Viral nature of the aquatic ecosystems

Authors and affiliations

Daichi Morimoto[1], Kento Tominaga[1], Hiroaki Takebe[1], Sigitas Šulčius[2], Takashi Yoshida[1]

[1]Graduate School of Agriculture, Kyoto University, Kitashirakawa-Oiwake, Sakyo-ku, Kyoto 606-8502, Japan

[2]Laboratory of Algology and Microbial Ecology, Nature Research Centre, Akademijos 2, 08412 Vilnius, Lithuania

Correspondence

Takashi Yoshida

Tel: +81-75-753-6217

Fax: +81-75-753-6226

E-mail: yoshiten@kais.kyoto-u.ac.jp

Abstract

Viruses infecting microorganisms are ubiquitous and highly abundant in aquatic environments. They considerably affect the dynamics, diversity, and evolution of their host microorganisms. In this review, we discuss the ecological implications of viruses from the perspectives of the biogeochemical cycles, microbial diversity, and virus–host coevolutionary dynamics in aquatic environments. Generally, viruses redirect host metabolism toward reproduction through molecular host–virus interactions characterized by the compositional and stoichiometric changes in intracellular metabolites, which are eventually released into the environment when the infected host cells are lysed, thus also changing the chemical composition of the water. Therefore, the modulation of metabolite biosynthesis and promotion of their recycling are major viral functions. Viruses also maintain microbial community diversity via increased infection and lysis rates of the dominant taxa and genotypes in a frequency-dependent manner, thereby allowing the co-existence of members with various competitive abilities. Finally, viruses can expand their own genotypic diversity and that of the host through complex defense and counter-defense interactions, including loss of host fitness due to the cost of resistance and the possible need for antiviral defense-specific (e.g., intra- vs. extracellular) changes in the hosts genome diversification. Continuous interactions drive

the coevolution of hosts and viruses, thereby increasing both the host and viral micro-diversity. Hence, these fundamental functions are viral “raison d’etre” and are essential for the functioning of aquatic ecosystems and its components.

Keywords

Virus-host interactions, Biogeochemical cycle, Microbial diversity, Coevolution, Lytic infection, Lysogenic infection

1.1 Introduction

Viruses infecting microorganisms are ubiquitous and abundant in aquatic ecosystems (Suttle 2005, 2007). They typically are small particles (generally 20–200 nm in length) comprised of nucleic acids (single- or double-stranded DNA or RNA) and structural proteins and have no intrinsic metabolism. Thus, their reproduction depends entirely on host cellular metabolism and replication machinery. Viral reproduction can be classified as lytic or lysogenic (Guttman et al. 2004). During lytic infection, viruses inject their genomes into host microorganisms, redirect host metabolism for efficient viral genomic nucleic acid replication and protein synthesis, and are finally released through host cell lysis (Guttman et al. 2004). In contrast, in lysogenic infection, the viral genome is integrated into the host genome as a provirus (also called prophage if the

55 virus integrates into the bacterial chromosome) and is propagated vertically within the
56 host lineage until the induction of the lytic cycle under specific conditions (e.g.,
57 depending on host cell density or environmental conditions) (Howard-Varona et al.
58 2017a).

59 Both types of viral infections, lytic and lysogenic, have great potential to affect
60 microbial communities in aquatic ecosystems. For example, viral-mediated cell lysis
61 releases nutrients and organic matter from cells to the environment, thus stimulating
62 biogeochemical cycling (Fuhrman 1999; Suttle 2005, 2007). In addition, viruses affect
63 host microbial diversity in at least three different ways (Marston et al. 2012). First,
64 viruses contribute to the maintenance of host microbial diversity by
65 frequency-dependent infection, often seeming to have a greater effect upon those
66 microbial taxa and genotypes that either are highly abundant or most metabolically
67 active in the environment (Thingstad 2000). Second, viruses increase host genetic
68 diversity via the reciprocal co-evolution of host resistance and viral infectivity
69 (Buckling and Rainey 2002a). Lastly, viruses affect the genomic evolution and the
70 fitness of microbial hosts through horizontal gene transfer (HGT) including the presence
71 and movement of auxiliary metabolic genes (Breitbart et al. 2007; Hurwitz and U'Ren
72 2016), generalized transduction during lytic infection (Thierauf et al. 2009; Touchon et

al. 2017), and specialized transduction during lysogenic infection (Gottesman and Yarmolinsky 1968; Fernandes et al. 1989; Campos et al. 2003; Touchon et al. 2017).

The ever-growing number of culturable viral isolates, together with recent advances in sequencing technologies and bioinformatics, provides us with a deeper understanding of the viral nature in aquatic ecosystems. This chapter summarizes current understanding of viral effects on biogeochemical cycles, microbial diversity, and virus–host evolutionary dynamics in aquatic ecosystems. The viral role in the promotion of HGT that affects host genomic evolution and fitness has been reviewed extensively elsewhere and is therefore not discussed here (e.g. Balcázar 2018; Yoshida et al. 2019; Chapter E and therein).

1.2 Viral influence on biogeochemical cycle

1.2.1 Viral modulation on patterns of geochemical cycling in the ocean

In the ocean, approximately 10^{29} cells of different microorganisms form the basis of the marine food web (Whitman et al. 1998). Photosynthetic eukaryotes and prokaryotes contribute to up to 50% of the total net primary production on Earth (Field et al. 1998). Approximately half of the resultingly fixed carbon is released into the environment, re-mineralized by heterotrophic prokaryotes, and then incorporated into higher trophic levels of the aquatic food web (Azam et al. 1983). This process of

92 recycling of photosynthetic products is called “microbial loop” and is an essential
93 pathway of biogeochemical cycling in the ocean (Azam et al. 1983).

94 Viruses outnumber prokaryotes, and up to 20% of marine microorganisms are
95 thought to be infected and lysed by viruses daily (according to a certain view in Suttle
96 2007). Lysis of infected cells leads to the release of organic matter and nutrients, which
97 would otherwise be incorporated into higher trophic levels by grazing (Fuhrman 1999;
98 Wilhelm and Suttle 1999). This pathway of carbon flux regulated by viruses is called
99 “viral shunt” (Wilhelm and Suttle 1999) (Fig. 1.2.1). Calculations based on the
100 presumed microbial biomass, its turnover rates, and the predicted daily lysis suggest
101 that viral shunts are responsible for the release of approximately 25% of primary
102 production in the surface ocean, which amounts to up to 3 gigatons of carbon into the
103 oceans per year (Wilhelm and Suttle 1999; Suttle 2005). However, the quantification of
104 virus-mediated carbon flux in natural environments remains challenging owing to
105 methodological limitations and ecosystem complexity. Recently, more advanced
106 nutrient–phytoplankton–zooplankton (NPZ) models, including heterotrophic bacteria
107 and viruses, have proposed that viral shunts accelerate organic matter recycling and
108 increase net primary productivity while reducing transfer to higher trophic levels (Weitz
109 et al. 2015). Moreover, the effect of virus-mediated carbon flux may depend on the

trophic status of the system and the limiting nutrients (Pourtois et al. 2020).

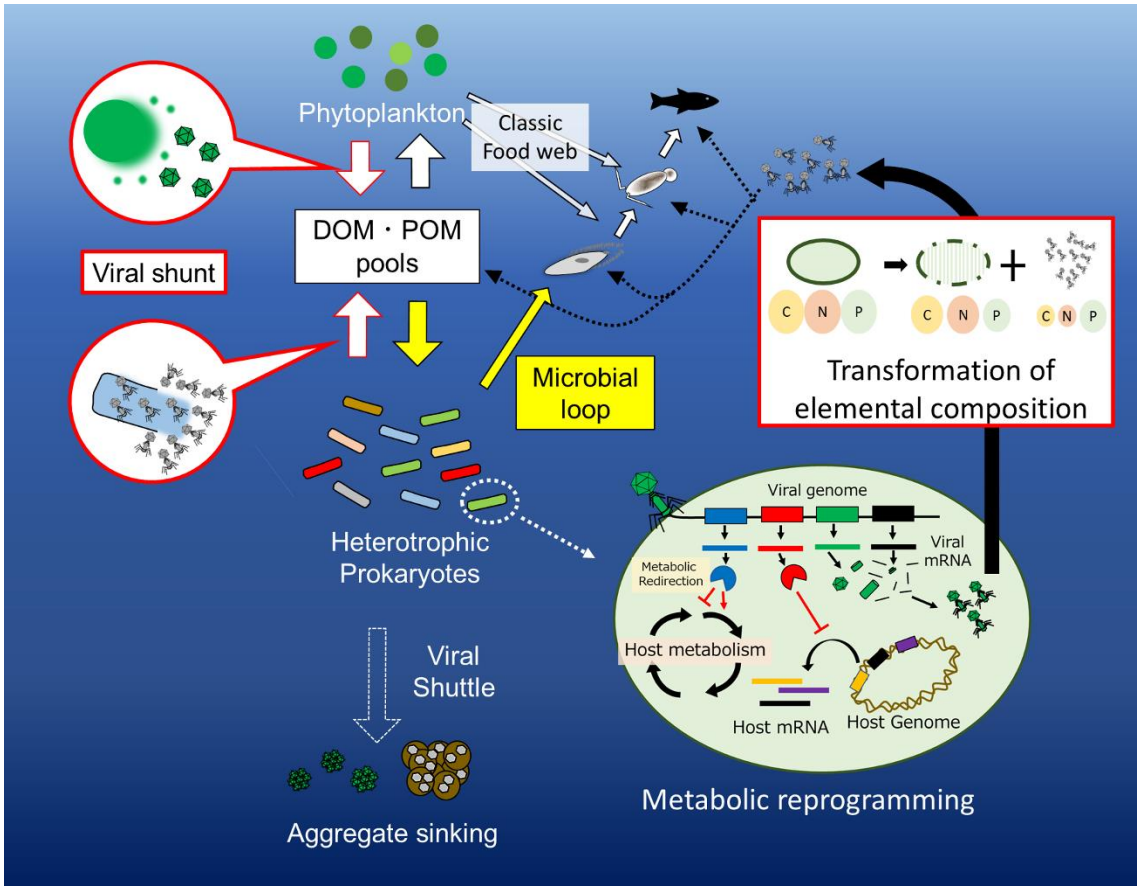

Fig 1.2.1. Overview of virus-mediated biogeochemical cycling in aquatic microbial ecosystem. When viruses lyse their host, intracellular organic matter is released from host cells to the particulate organic matter (POM) and dissolved organic matter (DOM) pools, a process that has been termed a Viral shunt. This process is accompanied by compositional and stoichiometric changes in chemical properties of intracellular metabolites via viral metabolic redirection, i.e., hijacking host transcription-translation systems and expression of viral auxiliary metabolic genes (AMG). Viral particles are also a source of phosphorus-rich DOM (compared with host debris) and consumed by direct grazing. Viral infection facilitates carbon export to the deeper layer (biological pump) through particle aggregation driven by the release of lysis products and

122 virus-induced alterations in host physiology (Viral shuttle).

123

124 On the other hand, viruses can also contribute to carbon removal from the
125 surface ocean (Weinbauer 2004; Sullivan et al. 2017; Laber et al. 2018). Cellular debris,
126 including cytoplasmic material and components of the cell wall, released via viral lysis
127 can easily aggregate and sink to the deeper layers leading to carbon sequestration
128 (Weinbauer 2004; Laber et al. 2018). This alternative viral influence on the geochemical
129 flux that promotes the biological carbon pump is referred to as the "viral shuttle"
130 (Sullivan et al. 2017) (Fig. 1.2.1). For example, virus-induced carbon transportation has
131 been extensively studied in *Emiliania huxleyi* (haptophyte) and its known virus (Laber
132 et al. 2018). Several laboratory studies have reported that viral infection stimulates the
133 production of transparent exopolymer particles (TEP), which increases the stickiness of
134 cells, thus promoting aggregation (Rosenwasser et al. 2014; Nissimov et al. 2018). Field
135 studies monitoring *E. huxleyi* blooms in the North Atlantic have revealed that TEP
136 concentrations increase during the early stages of infection and that infected cells are
137 preferentially transported to the deep ocean (Sheyn et al. 2018). Considering the huge
138 abundance of *E. huxleyi* (reaching 10^7 cells/mL during their bloom period; Silkin et al.
139 2020), the virus-mediated sinking of its cells would thus have a significant impact on
140 the available carbon in the surface ocean. Moreover, laboratory experiments have

141 reported that the virus-infected culture of *Chaetoceros tenuissimus* (Diatomea) is up to
142 59-fold enriched in particulate organic matter compared with uninfected controls
143 (Yamada et al. 2018). At the global scale, a metagenomic study based on data from the
144 Tara Ocean has suggested that the infection and lysis of the widespread and abundant
145 cyanobacteria *Synechococcus* significantly contribute to carbon export compared with
146 other microorganisms (Guidi et al. 2016). Further studies using quantitative methods are
147 required for a better understanding of the effect of viral shuttles in the global ocean.

148 In addition, viral particles themselves contribute to the biogeochemical cycling
149 of carbon and other nutrients. For example, approximately 0.03 Gt C per year (Bar-On
150 and Milo 2019), and most of the viral biomass is attributed to the dissolved organic
151 matter (DOM) fraction (< 0.45 μm) due to the size of the virion (e.g., bacterial viruses
152 generally range between 20 and 200 nm) (Zsolnay 2003; Leenheer and Croué 2003;
153 Findlay and Parr 2017). Recently, a relatively large number of marine viruses have been
154 identified to attach to non-host organisms and particles (Yamada et al. 2020). Thus, if or
155 when these non-host organisms or particles are predated, their attached viruses
156 indirectly contribute to classical marine food webs even when they are not infecting any
157 organisms. Altogether, viral particles could contribute to both DOM and the particulate
158 organic matter (POM) pools in the ocean.

159 A previous study investigating the elemental composition of both virus
160 particles and viral lysates eluted from their host debris revealed that viral lysates tend to
161 be more depleted in phosphorus than are uninfected cells because the amount of
162 genomic nucleic acids contained in progeny viral particles results in those viruses being
163 relatively phosphorus-rich as compared with their amounts of carbon and nitrogen
164 (Jover et al. 2014). By extrapolating this model to the ecosystem scale, marine viruses
165 are predicted to constitute a comparatively high proportion (> 5%) of the total DOP pool
166 in the surface ocean (Jover et al. 2014). Thus, viruses themselves can be regarded as an
167 abundant nutrient source.

168 Predation of viral particles by predators has been demonstrated in several
169 studies using culture experiments (Suttle and Chen 1992; Bettarel et al. 2005; Lawrence
170 et al. 2018; Welsh et al. 2020). For example, a co-cultivation study exposing
171 *Phaeocystis globosa* and its virus to various predators has demonstrated that viruses can
172 be effectively removed (up to 98% within 24 h) from the water column by non-host
173 organisms, including sea anemones, polychaete larvae, sea squirts, crabs, cockles,
174 oysters, and sponges (Welsh et al. 2020). Therefore, although the rate of viral particle
175 removal by aquatic protists may vary depending on both the virus and predator strains
176 (Suttle and Chen 1992; Gonzalez and Suttle 1993; Lawrence et al. 2018; Welsh et al.

2020), the ingestion of viruses can serve as a possible source of nutrients, especially phosphorus.

These viral influences on the biogeochemical cycles fluctuate across short- and long-time scales. On a long-term scale, for instance, the microbial community exhibits seasonal compositional changes (Cram et al. 2015; Parada and Fuhrman 2017; Needham et al. 2018; Choi et al. 2020), which are followed by the seasonal dynamics of their viruses (Needham et al. 2017; Ignacio-Espinoza et al. 2020). Furthermore, diverse taxa of photosynthetic microorganisms and even some heterotrophic ones show diel activity in culture and environmental studies, which is partly explained by the viral infection cycle (Morimoto et al. 2020 and references therein). Both the seasonality and the diel cycle activity of microorganisms and their viruses suggest that host–virus interactions could generate temporal fluctuations in geochemical cycles in aquatic environments.

1.2.2 Virus–host interactions-mediated modification of host cell metabolism

Viruses switch their host metabolism from cellular replication to progeny production. Compared with non-infected hosts, metabolically reprogrammed cells can be generally distinguished based on changes in the host transcription program,

eventually leading to distinctiveness in the proportion of end-point products between infected and uninfected cells (Ankrah et al. 2014; Jover et al. 2014; Rosenwasser et al. 2014; Ma et al. 2018) (Fig. 1.2.1). For instance, disproportioning of phosphorus between infected and uninfected hosts (as discussed in the previous section) could be attributed to a viral reprograming mechanism in which viruses degrade host DNA and utilize the resultant nucleic acids for the synthesis of viral DNA (Wikner et al. 1993; Kutter et al. 2018).

Currently, cell metabolic reprogramming by viruses has been studied using both transcriptomic and metabolomic analyses and is found to be a highly regulated process. For instance, the infection strategy of T4-like viruses follows the three temporal expression classes of early, middle, and late genes, corresponding to host takeover, replication, and virion morphogenesis, respectively, and occurs in accordance with the downregulation of genes related to host replication (Roucourt and Lavigne 2009). Such transcriptional regulation by viruses has also been investigated in several lineages of marine and freshwater prokaryotic as well as eukaryotic phytoplankton (Lindell et al. 2007; Rosenwasser et al. 2014; Bachy et al. 2018; Moniruzzaman et al. 2018; Morimoto et al. 2018; Ku et al. 2020) and heterotrophic bacteria (Ankrah et al. 2014; Howard-Varona et al. 2017b, 2020). The metabolic regulation of host cells may

213 also depend on host taxonomy and thus differ between various species (e.g.,
214 cyanoviruses with broad and narrow host range seem to have different infection
215 strategies; *E. huxleyi* virus EhV possesses five gene expression phases during infection)
216 (Lindell et al. 2005; Clokie et al. 2006; Doron et al. 2016; Morimoto et al. 2018; Ku et
217 al. 2020). In addition, it may be influenced by host physiological states, which in turn
218 depends on nutrient availability (e.g. phosphate) (Kelly et al. 2013; Lin et al. 2016;
219 Bachy et al. 2018). Thus, viruses could affect the proportion of end-point products in the
220 infected cells while those hosts either directly or indirectly are responding to
221 environmental conditions.

222 Viruses can also possess host-derived genes (also called as auxiliary metabolic
223 genes, AMGs) that are expressed during infection, thus altering host metabolism, and
224 increasing the efficiency of viral reproduction (Breitbart et al. 2007; Hurwitz and U'Ren
225 2016). These AMGs can largely be classified into two classes (Class I and II) based on
226 their function according to the Kyoto Encyclopedia of Genes and Genomes database
227 (Hurwitz and U'Ren 2016). Viral-encoded AMGs not only maintain cellular functions
228 necessary for viral DNA replication and virion production (e.g., ATP production and
229 nucleotide synthesis) during infection (Lindell et al. 2004, 2005), but also both down
230 and up-regulate a range of targeted metabolic pathways that can substantially alter cell

231 stoichiometry and nutrient metabolism (De Smet et al. 2016, 2017). Most AMGs that
232 have been identified to date are directly involved in either the utilization and uptake of
233 limiting nutrients or energy production (Enav et al. 2014; Hurwitz and U'Ren 2016),
234 which in turn may have (at least temporarily) a positive feedback effect on the host cell
235 by improving its fitness during infection (Zeng and Chisholm 2012): the acquisition and
236 metabolism of carbon (e.g., *psbA* and *psbD*; Lindell et al. 2004, 2005; Thompson et al.
237 2011), nitrogen (e.g., *amt*; Monier et al. 2017), and phosphorus (e.g., *pstS* and *phoA*;
238 Zeng and Chisholm 2012). New putative AMGs are continuously being discovered in
239 bacterial (Breitbart 2011; Crummett et al. 2016; Breitbart et al. 2018; Warwick-Dugdale
240 et al. 2019), eukaryotic (Schvarcz and Steward 2018; Needham et al. 2019), and archaea
241 viruses (Ahlgren et al. 2019) or the more broadly defined environmental viromes
242 (Williamson et al. 2008; Anantharaman et al. 2014; Hurwitz et al. 2015; Moniruzzaman
243 et al. 2020; Schulz et al. 2020; Kieft et al. 2020). Thus, considering that viral-encoded
244 AMGs are abundant and widespread in aquatic environments (Williamson et al. 2008),
245 AMG-mediated metabolic reprogramming can substantially contribute to major
246 biogeochemical cycles and ecosystem functioning at the global scale (Sieradzki et al.
247 2019).

248 Indeed, changes in metabolites mediated by virus–host interactions have been

observed in both eukaryotes and prokaryotes using a metabolomic approach (Rosenwasser et al. 2014; Ma et al. 2018). For example, *E. huxleyi* virus EhV downregulates host *de novo* sphingolipid genes and simultaneously promotes the induction of a viral-encoded homologous pathway, resulting in the metabolic shift toward viral sphingolipid production (Rosenwasser et al. 2014). A recent culture-based study on *Synechococcus* and its viruses revealed that the composition of chemical compounds (proteins, carbohydrates, and lipids) of organic matter differs between infected and uninfected cells (Ma et al. 2018). Such compositional changes induced by viruses have been detected during viral infection of *Sulfitobacter* (C:N ratio of host cell shifted to nitrogen-rich state compared with uninfected cells) (Ankrah et al. 2014).

Thus, from an ecological perspective, the virus-induced metabolic reprograming depends on both the virus-host pair (and therefore on the diversity and composition of microbial assemblages) and the host physiological state during infection and can modulate the generation as well as the diversity of end-point products, thus leading to altered biogeochemical cycling. It is also speculated that halting the viral reproduction at various infection stages using antiviral responses, including signal transduction, cell cycle regulation (Moniruzzaman et al. 2018), and metabolic pathway (Rosenwasser et al. 2014), might establish metabolite diversity in the infected cells via

267 the generation of intermediate products of viral progeny (Zborowsky and Lindell 2019)
268 or unusual proteins in the uninfected cells.

269

270 **1.3 Viral infection shaping microbial community diversity**

271 ***1.3.1 Contribution of lytic infection to microbial diversity maintenance***

272 In aquatic ecosystems, diverse microorganisms compete for nutrient resources
273 but can co-exist and account for a large proportion of total aquatic biodiversity, a
274 concept that has been known as the classical question “paradox of the plankton”
275 (Hutchinson 1961). Viruses are currently thought to contribute to the co-existence of
276 microbial species and genotypes.

277 Basically, viruses are believed to infect their specific microbial hosts in a
278 frequency-dependent manner (Fuhrman and Suttle 1993). Therefore, viral infection
279 checkmates microbial species that become dominant through the competition among
280 co-existing microorganisms that possess different substrate affinity, and thereby enables
281 the co-existence of multiple competing microbial species (“Kill the Winner” hypothesis)
282 (Thingstad 2000) (Fig. 1.3.1). Indeed, several culture and environmental studies have
283 demonstrated that viral top-down control modulates microbial abundance, which is
284 consistent with the results expected from a Kill the Winner hypothesis (Tarutani et al.
285 2000; Schwalbach et al. 2004; Bouvier and Del Giorgio 2007; Yoshida et al. 2008a;

286 Rodriguez-Brito et al. 2010; Kuno et al. 2012; Parsons et al. 2012; Kimura et al. 2013;
287 Needham et al. 2013; Cram et al. 2016).

288 The viral-mediated co-existence mechanism, by which viruses are expected to
289 affect host diversity in a frequency dependent manner according to the Kill the Winner
290 hypothesis, could provide a mechanism that explains the continuing co-existence of
291 diverse genotypes within a single microbial species (or closely related lineage) rather
292 than the co-existence of diverse microbial species. Conventionally, the philosophy has
293 been that phenotypic and genotypic diversity within a microbial population was
294 expected to become homogenized to a greater level of fitness in the environment. The
295 microbial population (species or closely related lineage) that are genetically cohesive
296 and ecologically distinct are called an “ecotype” (ecotype hypothesis) (Maharjan et al.
297 2006; Cohan and Koeppel 2008). The ecotype had been believed to be periodically
298 replaced as fitter ecotypes emerged after profitable mutation or preferable
299 environmental changes (Maharjan et al. 2006; Cohan and Koeppel 2008). However,
300 metagenome sequence alignment analyses have demonstrated that several genomic
301 regions (metagenomic islands; MGIs) are underrepresented even within a single
302 microbial population in similar environments (Coleman and Chisholm 2007;
303 Cuadros-Orellana et al. 2007; Kettler et al. 2007; Wilhelm et al. 2007; Frias-Lopez et al.

2008; Rodriguez-Valera et al. 2009; Rodriguez-Valera and Ussery 2012). This suggests that diverse genotypes coexist within a single microbial population. Furthermore, these MGIs include diverse accessory genes, such as extracellular structure-related genes that can be viral recognition sites (Reva and Tümmler 2008; Sharma et al. 2008; Rodriguez-Valera et al. 2009; Rodriguez-Valera and Ussery 2012) and antiviral response-related genes such as CRISPR in addition to genes that affect restriction-modification (Sorek et al. 2008; Wilmes et al. 2009). Therefore, MGIs are thought to play an important role in the ability of hosts to escape or survive from viral infection, in which host genotypic diversity is driven by viral predation pressure, thereby leading to the co-existence of multiple competing microbial genotypes ("Constant Diversity dynamics" model) (Rodriguez-Valera et al. 2009) (Fig. 1.3.1). Indeed, multiple genotypes of *Microcystis aeruginosa* possessing different CRISPR arrays and its virus Ma-LMM01 coexist and oscillate during the massive bloom of this nuisance and toxic species (Kuno et al. 2012, 2014; Kimura et al. 2013). Hence, lytic viruses play important roles in not only the co-existence of microbial species but also the maintenance of high diversity within a single microbial population.

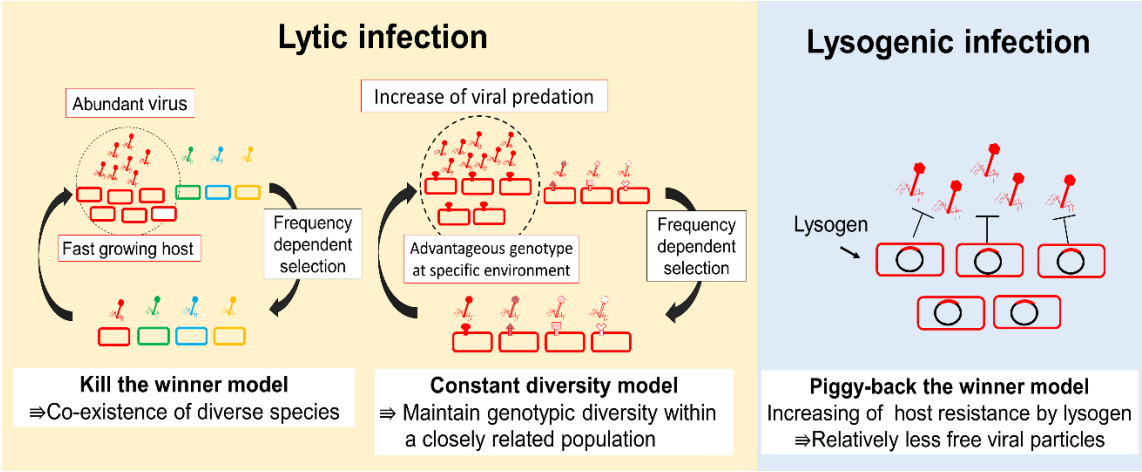

Fig 1.3.1. Schematic diagram of mechanisms in virus-mediated maintenance of microbial community diversity. Preferential viral infection of abundant species enables the co-existence of diverse competing microbial species by preventing the dominance of only few species ("Kill the Winner" hypothesis). Similar viral top-down control is proposed as a mechanism to maintain high genotypic diversity within a single microbial population ("Constant Diversity dynamics" model). Lastly, the prevalence of lysogeny in dominant microbial population may be another potential mechanism that allows abundant host species to be dominant by taking advantages benefit from lysogenic conversion such as superinfection exclusion ("Piggyback-the-Winner" model).

1.3.2 Potential contribution of lysogenic infection to microbial diversity maintenance

So far, we have focused on lytic viruses and described their contribution to the maintenance of microbial diversity in aquatic environments. Another key question related to viral impact on microbial diversity is whether temperate viruses also contribute to shaping microbial community diversity.

Provirus integration can occur either through repeated random transposition events or at specific integration sites (e.g., host tRNA genes; also called site-specific recombination) and is associated with the immediate transcriptional suppression (e.g. via specific virus repressors) of lytic promoters and genes associated with virion production (Casjens and Hendrix 2015). This mode of viral infection that generates lysogenic cells (Hobbs and Abedon 2016) is considered as an adaptive strategy of temperate viruses to ensure their persistence in the environment, in which novel phenotypic or metabolic advantages are sometimes conferred to host microorganisms via concomitant effects by mechanisms such as HGT (Hendrix et al. 2000; Howard-Varona et al. 2017a), the capability of up and down-regulation of host genes (Argov et al. 2017), and integration-driven gene disruption (Feiner et al. 2015).

Although one study estimated that approximately half of 100 marine bacterial isolates harbored temperate viruses in their genomes (Paul 2008), proviruses are rarely

found in the marine-dominant bacterial lineages (e.g., only one provirus was recently reported in SAR11 clades; see Morris et al. 2020) possibly due to genome streamlining, in which a bacterial genome is minimized to a highly constrained gene set that confers maximum fitness (Touchon et al. 2016). Therefore, the ecological significance of lysogenic infection on microbial diversity maintenance in marine ecosystems remains under debate. Traditionally, it was believed that bacterial viruses control their host abundances in a frequency-dependent manner as described above, and thus viral abundance is typically 10-folds higher than that of prokaryotes (Wommack and Colwell 2000; Weinbauer 2004). Therefore, lysogenic infection is presumed to be the preferred viral strategy under conditions of reduced host cell number and activity (Stewart and Levin 1984; Sime-Ngando 2014; Brum et al. 2016). However, viral metagenomic and metadata approaches have revealed that viral particles are relatively less abundant at high microbial densities (Knowles et al. 2016; Wigington et al. 2016). Likewise, it was demonstrated that the virus/host genome abundance ratio was negatively correlated with the host abundance at the genus or phylum levels (Coutinho et al. 2017). Additionally, the relative abundance of hallmark genes encoded by temperate viruses increased with microbial density in a coral reef (Knowles et al. 2016). These findings suggest that lysogenic infection may become dominant at high-cell densities because proviruses can

370 replicate quickly in a way that will keep pace with their fast-growing host and
371 provirus-mediated superinfection resistance might become increasingly important at
372 high cell densities (called “Piggyback-the-Winner” model) (Knowles et al. 2016, 2017;
373 Coutinho et al. 2017) (Fig. 1.3.1).
374
375 **Footnotes**
376 Paradox of the plankton: The concept arguing paradoxical situation of coexistence of
377 various plankton species competing for identical resources in homogeneous and
378 resource limited environment (Hutchinson 1961).
379 Kill the Winner hypothesis: A model proposing the dynamics of virus-host interactions
380 in which an increase of host population (winner) is accompanied with increasing of its
381 infectious viruses, and thereby viruses prevent their hosts from becoming dominant
382 through increased mortality of the winner (Thingstad 2000).
383 Constant Diversity dynamics model: A hypothetical model proposing that the diversity
384 of prokaryotic populations is maintained by viral predation, because the best-adapted
385 populations are selected by viral predation. The hypothesis assumes that each microbial
386 population has distinct viral receptor (Rodriguez-Valera et al. 2009).
387 Piggyback-the-Winner model: A hypothetical model proposing that lysogeny would be

388 favored when a bacterial host is dominated in the environment because a provirus can
389 replicate rapidly together with host DNA replication (Knowles et al. 2016).

390

391 **1.4 Evolutionary roles of viruses that generate genotype-level microbial**
392 **diversification**

393 In short-term laboratory experiments, host–virus coevolution appeared to be
394 suppressed by the emergence of a viral-resistant genotype, which the virus could not
395 evolve to overcome (Dennehy 2012). In particular, *de novo* mutations that cause
396 changes in those bacterial cell-surface structures which serve as viral receptor sites are
397 one of the major factors that prevent viral attachment, and thereby confer the potential
398 host with resistance against viral infection (Lenski and Levin 1985). Therefore,
399 host–virus coevolution has been considered to be constrained by the asymmetry of
400 evolutionary potential between hosts and viruses (Cannon et al. 1971; Cowlishaw and
401 Mrsa 1975; Barnet et al. 1981; Lenski and Levin 1985; Waterbury and Valois 1993;
402 Middelboe et al. 2001; Wei et al. 2010, 2011).

403 On the other hand, long-term evolutionary laboratory studies have indicated
404 that the host and its virus undergo persistent coevolution over a prolonged period, as
405 evidenced with the soil bacterium *Pseudomonas fluorescens* (Buckling and Rainey
406 2002a, b; Brockhurst et al. 2007; Hall et al. 2011a, b) and *E. coli* (Mizoguchi et al.

2003). Similar co-evolutionary dynamics have also been observed in the marine bacteria *Prochlorococcus* (Avrani et al. 2011), *Synechococcus* (Marston et al. 2012), and *Cellulophaga baltica* (Middelboe et al. 2009).

The above-mentioned co-evolution scenario, based on the one-virus-to-one-bacteria relationship, predicts that the genetic contents of both bacteria and virus would converge over repeated interactions. As described above, however, genotypic diversity is observed in MGIs even within a single microbial population (Coleman and Chisholm 2007; Cuadros-Orellana et al. 2007; Kettler et al. 2007; Wilhelm et al. 2007; Frias-Lopez et al. 2008; Rodriguez-Valera et al. 2009; Rodriguez-Valera and Ussery 2012). Additionally, under-represented genomic regions have been found in marine viruses (metaviromic islands) with a large fraction of their identified genes (e.g., 59 out of 138) associated with host recognition of viruses (Mizuno et al. 2014). Thus, the recent understanding of host–virus coevolution is based on multiple genotype (strain)-level interactions within both the microbial host and viral species which seem to represent defense and counter-defense strategies (e.g., CRISPR and mutation in protospacer) or resistance and overcome of resistance (e.g., mutation in cell surface and viral tail gene) (Fig. 1.4.1).

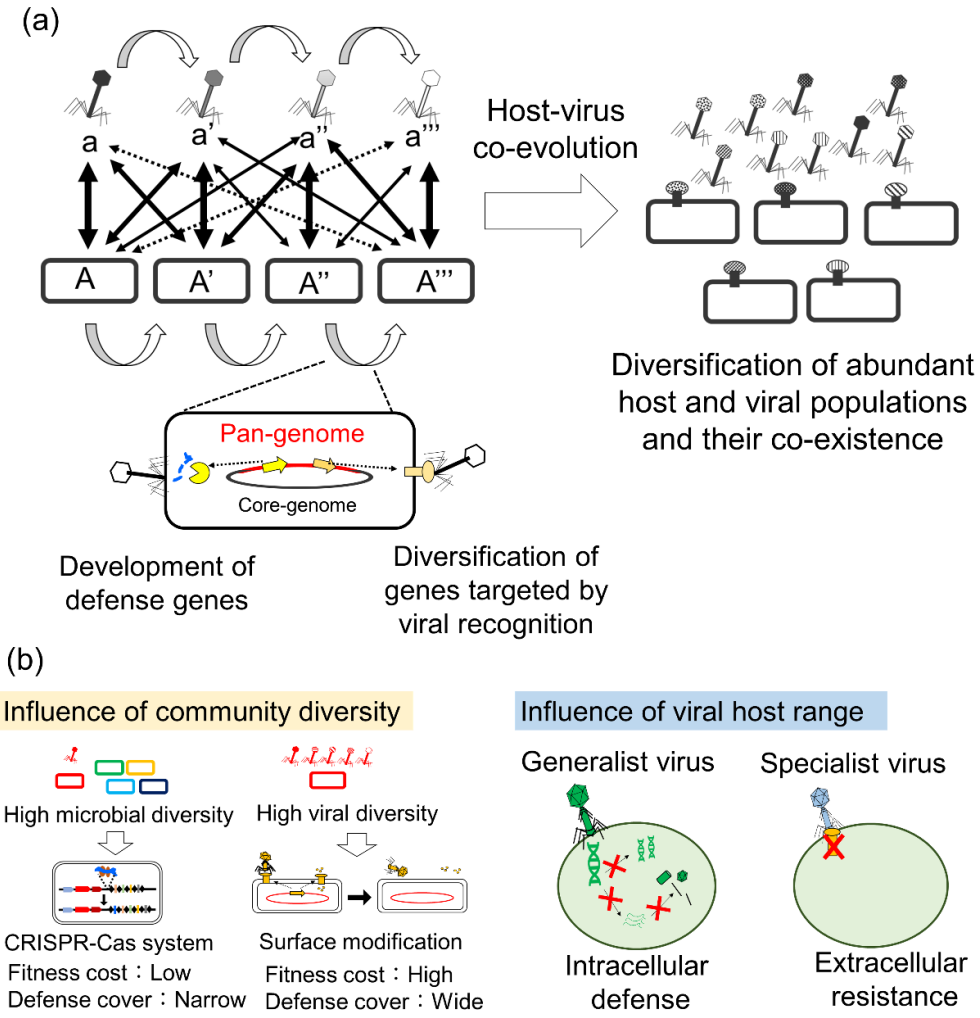

Fig. 1.4.1 Proposed mechanisms in host pan-genome expansion via virus–host interactions. (a) Under the viral top-down control toward dominant species and genotypes, "Red Queen" like host–virus co-diversification can be established in abundant host and abundant viruses. Continuous arms race via intracellular defense (e.g., CRISPR-Cas system) and extracellular resistance (e.g., viral recognition sites) plays a part in genomic diversification of both host and virus. (b) A complicated balance between trade-off and specificities of each defense mechanism can affect the arms race. For example, extracellular resistance (e.g., surface modification) is preferable to intercellular defense (e.g., CRISPR-Cas) under conditions of high viral genetic diversity

because the former promotes resistance toward against broader viral genotypes. However, because extracellular resistance may result in a higher cost, such as the impairment of nutrient uptake ability, intercellular defense is possibly preferable under competitive situations with host competitors.

In freshwater ecosystems, host-virus coevolution have been intensively studied in the bloom-forming cyanobacterium *M. aeruginosa* and its viruses (Yoshida et al. 2005, 2008a, b; Kimura et al. 2012, 2013, 2018; Kuno et al. 2012, 2014; Yoshida-Takashima et al. 2012; Morimoto et al. 2019). Interestingly, the most abundant *Microcystis* CRISPR genotype is known to coexist with that derived by novel spacer acquisitions from cyanoviruses in the environment. This finding suggested that both abundant host and viral genotypes have diversified in the bloom without a complete selective sweep (Kimura et al. 2018). Thus, the Red Queen like dynamics could be established, to some extent, between the abundant host genotype and its cyanoviruses under high viral contact rate; with reciprocal adaptation via defense and counter-defense continuously occurring in multiple-to-multiple relationships (Koskella and Brockhurst 2014), thus subsequently increasing the diversity of host organisms and viruses (Fig. 1.4.1). Also, a recent metagenomic survey revealed the co-existence of highly host-specific (narrow host range) and broad host range *Microcystis* viruses and the high

co-expression of antiviral defense and viral genes in the environment (Morimoto et al. 2019). Considering that they often induce antiviral responses, broad host range viruses might be important for host genotype diversification (Morimoto et al. 2019).

In contrast with freshwater cyanobacteria typically having the greatest overall numbers of defense genes (Makarova et al. 2011), marine prokaryotes rarely possess distinctive defense genes such as CRISPR-Cas due to their genome streamlining (Touchon et al. 2016). However, instances of co-existence between dominant marine prokaryotes and their viruses were observed, which are presumably sustained by Red Queen-like co-evolution dynamics. For example, the dominance of the SAR11 clade bacteria and their viruses was predicted to be maintained by host rapid adaptation to viruses. The rapid adaptation was achieved by high recombination rates among SAR11 in their variable genomic region that encoded genes involved in synthesis of cell surface proteins, and this hypothesis is possibly supported by their high host cell density (King of the Mountain hypothesis) (Zhao et al. 2013). Furthermore, constant turnover of single-nucleotide polymorphism variants in relatively abundant marine viruses also suggests that Red Queen-like virus–host coexistence could be established by perpetually changing minor variants.

As described in this section, one of the major forces driving host and viral

genotypic diversification is the reciprocal defense and counter-defense that occur through extracellular (e.g., *de novo* mutation of cell-surface structure) and intracellular resistance (e.g., acquisition of novel CRISPR spacers). Comparative antiviral resistance analyses in *Synechococcus* and *Prochlorococcus* provided new insights into host-favored antiviral defenses in narrow and broad host range viruses (Doron et al. 2016; Zborowsky and Lindell 2019). Host cyanobacteria resist against narrow host range viruses irrespective of the viral family by preventing viral entry into the cell, whereas intracellular resistance arrests the infection cycle of broad host range viruses at various infection stages (Doron et al. 2016; Zborowsky and Lindell 2019) (Fig. 1.4.1). These differences in antiviral responses that seemingly occur according to viral host range are speculated to be associated with fitness trade-offs in extracellular and intracellular antiviral responses. In extracellular antiviral responses, mutations in cellular surface structures can impair nutrient uptake and utilization but can protect against diverse viral attacks, leading to an increase in host fitness trade-off favoring the host (Winter et al. 2010; Avrani et al. 2012) (Fig. 1.4.1). On the other hand, choosing to modify intracellular antiviral responses techniques may be energetically favorable, especially the CRISPR-Cas system, because the cost of a new spacer acquisition is speculated to be low, although it is possible that additional types of resistance costs may

exist (Thingstad et al. 2014) (Fig. 1.4.1). Indeed, recent studies focusing on the differences in biotic complexity between *in vitro* and environments have revealed that coexistence among human pathogens amplified the fitness trade-offs associated with viral receptor mutations in *Pseudomonas aeruginosa* and therefore enhanced the evolution of CRISPR-based resistance (Alseth et al. 2019). Higher viral genetic diversity can also influence CRISPR-based evolution, with an example being that the majority of a *Pseudomonas* population more favorably evolved based on the mutation of viral receptors to resist a broader range of viral genotypes than CRISPR-based specific resistance (Broniewski et al. 2020). Thus, fitness trade-offs in bacterial host species and diversity of both bacterial host and viruses in the environment could be another important factor that affects host–virus coevolution. From the perspective of fitness trade-off, most recently, the “pan-immune system” concept has been proposed. This states that a single strain can access immune defense mechanisms in closely related strain via HGT, although it cannot possess all possible defense systems (Bernheim and Sorek 2020).

Footnotes

Red Queen like dynamics: A hypothesis proposing co-evolutionary process between

competing species (Valen 1973); in the case of virus-host interactions, this hypothesis explains continuous dynamics of resistance acquisition in microbial hosts and viral avoidance to the host resistance (Brockhurst et al. 2014).

King of the Mountain hypothesis: A hypothesis proposing that high recombination rate enables dominance of a competitive prokaryote in the ecosystem via horizontal transfer of genes involved in resistance to viral infection (Zhao et al. 2013).

1.5 Conclusion

Viruses, which are highly abundant biological entities lacking their own metabolism, can reprogram host cells toward the production of virus progeny, after which the host cell is lysed, releasing new virions into the surrounding environment. This reprogramming viral strategy can change the content and composition of host metabolites and releases a large amount of organic matter, thus considerably affecting biogeochemical cycles. In addition, viral infection checkmates not only microbial species that become dominant but also abundant genotypes within a single microbial species, and thereby enables the coexistence of diverse microbial species and genotypes in the aquatic ecosystem. Thus, viral infection is one of the key factors shaping microbial community diversity and maintaining high diversity within a single microbial population. Likewise, because temperate viruses may be prevalent under specific

526 combinations of environment and conditions, they could affect microbial diversity via
527 superinfection exclusion during either the lysogenic cycle or induction of lytic cycle.
528 Meanwhile, microorganisms have evolved extracellular and intracellular antiviral
529 mechanisms with different fitness costs and specificities. Therefore, viruses with diverse
530 host range and genetic diversity interact with abundant hosts by a complex balancing
531 between fitness trade-offs and the specificity of extracellular- and intracellular antiviral
532 resistance in hosts. Together, this results in continuous virus–host coevolution, leading
533 to diversification in aquatic ecosystems. Collectively, viruses are important biological
534 entities that sustain and generate microbial diversity and control the biogeochemical
535 cycle in aquatic environments.

536

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