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

Laurent Debarbieux

► To cite this version:

Laurent Debarbieux. Bacterial sensing of bacteriophages in communities: the search for the Rosetta stone.. Current Opinion in Microbiology, 2014, 20, pp.125-30. 10.1016/j.mib.2014.05.015 . pasteur-01539083

HAL Id: pasteur-01539083

<https://hal-pasteur.archives-ouvertes.fr/pasteur-01539083>

Submitted on 19 Jul 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Title

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

Author

Laurent Debarbieux

Institut Pasteur, Molecular Biology of the Gene in Extremophiles Unit, Department of Microbiology,
F-75015 Paris, France

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.

References

* of special interest

** of outstanding interest

1. Samson JE, Magadan AH, Sabri M, Moineau S: **Revenge of the phages: defeating bacterial defences**. *Nat Rev Microbiol* 2013, **11**:675-687.
 2. Labrie SJ, Samson JE, Moineau S: **Bacteriophage resistance mechanisms**. *Nat Rev Microbiol* 2010, **8**:317-327.
 3. Habann M, Leiman PG, Vandersteegen K, Van den Bossche A, Lavigne R, Shneider MM, Biemann R, Eugster MR, Loessner MJ, Klumpp J: **Listeria phage A511, a model for the contractile tail machineries of SPO1-related bacteriophages**. *Mol Microbiol* 2014, **92**:84-99.
 4. Hu B, Margolin W, Molineux IJ, Liu J: **The bacteriophage t7 virion undergoes extensive structural remodeling during infection**. *Science* 2013, **339**:576-579.
- ** Electron microscopy dissection of bacteriophage T7 binding steps to *Escherichia coli* cells
5. Hoffmann-Thoms S, Weininger U, Eckert B, Jakob RP, Koch JR, Balbach J, Schmid FX: **Initiation of phage infection by partial unfolding and prolyl isomerization**. *J Biol Chem* 2013, **288**:12979-12991.
 6. Molineux IJ, Panja D: **Popping the cork: mechanisms of phage genome ejection**. *Nat Rev Microbiol* 2013, **11**:194-204.
 7. Van Valen D, Wu D, Chen YJ, Tuson H, Wiggins P, Phillips R: **A single-molecule Hershey-Chase experiment**. *Curr Biol* 2012, **22**:1339-1343.
- * Direct visualization that DNA is the support of genetic information, 60 years after the radio-labeled experiment of Hershey and Chase

8. Makarova KS, Haft DH, Barrangou R, Brouns SJ, Charpentier E, Horvath P, Moineau S, Mojica FJ, Wolf YI, Yakunin AF, et al.: **Evolution and classification of the CRISPR-Cas systems.** *Nat Rev Microbiol* 2011, **9**:467-477.
 9. Sampson TR, Saroj SD, Llewellyn AC, Tzeng YL, Weiss DS: **A CRISPR/Cas system mediates bacterial innate immune evasion and virulence.** *Nature* 2013, **497**:254-257.
 10. Dupuis ME, Villion M, Magadan AH, Moineau S: **CRISPR-Cas and restriction-modification systems are compatible and increase phage resistance.** *Nat Commun* 2013, **4**:2087.
 11. Bondy-Denomy J, Pawluk A, Maxwell KL, Davidson AR: **Bacteriophage genes that inactivate the CRISPR/Cas bacterial immune system.** *Nature* 2013, **493**:429-432.
 12. Seed KD, Lazinski DW, Calderwood SB, Camilli A: **A bacteriophage encodes its own CRISPR/Cas adaptive response to evade host innate immunity.** *Nature* 2013, **494**:489-491.
 13. Dy RL, Przybilski R, Semeijn K, Salmond GP, Fineran PC: **A widespread bacteriophage abortive infection system functions through a Type IV toxin-antitoxin mechanism.** *Nucleic Acids Res* 2014, **42**:4590-4605.
 14. Lavigne R, Lecoutere E, Wagemans J, Cenens W, Aertsen A, Schoofs L, Landuyt B, Paeshuyse J, Scheer M, Schobert M, et al.: **A multifaceted study of *Pseudomonas aeruginosa* shutdown by virulent podovirus LUZ19.** *MBio* 2013, **4**:e00061-00013.
 15. Sberro H, Leavitt A, Kiro R, Koh E, Peleg Y, Qimron U, Sorek R: **Discovery of functional toxin/antitoxin systems in bacteria by shotgun cloning.** *Mol Cell* 2013, **50**:136-148.
- ** An elegant investigation to identify and characterize new toxin-antitoxin systems in bacterial genomes**
16. Le S, Yao X, Lu S, Tan Y, Rao X, Li M, Jin X, Wang J, Zhao Y, Wu NC, et al.: **Chromosomal DNA deletion confers phage resistance to *Pseudomonas aeruginosa*.** *Sci Rep* 2014, **4**:4738.

17. Hoyland-Kroghsbo NM, Maerkedahl RB, Svenningsen SL: **A quorum-sensing-induced bacteriophage defense mechanism.** *MBio* 2013, **4**:e00362-00312.
- * The first example of bacteriophage resistance mechanism based on diffusible molecules
18. Zahid MS, Waise TM, Kamruzzaman M, Ghosh AN, Nair GB, Mekalanos JJ, Faruque SM: **The cyclic AMP (cAMP)-cAMP receptor protein signaling system mediates resistance of *Vibrio cholerae* O1 strains to multiple environmental bacteriophages.** *Appl Environ Microbiol* 2010, **76**:4233-4240.
19. Maura D, Galtier M, Le Bouguenec C, Debarbieux L: **Virulent bacteriophages can target O104:H4 enteroaggregative *Escherichia coli* in the mouse intestine.** *Antimicrob Agents Chemother* 2012, **56**:6235-6242.
20. Maura D, Debarbieux L: **On the interactions between virulent bacteriophages and bacteria in the gut.** *Bacteriophage* 2012, **2**:229-233.
21. Weiss M, Denou E, Bruttin A, Serra-Moreno R, Dillmann ML, Brussow H: ***In vivo* replication of T4 and T7 bacteriophages in germ-free mice colonized with *Escherichia coli*.** *Virology* 2009, **393**:16-23.
22. Cortez D, Forterre P, Gribaldo S: **A hidden reservoir of integrative elements is the major source of recently acquired foreign genes and ORFans in archaeal and bacterial genomes.** *Genome Biol* 2009, **10**:R65.
23. Bobay LM, Rocha EP, Touchon M: **The adaptation of temperate bacteriophages to their host genomes.** *Mol Biol Evol* 2013, **30**:737-751.
24. Chen J, Novick RP: **Phage-mediated intergeneric transfer of toxin genes.** *Science* 2009, **323**:139-141.
25. Stern A, Sorek R: **The phage-host arms race: shaping the evolution of microbes.** *Bioessays* 2011, **33**:43-51.

26. Matos RC, Lapaque N, Rigottier-Gois L, Debarbieux L, Meylheuc T, Gonzalez-Zorn B, Repoila F, Lopes Mde F, Serron P: ***Enterococcus faecalis* prophage dynamics and contributions to pathogenic traits.** *PLoS Genet* 2013, **9**:e1003539.
- * A complete genetic assessment of interconnected roles of prophages in bacteria
27. Swanson MM, Reavy B, Makarova KS, Cock PJ, Hopkins DW, Torrance L, Koonin EV, Taliany M: **Novel bacteriophages containing a genome of another bacteriophage within their genomes.** *PLoS One* 2012, **7**:e40683.
28. De Paepe M, Hutinet G, Son O, Amarir-Bouhram J, Schbath S, Petit MA: **Temperate phages acquire DNA from defective prophages by relaxed homologous recombination: the role of Rad52-like recombinases.** *PLoS Genet* 2014, **10**:e1004181.
29. Lindell D, Jaffe JD, Coleman ML, Futschik ME, Axmann IM, Rector T, Kettler G, Sullivan MB, Steen R, Hess WR, et al.: **Genome-wide expression dynamics of a marine virus and host reveal features of co-evolution.** *Nature* 2007, **449**:83-86.
30. Gomez P, Buckling A: **Bacteria-phage antagonistic coevolution in soil.** *Science* 2011, **332**:106-109.
31. Shneider MM, Buth SA, Ho BT, Basler M, Mekalanos JJ, Leiman PG: **PAAR-repeat proteins sharpen and diversify the type VI secretion system spike.** *Nature* 2013, **500**:350-353.
- * Functional identification of T4 protein from crystallographic studies on bacterial protein secretion system.
32. Reyes A, Wu M, McNulty NP, Rohwer FL, Gordon JI: **Gnotobiotic mouse model of phage-bacterial host dynamics in the human gut.** *Proc Natl Acad Sci U S A* 2013, **110**:20236-20241.
- ** To date the most complex controlled microbiota model to characterize bacteriophages naturally present in human gut.

33. Iranzo J, Lobkovsky AE, Wolf YI, Koonin EV: **Evolutionary dynamics of the prokaryotic adaptive immunity system CRISPR-Cas in an explicit ecological context.** *J Bacteriol* 2013, **195**:3834-3844.

34. Levin BR, Moineau S, Bushman M, Barrangou R: **The population and evolutionary dynamics of phage and bacteria with CRISPR-mediated immunity.** *PLoS Genet* 2013, **9**:e1003312.

35. Cenens W, Mebrhatu MT, Makumi A, Ceyssens PJ, Lavigne R, Van Houdt R, Taddei F, Aertsen A: **Expression of a novel P22 ORFan gene reveals the phage carrier state in *Salmonella typhimurium*.** *PLoS Genet* 2013, **9**:e1003269.

* The first molecular evidence in favor of pseudolysogeny

36. Los M, Wegrzyn G: **Pseudolysogeny.** *Adv Virus Res* 2012, **82**:339-349.

37. Brussow H: **Bacteriophage-host interaction: from splendid isolation into a messy reality.** *Curr Opin Microbiol* 2013, **16**:500-506.

38. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, et al.: **Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders.** *Cell* 2013, **155**:1451-1463.

39. Rook GA: **Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health.** *Proc Natl Acad Sci U S A* 2013, **110**:18360-18367.

40. Barr JJ, Auro R, Furlan M, Whiteson KL, Erb ML, Pogliano J, Stotland A, Wolkowicz R, Cutting AS, Doran KS, et al.: **Bacteriophage adhering to mucus provide a non-host-derived immunity.** *Proc Natl Acad Sci U S A* 2013, **110**:10771-10776.

* From ecological observations to the molecular demonstration that viral proteins adhere to mucus.

41. Miedzybrodzki R, Borysowski J, Weber-Dabrowska B, Fortuna W, Letkiewicz S, Szufnarowski K, Pawelczyk Z, Rogoz P, Klak M, Wojtasik E, et al.: **Clinical aspects of phage therapy.** *Adv Virus Res* 2012, **83**:73-121.

42. Chanishvili N: **Phage therapy--history from Twort and d'Herelle through Soviet experience to current approaches.** *Adv Virus Res* 2012, **83**:3-40.
43. Abedon ST, Kuhl SJ, Blasdel BG, Kutter EM: **Phage treatment of human infections.** *Bacteriophage* 2011, **1**:66-85.
44. Reyes A, Haynes M, Hanson N, Angly FE, Heath AC, Rohwer F, Gordon JI: **Viruses in the faecal microbiota of monozygotic twins and their mothers.** *Nature* 2010, **466**:334-338.
45. Breitbart M, Haynes M, Kelley S, Angly F, Edwards RA, Felts B, Mahaffy JM, Mueller J, Nulton J, Rayhawk S, et al.: **Viral diversity and dynamics in an infant gut.** *Res Microbiol* 2008, **159**:367-373.
46. De Paepe M, Leclerc M, Tinsley CR, Petit MA: **Bacteriophages: an underestimated role in human and animal health?** *Front Cell Infect Microbiol* 2014, **4**:39.

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