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Title

Bacterial sensing of bacteriophages in communities: the search for the Rosetta stone

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Summary

Billions of years of evolution have resulted in microbial viruses and their hosts communicating in such a way that neither of these antagonists can dominate the other definitively. Studies of the molecular mechanisms underlying this dialog, initially in bacteriophages, rapidly identified several of the ways in which bacteria resist bacteriophage infections and bacteriophages defeat bacterial defenses. From an ecological perspective, recent data have raised many questions about the dynamic interactions between bacteria and bacteriophages, the densities of which, in complex microbial populations, are only beginning to be investigated. The next challenge will be determining how the dialog between microbial viruses and their hosts modulates complex ecosystems, such as those found in healthy humans or infected patients.

Introduction

Viruses infecting microbes (including those infecting Archaea, bacteria, fungi and protists) are considered to be the most abundant biological entity on Earth, with an estimated 10^{31} particles. They play a major biogeochemical role, by releasing material from the hosts they infect, but they also have a potentially useful but as yet untapped ecological impact on cellular populations. Bacteriophages, the most widely known and well-studied of these viruses, are predominantly virulent, their infectious cycle ending with the destruction of the bacterial host to release progeny. A minority of free bacteriophages is temperate and may, in some situations, initiate a lysogenic cycle rather than a lytic cycle, by integrating their genome into the bacterial chromosome to form a prophage. Bacteria have developed several molecular defenses against viral infection (bacteriophage resistance mechanisms have been described in detail elsewhere [1,2]). Instead this opinion focuses on recent publications related to bacterial sensing of bacteriophages from simple models to more complex situations such as microbial communities of mammals.

Binding to host receptor as first signal

Preceding resistance, bacterial sensing of bacteriophages operates at various stages (Figure 1). The first signal involves detection of the binding of a particular bacteriophage protein to a defined molecular structure present on the cell surface. Only for a few model bacteriophages have host and viral partners involved in this binding been identified [3]. Indeed, several genetic mutations were shown to interfere with bacteriophage binding, but no signaling-based mechanism has yet been identified. Recently, cutting-edge electron microscopy studies revealed how the T7 bacteriophage finds the most appropriate site for starting an infection [4]. The bacteriophage fibers, which remain

bound to the capsid, function primarily to facilitate the interaction of the bacteriophage tail with its specific receptor. Binding remains reversible until the fibers identify a suitable site. Infection begins only after stable adsorption of the bacteriophage into the bacterium, with i) the injection of the internal core proteins into the cell; ii) the formation of an extended tail and iii) injection of the viral genome into the cell. During this scanning process, which is also thought to occur for bacteriophage SPP1 and might be widely spread amongst tailed bacteriophages, the rate of successful fiber binding to bacterial receptors may be limited by the host, through a signal initiated in response to the first molecular contact. This signal may be propagated to neighboring receptors via conformational changes, decreasing availability for irreversible binding. Another possible mechanism can be extrapolated from the recent identification of the molecular mechanism underlying the binding of the filamentous bacteriophage fd to the bacterial pilus, coupling unfolding and the prolyl isomerization of viral protein Gp3 [5]. The partially unfolded Gp3 uncovers the binding site for bacterial protein TolA, the secondary receptor. As a defense signal, binding to the pilus may trigger signaling to the cell membrane, to decrease TolA availability. Such signals, which may be the least costly defense solution for hosts, have not yet been demonstrated in practice. They may be irrelevant in test tubes, due to the high frequency of contacts, but play a more important role in mixed bacterial populations, in which the frequency of contact is lower, and may then increase the threshold value for bacteriophage amplification.

Targeting the viral information

The second step, the injection of viral molecules (DNA and proteins) into the cytoplasm, is the last chance for bacteria to counteract viral infection. Once this process has begun, the host has a limited amount of time to react before the virus hijacks the functions of the cell to transform it into a

viral factory. Studies *in vitro* and *in vivo* led to the identification of two possible mechanisms for the physical ejection of viral information from the capsid and its injection into the cell [6]. The ejection of lambda bacteriophage genetic material and its entry into *E. coli* cells are estimated to take about five minutes, on the basis of single-cell fluorescence microscopy observations inspired by the famous Hershey and Chase experiment [7]. However, this time varies between cells, consistent with a mechanism driven by internal cell processes as opposed to a repulsive mechanism originating in the viral capsid [6]. The host must then respond to bacteriophage infection within these five minutes, targeting the viral information.

Restriction modification and CRISPR (clustered regularly interspaced short palindromic repeats) / Cas protein (CRISPR-associated protein) systems are the two major mechanisms by which bacteria interfere with viral genetic information (Figure 1). CRISPR/Cas, the most recently discovered bacteriophage resistance mechanism, has been found in many bacteria and archaea. Detailed studies revealed that several CRISPR/Cas systems fulfill various functions, from defense against virulent bacteriophage infection to bacterial pathogenesis [8-10]. Once DNA ejection from the capsid has begun, the CRISPR/Cas system provides the bacterium with a means of interfering with the viral cycle and disrupt the integrity of the viral information, by making use of a short nucleotide sequence present in the host genome, that matches a sequence in the bacteriophage genome. However, it remains unclear how this sequence is integrated into the host genome in the first place. It is possible that defective bacteriophages, unable to complete the viral cycle, provide the bacteria with an opportunity to acquire sequences for the development of immunity. The molecular dissection of CRISPR systems is currently underway and several examples of bacteriophages carrying anti-CRISPR systems are being discovered, suggesting that we may be in front of an additional example of the coevolution of defense and counter-defense systems in viruses and hosts,

such as restriction modification systems [11,12]. A third system, known as abortive infection, does not affect the viral information directly, instead acting on the infectious cycle by killing the host cell before the virus does [13] (Figure 1). This process, a sort of cell “suicide”, protects the host population by preventing the spread of bacteriophages.

All of these systems are highly adaptable to the rapidly evolving nature of bacteriophages, but they may not be sufficient to counteract the viral pressure observed in the many environments in which bacteriophages outnumber bacteria. There may be other, as yet unknown defense systems, which could be identified by global approaches, such as transcriptomic analyses of infected bacteria. For example, LUZ19, a podovirus infecting *Pseudomonas aeruginosa*, induces the overexpression of more than 200 host genes within five minutes [14]. Some of these genes, such as those maintaining active cell metabolism, are undoubtedly required for the infection to proceed, but others may be involved in new defense mechanisms. In such cases, these mechanisms are not efficient enough to prevent completion of the lytic cycle, perhaps because the bacteriophage has evolved mechanisms to counter these systems. Indeed, such countermeasures were recently demonstrated in a study applying a straightforward approach to identify new toxin-antitoxin systems from hundreds of microbial genomes [15]. This impressive work, beginning with bioinformatic analyses and, followed by bacteriophage plaque assays and protein-protein interaction studies, not only identified and functionally characterized new toxin and antitoxin proteins, but also identified a new protein counteracting bacterial defenses was identified in the T7 bacteriophage. Additionally, an original way for bacteria to resist viral infections has just been reported [16]. By a yet unknown mechanism, a large chromosomal deletion (200kb) led to the loss of at least one gene required for the synthesis of bacteriophage receptor.

Diffusible molecules to signal bacteriophage infection

A third means by which bacteria resist bacteriophage infection is based on the diffusion of molecules released from the lysed host. These molecules, such as DNA, may be perceived by surrounding hosts as a signal to increase resistance at the population level. No direct evidence for such signaling has yet been obtained, but a recent study provided support for this hypothesis, by linking quorum sensing molecules to bacteriophage infection. The production of large amounts of *N*-acyl-L-homoserine lactone by *Escherichia coli* decreases the number of LamB receptors, thereby altering the rates of bacteriophage lambda adsorption [17]. This is an example of a resistance mechanism coordinated by the host population and that affect gene expression within individual cells. This bacteriophage resistance mechanism was previously suggested on the basis of a link between cyclic AMP and the resistance of *Vibrio cholerae* strains to environmental bacteriophages [18]. Such bacteriophage resistance phenotypes, induced by variations of cellular gene expression, are probably widespread. They may be induced directly by signals released by an infected host, or indirectly by environmental signals, such as those produced by human immune cells. Additional data suggesting that the frequency of this resistance mechanism may be high were obtained in studies on bacteriophage replication efficacy within the gut of mice experimentally colonized with *E. coli* [19-21]. Such resistance, which is phenotypic in nature, can be easily overcome, rendering bacteria prone to bacteriophage predation in a situation resembling that of persister cells resistant to antibiotics.

Prophages for sensing virulent bacteriophages

Prophages have been found in the genomes of diverse bacteria, and genomic analysis suggests that there are probably many more incomplete prophage elements present on bacterial chromosomes [22]. Several examples of the contribution of prophages to bacterial evolution are described, such as the provision of new virulence factors, toxins and antibiotic resistance genes [23,24]. Prophages are also long known to prevent infection with virulent bacteriophages, as shown by the example of a lysogenic strain of *Escherichia coli* carrying a lambda prophage conferring resistance to bacteriophage T4. As the aforementioned abortive-infection systems are found in many genomes, and sometimes in prophages, it is tempting to speculate that bacteria retained prophages, or parts of them, such as toxin-antitoxin systems, to sense and prevent infection by new invading bacteriophages [25]. More generally, viral information is mobile and several types of crosstalk are identified within bacteriophages and with other genetic elements [26-28]. Clearly, these genetic exchanges may favor both the viral and bacterial populations, by disseminating beneficial genetic information and stimulating the spread of virions. Examples of a dynamic dialog between hosts and viruses are provided by genomic studies on marine viruses, which show that some viral enzymatic functions essential for bacteriophage were integrated into host genomes during the course of evolution [29]. Additional data from field studies of *Pseudomonas fluorescens* and its bacteriophage also highlight the real-time dynamics of genetic variation in these two antagonistic populations during coevolution [30].

Signaling in communities: from dual to multipartite interactions

The molecular mechanisms underlying direct interactions between bacteriophages and bacteria in test tubes are still not fully understood and may be implemented at various times, in different contexts. For example, studies of the type 6 secretion system recently led to determination of the

role of the Gp5.4 protein of bacteriophage T4 in puncturing the cell membrane [31]. Many uncharacterized viral proteins, the number of which is continuing to increase with the continued isolation of new bacteriophages, have yet to be functionally characterized, to provide a complete picture of the methods used by microbial viruses to infect their hosts. Yet another level of complexity is now being investigated, with studies on cellular and viral partners in microbial communities. Metagenomic studies confirm the abundance of microbial viruses in ecosystems, such as the human gut, but their role remains unclear [20,32]. The abundance of these viruses may account for the low level of efficacy of the various defense systems described above and the rapid evolutionary adaptation of viruses. A few of these defense systems, such as CRISPR systems, are currently being investigated in a relevant ecological context, but many others, such as diffusible molecules, have yet to be investigated [33,34]. Bacteriophages can also adopt a particular lifestyle, called pseudolysogeny, for which an elegant demonstration has just been provided using bacteriophage P22 and its *Salmonella* Typhimurium host [35]. Pseudolysogeny is defined as a bacteriophage carrier stage, where bacteriophage DNA is neither integrated on the host's chromosome nor drives the synthesis of proteins required for lysis, and it has been proposed as one of the major stages used by bacteriophages to resist unfavorable infection conditions [36].

Furthermore, we should not ignore the role of the third partner in microbial ecosystems present in mammals: the eukaryotic cell. Various cell types are in contact with these ecosystems and react to them. This is probably the most challenging environment and remains unexplored. Placing the virus-host relationship into a mammalian context raises questions about the effects of the three partners on each other [37]. For example, many roles are attributed to gut microbiota, from obesity to immunological and neurologic disorders, but the contribution of bacteriophages to these functions remains unknown [38,39]. A partial answer was recently put forward, based on the

observation that some bacteriophages bind specifically to gut mucins [40]. The authors suggest that bacteriophages adhering to mucins may provide immunity to bacterial pathogens, which may be interpreted as a form of cooperation between mucin-producing cells and bacteriophages.

Outlook

Despite numerous molecular studies performed on bacteriophage/bacteria interactions in a few bacteriophage models, we are still discovering new ways by which these two antagonistic populations dialog. Was the bacteriophage mucin binding protein specifically selected during evolution? How many other viral proteins may favorably interact with eukaryotic molecules? Are bacteriophage cocktails used for decades as therapeutic agents in Georgia, Russia and Poland, enriched in bacteriophages displaying such beneficial interaction [41-43]? Indeed, renewed interest in phage therapy and the development of new technics are now driving forces boosting research on bacteriophages [44]. In particular, studies on gut microbial communities will shed light on the behavior of bacteriophages and their hosts in such complex environments [44,45]. In addition, simple (one virus / one host) and complex (multiple viruses / various hosts) model systems will provide information that can be compared with descriptive data from global approaches to obtain a comprehensive view of the various interactions taking place in such systems. Improving our knowledge of these interactions and developing approaches to their manipulation, may provide new ways to manage various human diseases linked to microbial ecosystems [46]. In conclusion, eukaryotic cells and bacteria have long since established a dialog, and bacteria have also their own language with bacteriophages . It is now an ideal time to search for the “Rosetta stone” to decipher the communication flow between these three populations.

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** of outstanding interest

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Figure legend

Figure 1: Bacterial defense systems against bacteriophages.

a) Modifications of bacterial genetic information (mutations of genes encoding bacterial receptors, indicated by a star) can alter bacteriophage adsorption.

b) The modification of viral genetic information by restriction-modification (R/M) or CRISPR systems and self-suicide by abortive infection (Abi) prevent completion of the bacteriophage infectious cycle.

c) The modification of bacterial gene expression by diffusible molecules (purple dots) alter bacteriophage infection (by decreasing receptor synthesis, for example), leading to the spread of resistance phenotypes in the host population.

The bacterial genome is shown as a blue DNA molecule, with a red part corresponding to a prophage element. Arrows highlight the flow of information.

Figure 1

