanophages to their host marine *Synechococcus* WH7803 (Jia et al., 2010). Using unsynchronized *Synechococcus* WH7803 cultures, they found that the adsorption of myoviruses S-BnM1, S-PWM3, S-PM2, and podovirus S-BP3 was lower in the dark than that in the light (light-dependent adsorption), while the adsorption of myoviruses S-PWM1, S-BM3, S-MM4, S-MM1, and S-MM5 was not affected by darkness (light-independent adsorption) (Jia et al., 2010). Light-dependent adsorption of cyanophage S-PM2 was also seen with synchronized *Synechococcus* WH7803 cells, and the percentage of adsorbed phage did not change significantly at different times of the day, indicating that the adsorption of cyanophage S-PM2 was not influenced by the circadian rhythm of the host cells (Jia et al., 2010). The authors did not check whether the adsorption of light-independent cyanophages was affected by the circadian rhythm of the host cells. This light-dependent adsorption could



be explained by light-induced conformational changes in either the phage tails or the host receptors (Jia et al., 2010), but the exact mechanism is still unexplored.

EFFECT OF LIGHT ON CYANOPHAGE REPLICATION IN THE HOST CELLS

A strong positive correlation between light intensity and burst size has been shown on cyanophages infecting cyanobacteria *Plectonema boryanum* (Padan et al., 1970; Sherman and Haselkorn, 1971), *Nostoc muscorum* (Adolph and Haselkorn, 1972), *Synechococcus* (Mackenzie and Haselkorn, 1972; Sherman, 1976; Kao et al., 2005), and *Prochlorococcus* (Lindell et al., 2005; Thompson et al., 2011). Similar to darkness, photosynthesis inhibitors can also significantly reduce the burst sizes of cyanophages (Adolph and Haselkorn, 1972; Mackenzie and Haselkorn, 1972; Sherman, 1976; Lindell et al., 2005). When *Prochlorococcus* MED4 was infected by the T4-like myovirus P-HM2 in the dark, phage genomic DNA replication inside the host cells stopped, and phage transcript abundances decreased significantly (Thompson et al., 2011). These studies indicate that cyanophage replication derives most of its energy and certain resources from photosynthetic metabolism of the host cell (Sherman, 1976).

The importance of light to cyanophage replication is also revealed by phage-encoded genes for the light reactions of photosynthesis (Mann et al., 2003; Lindell et al., 2004; Millard et al., 2004; Sullivan et al., 2006). Cyanophages carry *psbA* and *psbD* genes, encoding the D1 and D2 proteins of the core of photosystem II, respectively (Mann et al., 2003). Phage D1 protein was detected when *Prochlorococcus* MED4 was

infected by cyanophage P-SSP7 (Lindell et al., 2005). Phage *psbA* was highly transcribed when *Synechococcus* WH7803 was infected by cyanophage S-PM2 (Clokic et al., 2006a; Millard et al., 2010). The expression of cyanophage-encoded D1 and D2 proteins is proposed to maintain the photosynthetic activity of the infected host cells and therefore provide energy for cyanophage replication (Mann et al., 2003). Many genes related to photosynthesis have also been found in cyanophage genomes (reviewed by Clokic and Mann, 2006; Puxty et al., 2015).

CYANOPHAGE INFECTION AND THE HOST'S CELL CYCLE

Studies on phages infecting *Escherichia coli* showed that the largest burst size was achieved after the completion of host DNA replication and immediately prior to cell division (Starka, 1962; Storms et al., 2014). This is likely due to the increased availability of intracellular resources for the formation of phage progeny (Storms et al., 2014). Under light-dark cycles, *S. elongatus* PCC 7942 cells divide mainly during the daytime and stop dividing early at night (Mori et al., 1996). The cell division pattern of synchronized *S. elongatus* PCC 7942 cells persists under continuous light for several days (Mori et al., 1996), and it is controlled by the circadian clock (Mori et al., 1996; Dong et al., 2010b). Using *S. elongatus* PCC 7942 and cyanophage AS-1, Kao et al. found that the infections started between dawn and noon resulted in larger burst sizes than the ones started in the afternoon or at night (Kao et al., 2005). It is not clear whether the diel infection pattern of cyanophage AS-1 is determined by the light-dark cycle or the cell cycle, or both. Future infection experiments using light-dark synchronized *S. elongatus* PCC

7942 cells under continuous light will help distinguish the effects of the light-dark cycle and the host cell cycle on burst sizes. Different from *S. elongatus* PCC 7942, *Prochlorococcus* cells replicate their DNA in the afternoon and divide at night (Vaulot et al., 1995; Liu et al., 1997; Shalapyonok et al., 1998; Holtzendorff et al., 2008; Zinser et al., 2009). It remains to be studied how the cell cycle of *Prochlorococcus* affects cyanophage infection.

POTENTIAL INTERACTION BETWEEN CYANOPHAGE AND THE HOST'S TIMING SYSTEM

For mammalian viruses, it has been shown that viral proteins can interact with the host's circadian clock proteins (Kalamvoki and Roizman, 2010), and these interactions are important for viral replication and gene expression (Kalamvoki and Roizman, 2010; Benegiamo et al., 2013). Kao et al. examined whether mutations in the circadian clock of *S. elongatus* PCC 7942 affected cyanophage AS-1 infection (Kao et al., 2005). They infected the wild-type strain and two mutants ($\Delta kaiA$ and $\Delta kaiB$) with cyanophage AS-1 under continuous light and did not see any significant difference in burst sizes (Kao et al., 2005). They did not examine whether the burst size of AS-1 was affected when infecting the $\Delta kaiA$ or $\Delta kaiB$ mutants under light-dark cycles.

While mutations in the circadian clock proteins of cyanobacteria do not seem to affect cyanophage infection, it is not clear whether cyanophage infection affects the host's circadian clock. In cyanobacteria, the Calvin cycle is linked to the pentose phosphate pathway, with several reactions shared by both pathways (Zinser et al., 2009; **Figure 1A**). During the daytime, the light reactions of photosynthesis harness energy from the sunlight and split water to produce NADPH (an electron carrier) and ATP (an energy carrier). The Calvin cycle consumes NADPH and ATP to fix CO₂ and to produce glucose 6-phosphate, which is stored as the branched glucose polymer glycogen (**Figure 1A**). At night, the Calvin cycle is inhibited by the Calvin cycle inhibitor CP12 (Wedel and Soll, 1998; Tamoi et al., 2005), and glycogen is mostly oxidized in the pentose phosphate pathway (Pelroy et al., 1972) to produce NADPH and ribose 5-phosphate (**Figure 1A**), which can be used for carbon skeletons. The rhythm of glycogen metabolism, which is controlled by the circadian clock, can affect the cellular ATP/ADP ratio (Pattanayak et al., 2014). Thus, the circadian clock outputs (glycogen) can feed back through metabolism to control the circadian clock inputs (ATP) (**Figure 1A**; Pattanayak et al., 2014). Cyanophage genomes contain the pentose phosphate pathway genes (Mann et al., 2005; Sullivan et al., 2005, 2010; Weigele et al., 2007; Clokie et al., 2010) and the Calvin cycle inhibitor gene *cp12* (Thompson et al., 2011). Experiments with *Prochlorococcus* and *Synechococcus* phages suggested (Thompson et al., 2011) that cyanophages can use these auxiliary metabolic genes (Breitbart et al., 2007) to enhance the host's photosynthesis and pentose phosphate pathway for the production of NADPH, ATP, and ribose 5-phosphate, which

can power nucleotide biosynthesis that is critical for phage reproduction (**Figure 1B**). During the daytime, cyanophage infection may inhibit the Calvin cycle by phage-encoded CP12 protein (**Figure 1B**). By reversing the host's metabolic rhythm, cyanophage infection might affect the cellular ATP/ADP ratio, which can control the circadian clock of the infected host cells.

DIEL OSCILLATIONS IN CYANOPHAGE ABUNDANCE IN AQUATIC ENVIRONMENTS

Several studies suggest that cyanophage infection of cyanobacteria in aquatic environments is synchronized directly or indirectly to the light-dark cycle. In natural aquatic environments, virus decay has been attributed to adsorption to heat-labile particles, inactivation by solar radiation, and grazing by flagellates (Suttle and Chen, 1992), which may not exist in lab cultures. Therefore, cyanophage abundances in aquatic environments are affected by both production and decay. Bettarel et al. (2002) measured the abundances of *Synechococcus*, heterotrophic bacteria, heterotrophic nanoflagellates, and viruses in September 2001 every 3 h for 3 days at a depth of 1 m in the N.W. Mediterranean Sea. They only found apparent diel patterns for *Synechococcus* and viruses: *Synechococcus* was maximal at midnight, and viruses were maximal in the late afternoon and were minimal at midnight (Bettarel et al., 2002). Although they did not measure *Synechococcus*-specific viruses, they suggested that the diel pattern of viruses was mainly due to cyanophage production through *Synechococcus* mortality since viral infection of heterotrophic bacteria was rare (Bettarel et al., 2002). Clokie et al. used marine *Synechococcus* WH7803 to measure cyanophages from seawater samples at different depths (10, 25, and 50 m) in the Indian Ocean (Clokie et al., 2006b). With sampling every 6 h for a 24-h period, cyanophage abundances were similar for most sampling time-points at 10 m, but showed a distinct peak shortly after midnight (Clokie et al., 2006b). Different from the 10 m sample, cyanophage abundances at 25 and 50 m did not show strong diel variations (Clokie et al., 2006b). Using real-time PCR and strain-specific primers, Kimura et al. measured *Microcystis* and its cyanophage abundances from surface waters of a freshwater pond in Japan (Kimura et al., 2012). They sampled every 3 h over a period of 24 h in two different days (Kimura et al., 2012). For both days, *Microcystis* abundances were highest after midnight, which may be caused by diel vertical migration of *Microcystis* (Kimura et al., 2012). The highest *Microcystis* cyanophage abundances were found at dusk in one day and about 3 h after dusk in the other day (Kimura et al., 2012). Recently, the growth and mortality of *Prochlorococcus* in the subtropical Pacific gyre was found to be synchronized to the light-dark cycle, with the highest mortality rate at night (Ribalet et al., 2015). This could be explained by light-dark synchronized infection of *Prochlorococcus* by cyanophages, although synchronized grazing by protists is also possible (Ribalet et al., 2015).

CONCLUDING REMARKS

Cyanobacteria exhibit biological rhythms as an adaptation to the natural daily light-dark cycle, with many biological processes connected by the circadian clock into a cellular network (Shultzaberger et al., 2015). Light is also crucial for cyanophage infection of cyanobacteria. It remains to be explored how cyanophage infection affects the biological rhythms of cyanobacteria. However, most cyanophage infection studies have been conducted under continuous light, and the host cells were not synchronized. Future infection experiments with light-dark synchronized cyanobacteria are needed to reveal the interaction between cyanophage infection and the host biological rhythms. Additionally, more field studies should be carried out to understand the diel infection patterns of cyanobacteria by cyanophages in different aquatic environments. Having

coevolved with cyanobacteria under light-dark cycles for millions of years, cyanophages will give us new insights into the biological rhythms of their host cells. With these data, we can begin to understand how the daily light-dark cycle shapes the interaction of cyanophages and cyanobacteria, which eventually influences matter and energy transformation in aquatic environments.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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