Chapter 1
What Does Communication of Phages Mean?

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Abstract Phages have serious effects on global energy and nutrient cycles. Phages actively compete for host. They can distinguish between 'self' and 'non-self' (complement same, preclude others). They process and evaluate available information and then modify their behaviour accordingly. These diverse competences show us that this capacity to evaluate information is possible owing to communication processes within phages (intra-organismic), between the same, related and different phage species (interorganismic), and between phages and non-phage organisms (transorganismic). This is crucial in coordinating infection strategies (lytic vs. lysogenic) and recombination in phage genomes. Therefore it is essential to investigate what communication of phages means and to identify the difference of the biocommunication approach to investigations that are restricted to the molecular biological perspective.

1.1 Introduction

Bacteria are evolutionarily one of the most successful living organisms, originating nearly since the beginning of life. Besides archaea, bacteria were the dominant cellular organisms in the first 2 billion years of biological evolution. In at least the last 3.5 billion years, they colonized nearly every ecological niche on earth. They are essential symbionts of all eukaryotic organisms and are required for their survival. On the other side, they cause diseases of even epidemic scales and not only modern medicine is in a permanent struggle with the consequences of bacterial infections worldwide. More recently, multidrug-resistant bacteria have necessitated the search for other ways to fight bacterial infections than mainstream research on antibiotics. Future-oriented researchers are currently projecting the post-antibiotic era.

Bacteria are important ecosystem determinants in the soil and oceans globally, with 1 ml seawater containing ca. 1 million bacteria (Williamson 2011). Bacteria

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are undoubtedly the best-adapted organisms on earth. An abundance of rapid genetic variations, together with genetic adaptations, occurs conferring resistance to environmental circumstances, including intense heat and radiation. Bacteria communicate in various ways (Witzany 2009). The most popular means of bacteria communication is the quorum sensing/quorum quenching research and cheating phenomena by which bacteria coordinate and organize their essential life strategies (Kaiser and Losick 1993; Schauder and Bassler 2001; Bassler and Losick 2006; Ben-Jacob 2014). The acquisition of complex genetic datasets by virally-derived infection events seems to be the main source of evolutionary adaptational processes, and this was not in the focus of bacterial research in the last decades. Thus, the main genetic resources and gene word order in bacteria genomes which determine their behavioural patterns primarily did not evolve from cellular predecessors or the genetic lineage of the bacterial population horizontally but are results of vertical natural genome-editing activities of viruses (Witzany 2011; Argov et al. 2017; Meaden et al. 2019).

The whole range of bacteria lifestyles is in constant interaction with its predators and co-evolutionary partners, the phages. Phages are the most abundant living agents and outnumber bacteria 10 times. Phages are also the most diverse inhabitants on earth. To date, they are completely underestimated in their number, skills and competences and remain the dark matter of biology (Youle et al. 2012; Hatfull 2015). They have serious effects on global energy and nutrient cycles. They determine bacterial virulence, eukaryotic fitness and the global carbon cycle (Díaz-Muñoz and Koskella 2014). Bacteriophages are found in nearly all ecospheres including sea and freshwater, the soil, polar regions, deserts and within other organisms (Abedon 2011; Armon 2011; Batinovic et al. 2019; Kavagutti et al. 2019; Warwick-Dugdale et al. 2019). Phages actively compete for hosts, hunt prey, sense their environments and make choices (Rohwer et al. 2014). They can distinguish between 'self' and 'non-self', which means they complement some and preclude others (Villarreal 2009). Phages process and evaluate available information and then modify their behaviour accordingly. Additionally, they are the evolutionary ancestors of eukaryotic dsDNA viruses (Koonin et al. 2015).

These diverse competences indicate that the capacity to evaluate information is possibly due to communication processes within phages (intraorganismic), between the same, related and different phage species (interorganismic), and between phages and non-phage organisms (transorganismic). Additionally the show typical reaction patterns to abiotic influences of the environment. This is crucial in coordinating infection strategies (e.g., lytic vs. lysogenic) and recombination in phage genomes.

We begin by asking what communication of phages means. Is it beneficial to study communication processes of phages instead of pure physical interactions? How can one define "communication" of phages?

1.2 Communication Means Interactions Mediated by Signs

In contrast to former definitions of communication (mathematical theories of communication, information theory, systems theoretical approaches or other mechanistic attempts to encompass the phenomenon of communication), the most recent empirically-based definition of communication is: Interaction of at least 2 living agents mediated by sign(al)s. Therefore, communication is basically a social event.

The crucial difference between biocommunicative interactions and interactions in abiotic environments is that biocommunication depends on signs, i.e., sign mediated. This means that interactions occur by the recognition and reaction (generation, submission and uptake, decision making) of signalling substrates, which include chemical molecules (soluble, airborne,) electric, tactile, or as in animals, vocal and visible signals (Witzany 1993, 2000, 2010b).

In contrast to abiotic interactions, where no signs are present, the use of signs in sign-mediated interactions follows three levels of rules (not laws): combinatorial rules - how to correctly combine single signs to sign sequences (syntax), content coherence rules - how to correctly combine signs with meaning (semantics), and contextual rules - how to correctly combine signs with the real-life context by the sign-using agent (pragmatics). If one level of rules is missing, no natural communication process occurs (Witzany 2019). In abiotic interactions – if e.g., water freezes to ice – no such rules are present.

Biocommunication of Phages is the first book that will compile contributions in the following sections (Fig. 1.1):

- Trans-organismic communication: interactions between phages and non-phage organisms (infection/defence strategies, host genome editing, symbiogenetic cooperation etc.)

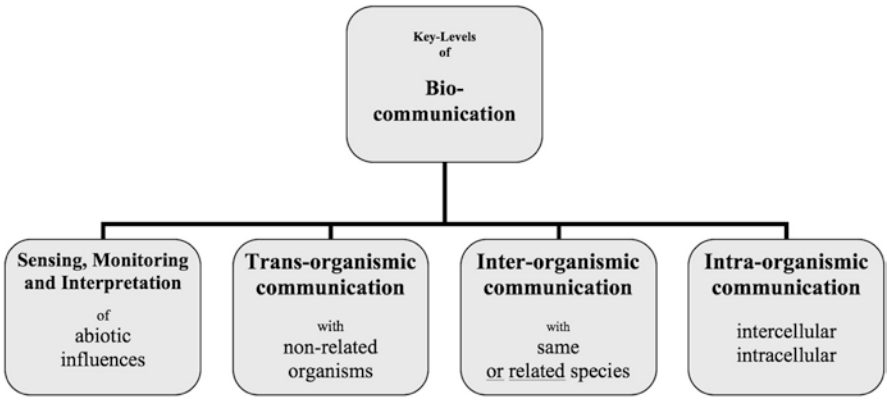

Fig. 1.1 The biocommunication approach identifies 4 levels involving living beings

- Inter-organismic communication: phage-phage interactions (competition, cooperation, etc.)
- Intra-organismic communication (reproduction, recombination, memory, learning, etc.).
- Vocabulary of phages (enzymes, signalling).
- Phagetherapy

At this point, it is important to also differentiate the signs into 3 different kinds: index, icon and symbol.

(a) There may be signs with a solely indicating function (*index*). This means the sensed sign represents something relevant to the sensing agent, a structure or chemical specificity, e.g. in plants, gravitational or dry/wet circumstances. In the case of phages, the density of chemical compounds was applied. It indicated that the phage could not attach to bacteria but remained in a persistent (temperate) style, followed by some internal phage regulatory processes.

(b) Another kind of sign is the function of an *icon* that represents a detectable similarity, e.g., certain colours of flower structures which look like female insects for male insects, the contour of a wolf which is a warning sign to dogs.

(c) The third important sign is *symbols* that do not mean what they represent but are signs that biotic agent groups use and share through conventions that the group members agree to by social learning experiences. This is seen in the dialects in the language of the bees or the main representative of symbol use, the human languages.

The biocommunication approach investigates all kinds of sign-mediated interactions in all domains of life (Witzany 1993, 2000, 2010a, b, 2011, 2012a, b, 2014, 2016a, b; 2018; Witzany and Baluška 2012; Witzany and Nowacki 2016), according to the biocommunication method: to identify interactions mediated by signs, according to the 3 levels of rules on all levels of interactions. This is essentially different from molecular biological approaches and adds some essential features of living agents to molecular biological results which molecular biology alone cannot investigate.

Additionally, the biocommunication approach transforms the general understanding of life into an empirically-based but non-mechanistic and non-reductionistic perspective (Fig. 1.2).

Research on phage communication can exclusively focus on indexing, which means that chemical molecules or receptors can cause phages to react appropriately. This is important to identify bacterial host from bacterial non-host, host defence system, helper phages, virophages, etc.

Different Paradigms: Explainung and Understanding „Life“

Concept of	Molecular Biology	Biocommunication
„dead“	pre-biotic chemical reactions	no sign-mediated interactions
„living“	replication/biological selection (molecular reactions)	sign-mediated interactions (social events)
determinants	natural laws (thermodynamics)	semiotic rules
RNA-ensembles	molecular assembly	agent-groups integrate or preclude non-self agents
viruses	escaped selfish parasites	essential agents of life
genetic variation	error replication	RNA interaction based innovation generation
genetic novelty	random mutations	viruses and subviral RNA-networks edit code
biological selection	fittest type	fittest consortium
genetic code	genetic material	semiotic text (according syntax, pragmatics, semantics)
communication	information transfer via coding/decoding mechanisms	agent-based social interactions mediated by signs according semiotic rules

Fig. 1.2 Different paradigms investigating living agents and defining life: the molecular biological paradigm explains all life processes primarily by the physical-chemical properties; the biocommunication approach explains life as a social event of cellular and sub-cellular (viral and RNA-network) agents that communicate, i.e. based on interactions that are sign-mediated according to 3 levels of semiotic rules, syntax, semantics, pragmatics

1.3 Phage Behaviour Motifs

Phages are not pure molecules like molecules in an abiotic planet. They share biotic features such as biotic behaviour. Forest Rohwer assembled some of the most obvious examples of behavioural strategies in a “lexicon of phage behaviors “and identified the concerned protein families (Rohwer et al. 2004). The following list is taken from this lexicon:

(A) Prowling for a Partner

Before finding a host, a phage responds to environmental assaults by resistance, genome defence, hide or succumb, or even dormancy.

- phages find some hosts by electrostatic intersections and dipole moments
- in prowling for some hosts, phages interact with the capsid and surrounding milieu
- virions search for a host cell surface in a bid to recognize and sense an appropriate host and identify its appropriateness for the touch-down movement. This indicates a relatively stable interaction between the capsid and host surface.

(B) Court Host

If phages bind irreversibly to a host-cell surface court host, a virocell is created. This includes several interaction motifs such as

- penetrate the host, infiltrate, extend appendage, plug membrane hole, digest, burrow or merge
- fertilize the host and deliver capsid content by secretion, remodel capsid to extend the tube, translocate the genome
- adsorption, which means acceptance of the host by attachment, latch onto pilus, hold on, grasp, ride flagellum

(C) Ensure Virocell Viability

After the takeover of the host cell, phages ensure virocell viability by

- dispatching host defences by camouflaging, hiding, avoiding, mimicking or disguising
- defending the virocell by recognizing kin, allowing superinfection or, in another context, preventing a super-infection
- maintaining metabolism by photosynthesis or preventing suicide, nursing the virocell
- garnering resources by hijacking, commandeering, seizing, redirecting, devouring
- coercing the host by outwitting or outshining, rendering helpless, killing or threatening, or injuring

(D) Hedge Life History

In various motifs, the main source or main motif is ensuring the life history of the species. This means to decide whether to replicate the genome now or later, which needs some fine-tuned and coordinated steps.

- temporally coordination by mutating the host, killing competitors, integrating into the host, excising, jumping around, defending the host and inactivating.

Also, increasing virocell fitness by enabling colonization of a new niche or production of a toxin

- linearize the genome or circularize the genome and/or expressing proteins
- maintain pace in the red queen race by evolution, going extinct, mutation and diversification (by capsid coat, modularity, modifying nucleotides, tropism switching)
- lytic replication by fixing errors, mass production of genome copies, open helix, genome replication initiation, innovating sequence structure, protecting single strands
- recombination by outcross (illegitimate recombination) or inbreed (homologous recombination)
- obtain materials by cannibalizing, reusing, thieving, stealing, recycling

(E) Morphogenesis of Progeny

Offsprings of phages are not passive molecules but are active agents coordinating and organizing survival. An ensemble of virions

- care for offspring development by baseplate assembly, capsid accessorization, scaffolding, tail assembly, care for symmetry, tail length measurement, DNA processing, shell building and head and tail joining.
- package DNA by pumping, stuff prohead by terminase, coat with protein
- obtain components by coercing, stealing, synthesizing, scavenging, cheating and quality control
- building the virion factory by managing mass production, building the nest, coordination and organization, preparing the tools

(F) Wean Progeny

The last step in the replication cycle of phages we consider is the process of freeing virions from the virocell. The virocell concept – originally developed by Patrick Forterre – states that the bacterial host cell does not represent its original identity (Forterre 2013). The identity is captured and manipulated according to the phage life strategy. If the mass production of virions is finished, the bacterial cell membrane is lysed. This includes several steps of active behaviour such as

- annihilate outer membrane
- build pyramids
- degrade cell wall
- light fuse
- set timer
- sabotage

Although manipulated into another identity, the virocell is still involved in the rich social life and metabolic activities of the microbial host population until host cell bursts.

1.4 Trans-Organismic Communication: Communication of Phages with Non-phage Organisms

If a bacterial strain is persistently infected by a phage and caused to compete with a bacterial strain which is not infected by the same virus, the uninfected strain will undergo lysis. This means that infection and colonization of bacteria are connected with the acquisition of an immunity function which does not allow the destruction of the infected one by the uninfected one. Infected bacteria share a common immunity which is absent in uninfected bacteria. Phage colonization in a nonlytic but persistent lifestyle has a symbiotic function which protects host cells and host strains (Villarreal 2016).

It is well known that half of the bacteria in the oceans are killed daily by phages. The remaining half is the result of the incredible reproduction rate, which is the main reason for their survival. The adaptive immune system, known as CRISPR/Cas, which copies and pastes relevant sequences out of phage genomes and integrates them into the genome of infected bacteria, also plays a critical role, serving as indicators for identifying similar infecting phages that may trigger a restriction protein to kill the invading agent (Koonin et al. 2019; Koonin and Makarova 2019). CRISPR–Cas systems integrate phage DNA sequences into CRISPR loci on the host genome. This leads to heritable immunity against invading agents. This is a complex reaction motif: the integration of the sequence tool of the phage genome into the bacterial genome is not random. It must fit the remaining genome structure, should not damage the previous functional structure of the bacterial genome and should fit into the order of previously integrated sequences. The syntax rules to achieve this are currently unknown.

The defence system of CRISPR Cas is a rather complex immune system, which includes a process to prevent self-targeting and destruction processes, that defends bacteria from phages and plasmids by recognizing invading DNA (Harrington et al. 2018). Besides that, CRISPR Cas serves as signalling within the bacterial host (see below) and can guide sequence-specific transposition (Strecker et al. 2019; Dimitriu et al. 2019). Therefore CRISPR Cas contributes relevantly to the evolutionary variants of bacteria in certain adaptation processes through the generation of new genetic identities (Westra et al. 2014).

1.4.1 Interaction Motifs with Far-Reaching Consequences

The interaction motifs of phages and their prey bacteria are very complex because, through their intensive impact on bacteria, phages are relevant for bacterial distributions, populations and communities in all known ecospheres on earth (Brüssow 2018). This includes the way bacterial communities are successful in competition with other bacterial communities, how they establish equilibrium with other bacterial communities in symbiotic ecospheres, such as the human oral cavity with 700

different bacterial communities. The well-balanced equilibrium of bacterial communities is the main source of oral cavity health (Kohlenbrander et al. 2002, 2005). Asides infections, diet or daily hygiene procedures may disturb this equilibrium.

A more powerful relationship exists in the human gut (Manrique et al. 2017; Guerin et al. 2018; Shkoporov et al. 2019; Sausset et al. 2020). These phage bacterial interaction profiles are important for humans and all eukaryotic organisms with essential symbiotic relationships with bacteria (Bondy-Denomy and Davidson 2014; Carroll-Portillo and Lin 2019). About 80% of the fecal waste of animals is bacteria. Faecal waste thus represents an excellent habitat for phages. In all cases, phages determine how this symbiotic interaction can function or may even be disturbed and unbalanced. Any impact of bacterial populations on the whole range of eukaryotic organisms thus strongly depends on how these bacterial communities are affected, infected by phages and how phages remain in a persistent or lytic lifestyle with relevant impacts on the competing bacterial communities (Villarreal 2005; Feiner et al. 2015). Clearly, this persistent lifestyle of phages cannot be described as predatory against bacteria but as cooperation in most cases with co-evolutionary relevance (Borges et al. 2018; Fillol-Salom et al. 2019; Argov et al. 2019).

Phages also relate with bacteria in the carrier state in which phages cause chronic infection in bacteria. Here, the phages do not integrate into the host genome or have lytic consequences. The phage remains in this infection state, and its progeny is passed to daughter cells asymmetrically after division (Cenens et al. 2013). This relationship between phage and bacteria is a co-existence lifestyle (Roux et al. 2019). It affects the host of bacteria in that it alters some relevant ecological consequences (Siringan et al. 2014).

More recently, another kind of persistent infection has a defence which is termed "Hibernation". The persistent state of phages in the host is reversible and is regulated by the availability of appropriate nutrients (Bryan et al. 2016), such as host DNA after host DNA breakdown and glucose.

The way phages respond to bacterial defence strategies is rather interesting (Ofir and Sorek 2018). If bacteria are infected by phages, they mobilize defence activities such as e.g., CRISPR Cas. Phages may counteract these defence activities by changing attachment sites by e.g., modifications in phage protein, or as shown more recently find ways to cooperate to overcome phage resistence (Landsberger et al. 2018; Stanley and Maxwell 2018). Another reaction motif is importing a degradation system into the host that destroys bacterial nucleic acid sequences (Seed et al. 2013). More recently, research has shown that phage infection may abolish the swarming motility of host bacteria and induce the release of signalling molecules that warn uninfected subpopulations to move towards uninfected areas and promote the survival of the overall population (Bru et al. 2019).

It is noteworthy that a key role in this transorganismic communication is played by the various toxins such as holins, endolysins, bacteriocins, pyocins and colicin which are involved in generating pores - clear features of bacteria that derived from phage infections (Riley 1998; Young 2002; Nakayama et al. 2000; Bull and Regoes 2006; Villarreal 2009). This means that without phage infections bacteria would not have these features.

1.5 Inter-Organismic Communication: Communication of Phages with Other Phages and Viruses

Nearly all behavioural motifs of phages are commonly shared within phage communities (Turner and Chao 1999; Lima-Mendez et al. 2011; Stedman 2015). The prophages, i.e. phage sequences within the bacterial genome interact with other prophages. Prophages also interact with lytic phages. In such cases, the prophages serve as signs (indicators) for lytic phages to remain in a persistent lifestyle or become lytic if other indicators of the bacterial environment transport that information (Gallego Del Sol et al. 2019; Argov et al. 2019). In contrast to prophage, i.e., integrated state of phages within bacteria genome, we also know non-integrated persistence such as episomes that resemble plasmids and replicate independently from the host genome (Villarreal 2005).

Also, helper viruses such as satellite phages are common in infection cycles if phages deficient for capsid and/or tail production and lytic virulence need helper prophages that help the phage with carrying out specific functions (Liu et al. 1997). Such phage-phage interactions have relevant implications for bacterial communities in their symbiotic macroorganisms, such as in the human gut (Moelling 2016). It is important here to note that social interactions of phages are usual und determine viral fitness (Abedon 2009; Bernheim and Sorek 2018). Coinfection increases the complexity of interaction patterns for both phage communities, bacteria communities and their affected macroorganisms in shaping their community compositions.

Additionally, we should mention the dual lifestyle of genome-integrating virophages. Virophages act as a parasite of giant viruses (Paez-Espino et al. 2019). For example, they coinfect with Mimivirus and reduce burst size. This means virophage coinfection increases the survival of infected populations (La Scola et al. 2008; Berjón-Otero et al. 2019). In other behavioral motifs virophages play key roles as target of host defence in the interaction network of host cell, giant virus and virophage (Koonin and Krupovic 2017; Mougari et al. 2019).

1.5.1 Addiction Modules: Complementarity of Transorganismic and Interorganismic Communication

Addiction modules represent at least two competing genetic parasite clouds, which try to invade host genomes. This represents a complementary interaction event (transorganismic and interorganismic). Addiction modules can be defined as features that consist of a stable, toxic component, which is counterbalanced by an unstable component inhibiting and suppressing the toxic component. This behavioral motif of phages originally was described by Lehnherr and Yarmolinsky and later generalized by Villarreal (Lehnherr et al. 1993; Lehnherr and Yarmolinsky 1995; Villarreal 2012a, b; Villarreal 2015; Villarreal 2016).

This is an important impact of phages on bacterial hosts: the integration of toxins of various kinds, even more than one, so that bacteria may integrate toxins that do

not harm the host because the toxin (T) is counterbalanced by an antitoxin (A) derived from a competing phage infection (Harms et al. 2018). If such T/A module-based bacteria contact other bacterial populations that don't possess the whole module, it may kill these populations. The same happens with restriction/modification enzyme modules that are relevant for several interaction motifs (Kobayashi 2001; Yahara et al. 2007; Mruk and Kobayashi 2014).

It is particularly interesting that mixtures of cryptic prophages, i.e., defective and silent, may take up a large portion of the genome, as documented in E.Coli, where K12 may represent 20% of the total genome. This may be up to 35 sets of Toxin/Antitoxin sets out of several cryptic prophages (Wang et al. 2010). If we remove these viral TA sets, prokaryotic cells may become more sensitive to various stressors, such as antibiotics, osmotic, oxidative and acid stress. Deletions of such TA modules in K 12 phage lead to the loss of the ability to form biofilm in small media and therefore resembles a kind of group effect phenotype (Villarreal and Witzany 2015). The persistent (temperate) lifestyle of phages in host genomes may lead to high-density regions which do not serve as genetic fossils but a kind of spread community of active agents. Importantly, this demonstrates how host genetic identity depends on how phages or defective parts of phages determine host gene structures (Hambly and Suttle 2005; Villarreal 2009).

The emergence of genetic identities, first in prokaryotic organisms, then in the evolution of multicellular communities such as whole tissues or organs may start with such addiction modules. Such identity networks are constituted by the cooperation of self-harm and self-protection, without amalgamating them into one feature. They remain two capacities, that are temporally counterbalancing, but may provide other cooperation networks that compete and/or destroy the other one in certain circumstances (context) and are, therefore, open to generate new identities, even evolutionary ones. It should be noted that all these interaction motifs may vary according to methylated properties, i.e. epigenetic imprintings that change expression patterns and variable protein meanings without changing the primary DNA sequence.

Importantly, from a "virus first "perspective, this interaction motif of addiction modules is a dominant motif of genetic counter-regulation in all domains of life not restricted to T/A or R/M motifs and a key element in the generation of diversity and host genetic identities (Villarreal 2012b). Addiction module generation integrates competing (counter regulating) genetic information of parasites (present in organisms of all domains of life) into host genetic identities, which non-infected hosts from the same or related species do not possess (van Sluijs et al. 2019). This may alter host phenotype by complex genetic information in a single event, not depending on error replication (chance mutations) and their selection over long periods. Such complementing – in most cases defective – viruses or virus-derived parts may cause disease or even kill the host if counter-regulation becomes unbalanced or recombined with other remaining defective minorities of former viral infections (Villarreal 2005, 2011). This indicates that defective minorities do not remain as waste or "junk "but as important re-usable module like tools (Villarreal and Witzany 2019). Additionally, such addiction modules serve as immune functions against the same or related infective genetic parasites. This means it will protect infected hosts and kill non-infected ones (Fig. 1.3).

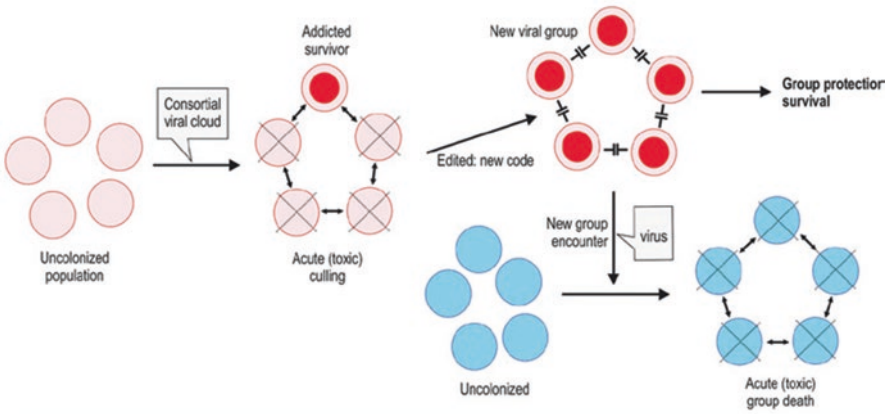

Fig. 1.3 Generalized interactional motif of infection-derived group identities: the addiction module as a result of counterbalanced (addicted survivor), infection-derived, and persistent genetic parasites that initiate evolutionary inventions (new viral group) by natural genetic engineering of host genetic identities, some we can find as toxin/antitoxin, restriction/modifcation, or insertion/deletion modules. (From Villarreal, L.P. Viruses and host evolution: Virus-mediated self identity. In López-Larrea, C. (ed.), Self and Nonself, Springer Science+Business Media, Austin, LandesBioscience, New York, pp. 185–217, 2012b. With permission)

1.5.2 Addiction Modules and the Evolution of Programmed Cell Death (PCD)

P1, formerly seen as a plasmid not virus is such an example: Eventually, it became recognized as a real virus that persists as a stable episome that does not integrate into the host genome. If E. coli is colonized by P1, it reaches at least one T/A module by which expresses an immunity function. But if P1 colonized E. coli and is infected by other phages such as e.g., T4, the antitoxin gene is destabilized and the remaining stable toxin will kill this infected cell, thereby preventing T4 transmission to uninfected bacterial neighbours. This means, that a P1-colonized bacteria will start suicide to prevent T4 replication and transmission of a harbouring colony (Lehnherr and Yarmolinsky 1995). Therefore, P1 plays an essential role in group identity formation of bacteria and represents a general model in that persistence generates group identity by the integration of addiction modules. The addiction module has been first seen at P1 and the post-segregation killing of the host if the host lost the virus (Lehnherr et al. 1993; Engelberg-Kulka and Glaser 1999; Hazan et al. 2001).

Single cells die to protect the remaining group identity. If reminded that development of cells, tissues, organs and whole organisms depends on certain developmental stages in that parts of the whole organisms follow expression stages determined by epigenetic imprintings that differentiate the growing tissue cells and allow some cells die and others to grow, we can imagine that certain gene regulatory pathways

from early times in biology evolution such as bacteria and phages may be co-opted and exported to later-evolved organisms.

Programmed cell death is a consequence of an unbalanced addiction module (T/A or R/M). If the balance is stable, it determines the genetic identity of a host and temporally imprints the host population. This imprinting is absent in host populations that are not infected by such balanced modules. Such imprinting may become unbalanced by several defectives of former infections such as introns, transposons or hyperparasite invasions (intene, retroposon) (Villarreal 2009). The new identity of a bacteria population (with its certain group behaviour and preferred host organisms) by such R/M modules on the genetic level (R/M addiction genes) and epigenetic level (methylated DNA). The interesting aspect here is that this focuses on infection techniques via addiction module building and its consequence, the imprinting of host genetic identities and integrates complementary features, the colonization, new immunity and new identity.

Now we can consider the crucial feature for the process of acquiring all the genetic content of bacteria and the processes that caused their diversity (group identities). This has serial, cumulative and episodic consequences which are important aspects in understanding the cumulative evolution of complexity also.

Interestingly, most evolutionary biologists engage fitness determinants only from the role of cellular genes. The roles of persistent genetic parasites and their interactions within the host genome on survival have been overlooked for decades. Additionally, the roles of defective genetic parasites as key players in communication (sign-mediated interaction) with non-defective parasites are also essentially absent from evolutionary biology. Indeed, the crucial role of communication per se is poorly developed in evolutionary biology.

The fundamental interplay of addiction modules through their temporal stability and immunity functions and their harmful consequences to excluded individuals via altered addiction module status results in stabilized group survival as a key feature of most organisms, including eukaryotes.

Phage-bacteria and phage-phage interactions are the most pragmatic concepts to coherently explain the regular control of bacterial populations and their harmfull and beneficial roles to eukaryotic host organisms after understanding the evolution and emergence of bacterial genetic identities and diversity of interactions of bacteria, their persistent viruses and their eukaryotic host organisms (Witzany 2011; Guglielmini et al. 2019).

1.6 Intra-Organismic Communication: Communication Within Phages

All relevant interactions of phages on the transorganismic and interorganismic level need a variety of internal organisation and coordination processes such as that used for their genetic expression. The genome of the phage must be coherently expressed

in most cases by hijacking the bacterial transcription process to reach these goals, although some giant phages do not depend on a bacterial host for replication (Ceyssens et al. 2014). The activity of the bacterial transcription process by RNA polymerase (RNAP), is regulated by a variety of small phage-encoded proteins (Tabib-Salazar et al. 2019). In considering the infection of bacteria in the animal gut, we should remember that the genetic expression pattern of the phage may also react to some satellite phage that is currently present as well as the signalling molecules of the other phages that induce a persistent lifestyle. Such signaling may change if the environmental conditions (context) of the host changes rapidly, or/and the bacterial adaptive immunity in certain strains is increasingly strong, because bacteria-host interactions are relevant in a certain stage of gut microbiome situation (context). This means the phage (and host) genetic expression is rather context-dependent and needs some context coherent reaction modes.

The reaction patterns of phage expression is also dependent on the status for methylation of certain sequence in host strains which is enhanced following repeated similar situations (infections), a feature that seems to be a relevant memory/learning behaviour of phages to increase successful interaction. The interaction within phages is thus very complex and has to sense (interpret) complex incoming information from other parasites in a rather fast and appropriate way. Otherwise, the phage response would not be successful for survival (Casadesús and D'Ari 2002).

1.7 Phage Communication Vocabulary: Examples

Persistent phages in bacterial host genomes may switch between lytic and lysogenic life cycles. Recently it was shown that *Bacillus subtilis* SPbeta phage produce a peptide (AimP) which serves as a signal within a communicative interaction during phage infection (Erez et al. 2017; Abedon 2017). AimP reduces the expression of the negative regulator of lysogeny (AimX) by binding to the transcription factor (AimR) promoting lysogeny. Thus, persistent phages have to decide every time they infect a bacterial cell on starting the lytic cycle or lysogenic cycle (Weitz et al. 2008). Several phages and infection-derived mobile genetic elements encode peptides (e.g. arbitrium) that serve as signs in communicative interactions. This is counter-regulated by a non-coding RNA that serves as peptide response and controls regulation of the lysogenic state (Stokar-Avihail et al. 2019).

In the type III CRISPR Cas system, the recognition of foreign DNA leads to the production of a small molecule (cyclic oligodenylate) which activates a CRISPR-associated RNAse which cleaves cellular RNA nonspecifically (Amitai and Sorek 2017). Phages may produce a specific response: an anti-CRISPR protein (acr) that inhibits CRISPR Cas immune function (Landsberger et al. 2018). This is the result of phage-phage cooperation to overcome CRISPR resistance (Borges et al. 2018). First, phages block the CRISPR Cas immune system of bacteria: this allows a second infective phage to replicate within the host. The success of this cooperation, however, depends on the density of phage populations.

Additionally, bacteria defence systems also rely on communicative interactions within the bacteria as documented in the GMp-AMP synthase –STING pathway, an immune response of animals that acts as a sensor of cytosolic viral DNA and produces a cyclic FMP-AMP signalling molecule that activates the immune response by binding to the STING protein. This can be found in bacteria as an antiphage defence also (Cohen et al. 2019). Additionally, bacteria may produce various other molecules that can block a successful viral infection (Clokie 2018).

1.8 Phagetherapy

Bacterial multidrug-resistance is a serious medical problem with rapid progression worldwide. The common use of broad-range antibiotics leads to antibiotic crisis and resistance of many human bacterial pathogens. Bacteriophages infect and kill bacteria, even multidrug-resistant ones and so-called superbugs (Rohde et al. 2018a, b; Pirnay et al. 2018; Sakr et al. 2018). Their noninfectious nature to humans should make them safe for human biomedicine (Rehman et al. 2019).

1.8.1 Historical Notes

Phages were applied as anti-bacterials first by Felix D'Herelle in Paris in the early 1920s. D'Herelle collaborated with Georgi Eliava at the Pasteur Institute and, later on, after Eliava returned to Tbilisi, Georgia, both founded the Institute of Bacteriophage Microbiology and Virology in 1933. Phages had to be isolated from the environment, cultivated on bacterial hosts, and purified with technology that was available at that time. In the following decades, this institute developed to the world's biggest phage research and production centre. During and after world war II, this research increased, especially in Russia. Many patients visited and still visit this centre for individualized phagetherapy, mainly using complex phage cocktails (Ajuebor et al. 2018; Rohde et al. 2018a, b). The best-documented applications stemmed from former Russia (in Georgia) in the 1960s, of successful prophylaxis against Shigella dysentery and E. Coli diarrhoea.

Another "hot spot" of phagetherapy was established in Poland with high efficiency in appropriate phagetherapy applications, especially in investigations of immune response under phagetherapy. In contrast to the phagetherapy practice in Georgia, the Polish used monophage preparations exclusively (Górski et al. 2018; Górski et al. 2019).

In the following decades, in Belgium (Astrid Military Hospital, Brussels), France (Pasteur Institute), Switzerland (ETH Zurich), and Germany (Charité University Hospital, Berlin), promising clinical applications of phagetherapy were established and officially supported (Sakr et al. 2018; Wienhold et al. 2018). A more recent trial

in Bangladesh failed to show successful applications, but a second trial was more promising (Sarker et al. 2017; Bolocan et al. 2019).

Soon after the discovery of antibiotics in the 1940s, interest in using phages for therapeutic purposes was nearly lost, except in the Tibilisi Institute (Georgia). The public health crisis from multidrug-resistance of bacterial strains led to increasing interest in alternatives to antibacterial agents, integrating a variety of therapeutics and prevention strategies. In 2018, 100,000 persons died from antibiotic-resistant bacterial infections definitively, of the 700,000 persons estimated to die from antibiotic-resistant bacterial infections annually.

1.8.2 Reasons for Multidrug-Resistance

The increase in multi-resistant bacteria is attributed to the excessive use of antibiotic substances in human medicine and argriculture. This abuse of antibiotics has been seen in human and veterinary practices as well as industrial and agricultural practices that have increased the prevalence of drug resistance among many bacterial strains.

Animal farming also contributes to bacterial resistance, creating a vast reservoir of antimicrobial drug resistance in combination with zoonoses. Unfortunately, major zoonotic bacteria belong to the ESKAPE group. The ESKAPE group includes *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp*. They possess increased resistance to antibiotics such as penicillin, vancomycin, methicillin, carbapenems and others. (Santajit and Indrawattana 2016; Mulani et al. 2019).

The human microbiome inhabits very different sites. The skin is an important site, with staphylococci as one of the most prevalent residents. If the skin is damaged, the microbiome may colonize the skin injury and cause infection. Many problems with bacterial biofilms occur on implantation material, skin transplantation, several injuries in the oral cavity or lung, chronic wounds such as diabetic foot ulcers and unbalancing of the intestinal gut microbiome. More different indications for both chronic and acute conditions, including bone-and-joint, urogenital, respiratory, wound, cardiac, and systemic infections are reported meanwhile. Here phagetherapy looks very promising because phages may degrade biofilms that cause diseases (Rohde et al. 2018a, b).

1.8.3 Current Plans to Fight Multi-Drug Resistance by Phagetherapy

Phages penetrate biofilms much better than antibiotics substances because they express exopolymer-degrading enzymes, such as polysacharide depolymerases, which are more efficient in multilayer biofilms than antibiotics. The efficiency of

antibiotics decreases through the various layers of biofilms. Furthermore, phages may cause beneficial immune responses.

Therapeutic use of phages as a future-oriented alternative to conventional antibiotics is a relevant focus, according to WHO assembly resolution (68.7.3.) from 2015 which called for national action plans by May 2017 to combat the antimicrobial drug resistance crisis ("...inappropriate use of antimicrobial medicines in all relevant sectors continues to be an urgent and widespread problem in all countries..."). The G7 Health Ministeries initiated a global "One health" approach in 2015 and 2017. The EU initiated such a strategy by the Horizon 2020 program. If nothing changes, ten million persons have been predicted to die from AMR in 2050.

European One Health Action Plan against Antimicrobial Resistance (AMR) (2017/2254(INI)) is a further step followed by Antibiotic Resistance Threats in the United States, 2019 (Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019) which states that more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die. There are a variety of judicial cases in several states regarding research on the subject. Mostly, they derive because national laws follow suggestions of definitions that are congruent with antibiotic economics.

The realization that phages and bacteria have a variety of interaction patterns by various signalling ways, i.e. communicative interactions, invites research on how humans can apply this competence of phages to kill bacteria with dangerous impacts on human health (Wienhold et al. 2018; Rohde et al. 2018a, b). This includes bacteria immune systems and reactions to phage infection and colonization and the various ways phages can counteract these immune functions. At this time, phagetherapy seems like a curious therapy method besides the mainstream antibiotic era (Domingo-Calap and Delgado-Martínez 2018). In the next 20 years, this will surely turn around to protect millions of humans that are confronted with the consequences of multidrug resistance.

1.9 Conclusion

The rich variety of communicative interaction, i.e. interactions between phages and bacteria, phages and other phages and phages on other living organisms that depend on sign(alling) undoubtedly demonstrates that phages are essential agents within the animate nature. The rich interaction motifs of phages also indicate that viruses are essential agents within the roots and stems of the tree of life. Bacterial genome construction is under the crucial influence of phages, and the disease-causing toxins of bacteria, in most cases, are results of former viral infections that transferred toxins and antitoxins to host bacteria. Interestingly, the communicative competences of phages are often found in a complementary way. This means transorganismic communication is intertwined with interorganismic and intraorganismic communication as demonstrated by the most important result, the addiction modules. It is thus

essential that we better understand phage interactions if we are to succeed in developing phage therapy to bacterial multi-drug resistance.

As a further result, the old question of whether viruses are alive or not remains a historical curiosity, because it is impossible to examine bacteria without the co-evolutionary role of phages and the constant interactions of phages on bacterial populations. Defining viruses not to be alive is based on a wrong definition of life in general because it ignores communication and the inability of communicated viruses to self replicate is not a deficiency. Meaningful and consequential communication has occurred. And it results in effective adaptation to a planetary cellular world that ensures virus replication without dependence on its own replication apparatus which would contradict low energy cost determinants.

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