Cell Host & Microbe

Preview

Viral theft of light: A cyanophage protein dismantles cyanobacterial photosynthesis to accelerate infection

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https://doi.org/10.1016/j.chom.2025.12.012

Auxiliary metabolic genes, acquired by cyanobacterial viruses (cyanophages) from their hosts, are thought to manipulate host metabolism during infection. A recent study by Nadel et al. performed *in vivo* experiments to reveal how cyanophages use a viral *nblA* gene to accelerate infection by degrading the photosynthetic machinery of marine cyanobacteria.

Marine picocyanobacteria, primarily comprising the genera *Synechococcus* and *Prochlorococcus*, are the most abundant photosynthetic organisms on Earth and are responsible for over half of the gross primary production in some oceanic regions.[1] However, their ecological success is continually threatened by cyanophages, the viruses that infect them. A fascinating adaptation of cyanophages is the acquisition of host-derived auxiliary metabolic genes (AMGs). First proposed in cyanophage research, the term AMG refers to viral genes that are not directly involved in viral replication but are hypothesized to manipulate host metabolic pathways to optimize conditions for viral production.[2] The earliest identified AMGs are *psbA* and *psbD*, which encode core subunits of photosystem II.[3] Subsequent studies have revealed AMGs involved in a wider range of metabolic processes, including carbon fixation,[4] nitrogen assimilation,[5] and phosphorus uptake.[6] However, current understanding of AMG function relies heavily on bioinformatic predictions, which carry inherent risks of misannotation and often lack experimental validation.[7] Experimental insights into AMG activity have primarily been obtained through indirect approaches, such as transcriptomic (RNA sequencing) and proteomic profiling of infected host cells,[4,6] or through heterologous expression of AMGs.[5] These methods lack direct evidence to precisely define the function of AMGs in viral infection. Moreover, until the recent development of efficient genetic editing systems for marine cyanophages,[8] conducting definitive functional studies through *in vivo* experimentation remained a considerable challenge.

A recent study published in *Nature* by Nadel et al.[9] bridges this critical knowledge gap by systematically investigating the role of the cyanophage-encoded NblA during infection. In cyanobacteria, the NblA protein is known to function as a proteolysis adaptor under nitrogen-deprivation conditions to degrade the massive light-harvesting antenna complexes called phycobilisomes. After the *nblA* gene was discovered in cyanophage genomes, *in vitro* experiments were conducted to demonstrate that the phage-encoded NblA protein performs functions similar to those of the host NblA protein.[5] Using the newly developed genetic-editing method,[8] Nadel et al. constructed a precise knockout *nblA* mutant (Δ*nblA*) in the cyanophage S-TIP37, which infects the marine picocyanobacterium *Synechococcus* sp. WH8109. By comparing the infection dynamics of the Δ*nblA* mutant with those of the wild-type phage (WT), the authors revealed a profound advantage conferred by NblA to the phage. Specifically, the Δ*nblA* mutant exhibited a dramatically extended latent period of 8–10 h, compared with ∼3 h for the WT phage. Complementation experiments confirmed that this extended latent period was due to the loss of *nblA*, underscoring its critical role in accelerating the infection cycle.

The mechanistic basis for this acceleration lies in the targeted degradation of the host's photosynthetic apparatus (Figure 1A). The authors showed that infection with the WT phage, but not the Δ*nblA* mutant, led to rapid and substantial disassembly and degradation of the phycobilisome. This degradation directly impaired the energy transfer from phycobilisomes to the photosynthetic reaction centers, resulting in a 50% reduction in the photochemical quantum yield of photosystem II during infection. The proteomics data further revealed that viral NblA directs a stepwise dismantling of phycobilisomes, starting from the peripheral rods and moving inward, similar to the process found previously in uninfected cyanobacteria. Moreover, viral NblA targeted not only the phycobilisome subunits but also other photosynthesis-related proteins, including photosystem proteins and carbon fixation enzymes. More broadly, proteins involved in translation, carbon metabolism, and cell division were cleaved, suggesting that NblA-mediated proteolysis disrupts multiple host processes beyond light harvesting. This widespread proteolysis likely liberates a massive pool of amino acids and cellular resources that are repurposed for the synthesis of progeny phage particles (Figure 1A).

The ecological and evolutionary significance of these findings is underscored by comprehensive metagenomic analyses. The authors revealed that *nblA* is

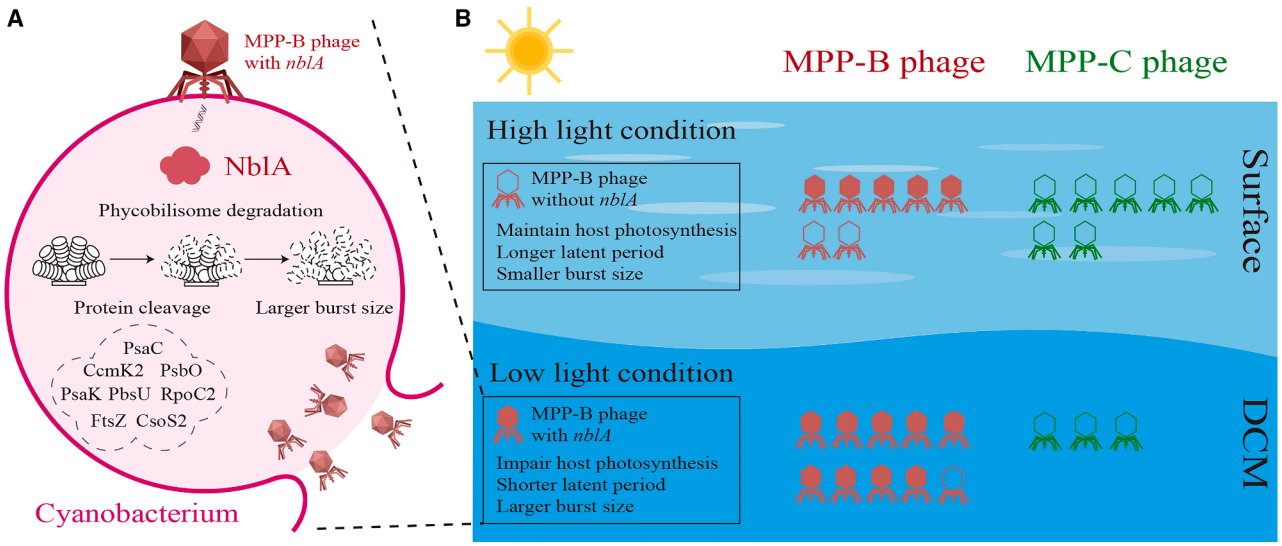

Figure 1. Ecological impact and depth distribution of cyanophages with the *nblA* gene

(A) Functional mechanism of viral NblA during infection. Upon infection by an MPP-B cyanophage carrying the *nblA* gene, the viral NblA protein is expressed and directs proteolytic degradation of phycobilisome subunits as well as other host metabolic proteins. The targeted protein breakdown leads to an increased phage burst size.

(B) Depth-dependent distribution of *nblA* among dominant T7-like cyanophage groups. MPP-B and MPP-C cyanophages constitute the majority of T7-like cyanophages in marine ecosystems. The phage cartoon illustrates their relative abundance in surface waters versus the deep chlorophyll maximum (DCM). Most MPP-B phages carry *nblA* (solid red) and are more abundant in the DCM, whereas MPP-C phages lack *nblA* (hollow green) and are more abundant in surface waters. The distinct infection strategies employed by cyanophages without and with *nblA* enable them to adapt to high-light and low-light conditions, respectively.

a common AMG, present in 46.4% of T7-like cyanophage genomes and found in phages infecting all major picocyanobacterial lineages, including the phycobilisome-lacking *Prochlorococcus* strains. Quantifying its distribution in the global oceans showed that *nblA* is particularly prevalent in the abundant marine picocyanobacteria podovirus clade B (MPP-B) clade of T7-like cyanophages, with 72% carrying *nblA* in surface waters and 89% at the deep chlorophyll maximum (DCM). This depth-dependent distribution aligns with the ecological hypothesis that NblA provides a greater advantage under low-light conditions in the DCM layer, where cyanobacteria invest more resources in their photosynthetic machinery, thereby providing a richer nutrient reservoir for phages to exploit (Figure 1B). In contrast, a previously identified marine picocyanobacteria podovirus clade C (MPP-C) clade, although reaching abundances comparable to that of the MPP-B clade in surface waters, shows a marked decrease in relative abundance with depth.[10] This distribution pattern aligns with its lack of AMGs, including the *nblA* gene.[10] The distinct depth-dependent distribution patterns of MPP-B and MPP-C phages suggest that, much like their cyanobacterial hosts, cyanophages have evolved divergent light-adaptation strategies across different water layers.

Intriguingly, cyanophages often carry functionally opposing AMGs, such as *nblA* and *psbA* (a photosystem II gene).[3] These genes, though both involved in photosynthesis, may exert antagonistic effects during infection, which warrants further mechanistic investigations. The authors proposed a plausible resolution: the fitness benefit of each gene may depend on ambient environmental conditions. For instance, *psbA* likely supports photosynthesis under high-light stress by repairing photodamage, whereas *nblA* may be particularly advantageous in low-light environments, where the hosts invest heavily in light-harvesting complexes that can be degraded and repurposed by the phage.

In conclusion, Nadel et al. provided a mechanistic and ecological narrative of how a cyanophage AMG can tip the scales in favor of phage fitness at the expense of host function and cellular integrity. The authors estimated that cyanophage-encoded NblA proteins collectively reduce light harvesting by oceanic picocyanobacteria by 0.2%–5% across the global photic zone. This represents a previously unrecognized yet significant viral-mediated constraint on marine primary production. A large number of phage AMGs still require experimental validation. This research provides implications for conducting *in vivo* functional studies to analyze how cyanophage AMGs affect the biogeochemistry of the world's oceans.

ACKNOWLEDGMENTS

This work was supported by grants to Qinglu Zeng from the National Natural Science Foundation of China (project number 92451302), the Research Grants Council of the Hong Kong Special Administrative Region, China (C6012-22G), and the Southern Marine Science and Engineering Guangdong Laboratory (Zhuhai) (SML2024SP022 and SML2024SP002). We thank Lanlan Cai for useful discussions.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used Deepseek in order to improve the language

and readability. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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