Impact of lysogeny on bacteria with a focus on lactic acid bacteria

Xingmin Sun[1], Douwe van Sinderen[2], Sylvain Moineau [3]

[1]Tufts University, Department of Biomedical Sciences, Boston, U.S.A.
[2]University College Cork, Department of Microbiology, Western Road, Cork, Ireland
[3]Département de biochimie et de microbiologie, Faculté des sciences et de génie,Université Laval, Québec, Canada

ABSTRACT

Lysogeny is a widespread occurrence in bacteria and represents a highly co-evolved adaptive state between bacteriophages and their hosts. Different lysogenic conversion phenomena have been described for various bacterial species. This review outlines recent progress on the molecular analysis of bacteriophage lysogenic conversion, immunity systems, temperate phage-encoded phage resistance, as well as transduction. Since phage-host interactions in lactic acid bacteria (LAB) are commercially relevant and have received a lot of scientific attention in recent years, a special focus will be given to the impact of lysogeny in LAB.

1. INTRODUCTION TO LYSOGENY

Following infection of their host temperate bacteriophages have to make an important decision with respect to the particular pathway they will follow. One option is to grow lytically during which the host cell is completely reprogrammed to facilitate multiplication of the infecting phage. This ultimately results in cell lysis and release of progeny phages. Exceptions to this are the filamentous phages, which are extruded into the surrounding media without causing cell lysis. In contrast, and representing the alternative choice to the lytic option, some phages enter the so-called lysogenic pathway to essentially become dormant. Lysogeny, which was discovered independently by Bail and Border [1925], occurs when (1) a phage genome integrates either at a specific site (e.g., λ) [Ptashne, 1992] or at a random site (e.g., Mu) [Howe, 1987] into the host chromosome to form a prophage, which replicates as part of this chromosome, or when (2) the phage genome is maintained in the form of a plasmid as one of the host's replicons (e.g., P1) [Yarmolinski and Sternberg, 1988]. A cell, which carries a temperate bacteriophage, is referred to as a lysogen, while a cell carrying multiple prophages is called polylysogenic [Birge, 2000; Chopin *et al.,* 2001; Casjens, 2003]. Thus, a lysogenic bacterium or lysogen habors and transmits the genetic property to produce bacteriophages [Lwoff, 1953].

The lysogenic state is the result of a highly co-evolved adaptive process between bacteriophages and their hosts in nature. Some of the evolutionary factors that favor lysogeny over the lytic pathway can be summarized as follows: (i) self-extinction of virulent phage-host systems; (ii) advantages to the host, such as superinfection immunity, phage exclusion, and antibiotic resistance; (iii) general increase in cellular fitness; and (iv) phage propagation at low host cell densities [Paul & Kellogg, 2000]. It is therefore not surprising that lysogeny is widespread in nature. Classically, two criteria are required for the identification of lysogeny: (i) the lysogen can be cured of its prophage; (ii) the cured derivatives can be relysogenized by the same phage [Lwoff, 1953]. However, lysogeny should be distinguished from pseudolysogeny, which is a phenomenon where a bacterial strain has a chronic phage infection and where the viral

DNA is not integrated into any of the host's replicons. Pseudolysogeny is also called "carrier state" and usually occurs when either the phage-host system is a mixture of sensitive and resistant cells, or a mixture of prophage-containing cells and virulent phages [Paul & Kellogg, 2000].

Lysogeny occurs extensively in a wide variety of genera and species, such as *Bacillus cereus* [IvÅnovics *et al*., 1974], *Bacillus subtilis* [Osburne and Sonenshein, 1976], *Bordetella* [Holzmayer *et al*., 1988], *Bukholderia cepacia* complex [Langley *et al*., 2003], *Klebsiella pneumoniae* [Satta *et al*., 1978], *Lactococcus* [Jarvis, 1989], *Lactobacillus* [Stetter, 1977], *Leuconostoc oenos* [Arendt *et al*., 1991], *Pasteurella* [Lawton and Molnar, 1972], *Propionibacterium freudenreichii* [Gautier *et al*., 1999]. *Pseudomonas aeruginisa* [Vaca-Pacheco *et al*., 1999], *Mycoplasma arthritidis* [Voelker and Dybvig, 1998], *Rhizobium trifolii* [Barnet and Vincent, 1970], *Salmonella typhimurium* [Mirold *et al*., 1999], *Selenomonas ruminantium* [Cheong and Brooker, 1998], *Staphylococcus aureus* [Żabicka *et al*., 1993], *Streptococcus thermophilus* [Josephsen and Neve, 1998], group A Streptococci [Johnson *et al*., 1980], *Shigella flexneri* [Kętyi, 1974], Streptomycetes [Greene and Goldberg,, 1985], *Vibrio cholerae* [Faruque *et al*., 1998; Waldor and Mekalanos, 1996], *Vibrio mimicus* [Faruque *et al*., 1999], *Xanthomonas campestris* pv. *citri* [Cheng *et al*., 1999], and *Yersinia enterocolitica* [Tsubokura *et al*., 1982], Surprisingly, only a small number of reviews are available on the prevalence of lysogeny [Lwoff, 1953; Bertani, 1958; Davidson *et al*., 1990; Bertani, 2004].

In addition to the traditional identification of lysogeny prohages have also been identified through bacterial genome analysis. Prophages can be present in varying levels of completeness, such as inducible prophages, defective prophages that appear to have suffered from deletions, insertions, and rearrangements, and prophage remnants that have lost most of their genome. Recent microbial and prophage genomics revealed that prophages can constitute as much as 10-20% of a bacterium's genome, while the majority of sequenced bacterial genomes do appear to possess bacteriophage-derived DNA (Casjens, 2003). In fact, prophage-containing genomes are more the rule than the exception in bacteria. It is also common for bacterial chromosomes to contain multiple prophages, which may even constitute a sizable part of the total bacterial DNA. For instance, the food pathogen *E. coli* O157:H7 strain Sakai contains as many as 18 predicted prophage-derived elements, which amount to 16% of its total genome content. Many prophages appear to be defective, non-inducible and in a state of mutational decay [Casjens, 2003; Canchaya *et al*., 2003 & 2004]. However, many genes in defective prophages remain functional and confer properties to the host or represent DNA reservoirs for virulent phage recombination [Labrie &

Moineau, 2007]. This review will focus on the impact of lysogeny on bacteria, with an emphasis on lactic acid bacteria (LAB).

2. LYSOGENIC CONVERSION

2.1. Different lysogenic conversion phenomena

In a lysogenic strain, certain prophage-derived genes may contribute to the phenotype of the cell, being unrelated to the phage immunity system. Such a phenomenon, which is brought about through lysogenization by a normal temperate phage, is called lysogenic conversion or phage conversion [Madigan *et al.,* 2000].

Different lysogenic conversion phenomena have been described for various bacterial species. These phenomena include production of toxins or other virulence factors [Table 1: Miao & Miller, 1999], and modification of phage receptors at the cell surface of lysogens (Table 2). Toxins or other virulence factors encoded by temperate bacteriophages may broaden the host range of lysogens and thus increase their fitness in a particular environmental niche by promoting evasion of host immunity systems [Brüssow *et al*., 2004]. For example, certain *Streptococcus pyogenes* strains benefit from host-mediated induction of a toxin-encoding temperate phage, which results in its conversion from a Tox^- microorganism into a Tox^+ variant [Broudy & Fischetti, 2003]. In some Gram-negative bacteria, the O antigen, a component of the bacterial lipopolysaccharide (LPS) present on the outer membrane of the cell, can be modified by prophages. Such serotype conversion by temperate phages is a very important virulence-enhancing mechanism for many pathogens. Such conversions may also provide a safeguard, additional to that of cytoplasmic immunity, by preventing the adsorption of other phages to the host cells if the altered cell envelope component is required for the infection process.

Other documented phage conversions include production of antibiotics [Martinez-Molina & Olivares, 1979; Lawton & Molnar, 1972], production of lipoproteins interacting with phage receptors [Vostrov *et al.,* 1996; Rybcin, 1984], production of phospholipase A [Ivånovics *et al*., 1974], and the appearance of specific outer membrane proteins [Verhoef *et al.,* 1987; Schnaitman *et al.,* 1975; Pacheco *et al.,* 1997]. Moreover, Bor and Lom are representatives of yet another example of lysogenic conversion, by providing a phage-encoded protection from host immune defences [Barondess & Beckwith, 1995; Pacheco *et al*., 1997]. Interestingly, the temperate bacteriophage Gifsy-1-encoded protein GogB was reported to act as a modular lysogenic factor

displaying autonomous expression and type III secretion with respect to other Gifsy phage-encoded factors [Coombes *et al*., 2005].

As opposed to providing benefits to the host, lysogenic conversion can also lead to loss of properties in lysogens [Canchaya *et al*., 2002; Maurelli *et al*., 1998; Lee and Iandolo, 1986; Mason and Allen, 1975]. Well characterized cases are the lipase- and the β-toxin-negative phenotype due to the integration of prophage L54a and phi13, respectively into the *S. aureus* genome [Coleman *et al*., 1991]. In this context it should be noted that tRNA genes represent prominebt genetic targets for prophage integration. However, many phage attachment sites carry the necessary DNA sequences to reconstitute a functional tRNA after prophage integration into the tRNA gene, which would suggest that loss of tRNA genes results in reduced fitness of the lysogen. Nevertheless, not all prophage integration events reconstitute a functional tRNA gene [Ventura *et al*., 2003].

Table 1. Examples of toxins or other virulence factors encoded by temperate bacteriophage

Host	Toxin or other virulence factors	Phage designation	Reference
Clostridium botulinum	Botulinum toxin C1 and D		Inoue and Iida, 1971
Corynebacterium diphtheriae	Diphtheria toxin	ß-phage	Groman, 1984
E. coli	Shiga-like toxin-1 and -II	H19A	Strockbine *et al*., 1986; Sjogren *et al*.,1994
E. coli	Bor	λ	Barondess & Beckwith, 1995
E. coli	Lom	λ	Pacheo *et al*., 1997
Pseudomonas aeruginosa	Cytotoxin	ΦCTX	Hayashi *et al*., 1993
Streptococcus pyogenes	Pyrogenic exotoxin A and C	T12, 3GL16	Johnson *et al*., 1986; Yu & Ferretti, 1991
S. pyogenes	Erythrogenic exotoxin C	CS112	Goshorn & Schlievert, 1989
Staphylococcus aureus	Enterotoxin A and staphylokinase	Φ42, ΦA1, ΦA3, Φ13	Coleman *et al*., 1989
S. aureus	Leucocidin		Van der Vijver *et al*., 1972
S. aureus	Exfoliative toxin A	ϕ-ZM-1	Yoshizawa *et al*. 2000
Salmonella typhimurium	SopE	SopEΦ	Mirold *et al*., 1999
S. typhimurium	SodC	Gifsy-2	Figueroa-Bossi & Bossi, 1999
Vibrio cholerae, Vibrio mimicus	Cholera toxin (CT)	CTXΦ	Waldor & Mekalanos, 1996; Faruque *et al*., 1999
Vibrio cholerae	Toxin-coregulated pilus and CTXΦ receptor	VPIΦ	Karaolis *et al*., 1999

Table 2. Modifications of phage receptors by lysogenic conversion

Host	Modifications of phage receptors	Phage designation	Reference
Klebsiella pneumoniae	Receptor for coliphage T7	AP3	Pruzzo *et al*., 1980
Pseudomonas aeruginosa	O-antigen	FIZ15	Vaca-Pachcco *et al*., 1999
P. aeruginosa	Acetylated fucosamine residue and modified binding between trisaccharide repeating units of O-antigen	D3	Kuzio & Kropinski, 1983
Rhizobium trifolii	O-antigen	Φ7, Φ7cr, Φ8	Barnet & Vincent, 1970
Salmonella anatum	O-antigen with ß-galactosyl linkage	ϵ^{15}	Losick, 1969
S. typhimurium	O-acetylation of the rhamnosyl residue of O-antigen	ΦA3, Φa4	Wollin *et al*., 1987
Shigella flexneri	Glucosylated O-antigen	ΦI, ΦPE5, Φf7,8	Kétyi, 1974

2.2. Lysogeny and lysogenic conversion in lactic acid bacteria (LAB)

Most investigations of lysogeny in LAB involved screening strains for lysis due to phage induction following treatment with UV or mitomycin C, even though spontaneous release of temperate phages is also common [Baldwin & McKay, 1987; Christiansen *et al.,* 1994; Husson-Kao *et al.,* 2000].

2.2.1. The extent of lysogeny in LAB

The occurrence of lysogeny among *Lactococcus lactis* was first demonstrated by Reiter in 1949 [Reiter, 1949]. It was later shown that lysogeny is in fact widespread in this species. More than 300 strains of *L. lactic* subsp. *lactis* and *cremoris* have been reported to be lysogenic [Davidson *et al.,* 1990; Jarvis, 1989] and some are even polylysogenic [Jarvis *et al.,* 1992]. Chopin *et al*. [2001] described the genetic organization of six prophages present in the genome of *L. lactis* IL1403. The three larger prophages (36-42 kb) belong to the so-called P335 group of temperate phages, whereas the three smaller ones (13-15 kb) were proposed to be satellites, relying on helper phage(s) for multiplication because they lack genes required for phage

morphogenesis and lysis of the host cell. In a similar study by Ventura *et al*. [2007] it was recently shown that *L. lactis* subsp. *cremoris* strains MG1363 and SK112 harbor six and five prophage-like elements, respectively, all of which could be assigned to the P335 group of temperate phages. Among these 11 prophages four possible satellite phages were proposed, although they could also represent remnant prophages.

Lysogeny in the genus *Lactobacillus* was first described by Coetzee & de Klerk [1962]. Later, several authors reported that the frequency of lysogeny ranged from 20% to 81% in the *Lactobacillus* strains tested [deKlerk & Hugo, 1970; Yokokura *et al.* 1974; Tohyama *et al.,* 1972; Stetter, 1977]. This difference in frequence is likely explained by the diversity in this genus, which contains at least 106 validly recognized species [Felis and Dellaglio, 2007]. Nontheless, lysogeny appears to be common among lactobacilli, and this notion was further supported by a recent genome-based prophage analysis of three different *Lactobacillus* species, where it was also shown that a *Lactobacillus salivarius* strain contains multiple prophages [Ventura *et al*., 2006].

In contrast to lactococci and lactobacilli, lysogeny appears to be rare among the LAB species *S. thermophilus* [Le Marrec *et al*., 1997; Josephsen & Neve, 1998]. However, three temperate *S. thermophilus* phages have been investigated at the molecular level, ΦO1205 [Stanley *et al*., 1997], TP-J34 [Neve *et al.,* 1998] and ΦSfi21 [Desiere *et al.,* 1998], whose genome sequence is elther fully (ΦO1205 & ΦSfi21) or partially (TP-J34) available.

Arendt *et al.* [1991] reported a lysogeny frequency of 63% among 30 *Leuconostoc oenos* (now *Oenococcus oeni*) strains investigated. More recently, Poblet-Icart [1998] described that 45% of 167 *O. oeni* strains were inducible with mitomycin C. These data indicates that lysogeny is also widespread in this species. To date, no published data on lysogeny is available for other LAB spicies.

2.2.2. Lysogenic conversion in LAB

Lysogenic conversion by temperate phage has only been reported for two lysogenic LAB strains, i.e., *Lactobacillus delbrueckii* subsp. *bulgaricus* LT4 [Cluzel *et al*., 1987] and *S. thermophilus* J34 [Neve *et al*., 1998 & 2003; Sun *et al*., 2002]. The first strain harbours a prophage designated mv4. This phage confers three distinctive phenotypes on lysogenized cells: (i) a superinfection immunity phenomenon against phage mv4 and other phages related to mv4, (ii) a modification of the phage sensitivity against virulent phages, (iii) a modification of the colony morphology on agar plates. *S. thermophilus* J34 is lysogenic for a temperate phage

designated TP-J34, which mediates a conversion phenotype as streptococcal lysogenized cells grow homogeneously, while prophage-cured derivatives have a sedimenting/clumping phenotype [Neve *et al*., 2003; Sun *et al*., 2002 & 2006].

3. IMMUNITY AND OTHER PHAGE-ENCODED PHAGE EXCLUSION SYSTEMS

3.1. Superinfection immunity systems of bacteriophages

In the lysogenic state, prophages synthesize repressors and often additional regulators, which block the lytic pathway while also making the lysogen immune to superinfection by phage that employ homologous regulators. This phenomenon is referred to as superinfection immunity [Roberts *et al*., 2007]. This phage immunity system operates either through the binding of repressor proteins or through RNA-RNA interactions, or both. Repressor proteins prevent transcription initiation at key promoters, which are required for lytic gene expression. RNA-RNA interactions modulate translation of certain mRNA through base-pairing with their corresponding ribosomal binding sites, thereby preventing efficient translation initiation. RNA-RNA interactions may also end the transcription prematurely through the formation of terminator-like structures. So far, several types of phage-encoded superinfection immunity systems have been reported and some of them will be discussed below.

Some phages possess only one immunity region. In this type, immunity is elicited by a repressor protein, which can bind to an operator, thereby preventing the transcriptional initiation at a promoter controlling the expression of lytic functions. This repressor also neutralizes the lytic pathway of homologous phages infecting a lysogen (this homology specifically pertains to the DNA-binding region of repressor; homologous phages that encode non-homologous repressors will not be subject to immunity through this mechanism). This simple model seems to predominantly operate in phages lambda [Ptashne, 1992], Mu, P2 [Bertani & Six, 1988] and L5 of *Mycobacterium* spp. [Brown *et al*., 1997].

A second more complex immunity is based on two additional components. First an antirepressor blocks the expression of the repressor described above, and an additional repressor called anti-immunity repressor inhibits expression of the antirepressor. Such a system is found in phages of P1, P22 [Shearwin *et al*., 1998], 186 [Lamont *et al.,* 1989], and 105 [Dhaese *et al.,* 1985]. For instance, phage P1 contains a bipartite immunity system, consisting of two repressors specified by different immunity determinants. The *c1* repressor gene, located within the *imm*C region, maintains the lysogenic state by directly repressing the transcription of key lytic genes,

while the *c4* locus, positioned within the *imm*I region, prevents the expression of the antirepressor, which is encoded by the *ant* gene located to the right of *c4*. The *c4* locus specifies a small RNA that prevents *ant* expression by eliciting premature transcription termination of *ant*, thereby sustaining lysogeny maintenance [Biere *et al*., 1992]. The *c4* mRNA may also convey immunity by preventing expression of a homologous antirepressor gene from a superinfecting phage [Sternberg & Hoess, 1983]. The immunity system of *Salmonella typhimurium* phage P22 also consists of two immunity regions: the *imm*C region, which contains the *c2* repressor gene, and the *imm*I region, which harbors the *mnt* repressor gene. The c2-repressor plays a primary role in the P22 immunity system while the mnt-repressor appears to play an auxiliary role in preventing the expression of the *ant* gene, whose product, the antirepressor, interferes with the synthesis or activity of the c2-repressor [Levin, 1972]. Phage 186 codes for a similar repressor-antirepressor system. However, the anti-immunity repressor of 186 is not phage-encoded but is the host *lexA* gene product [Lamont *et al*., 1989].

The genetic switch of the *Rhizobium meloloti* temperate phage *16-3* has been mapped to three distinct regions: the *immC*, *immX*, and *averT* regions. The *immC* region codes for a typical repressor flanked by operators. The *immX* region encompasses two parts: $X_{U/L}$ and X_V. The $X_{U/L}$ part contains two overlapping genes, X_U and X_L, which code for proteins pXU and pXL, respectively. Activation of either X_U or X_L gene inactivates the repressor function specified by the *immX* region. The X_V part contains a target for $X_{U/L}$ repression action. So far little is known about the function of the third region *averT* [Csiszovszki *et al*., 2003].

Another superinfection immunity type is represented by *E. coli* phage P4 [Lindqvist *et al.,* 1993]. This immunity system is distinguished from the above model in that (a) the P4 immunity factor is not a protein but a short, stable RNA (cI RNA) containing *seqB*; (b) the expression of the prophage replication operon is prevented by premature transcription termination rather than by repression of transcription initiation [Forti *et al.,* 1999]; (c) transcription termination is controlled via an RNA-RNA interaction between the CI RNA and two complementary target sequences *seqA* and *seqC,* located upstream and downstream of *cI*; and (d) the cI RNA is produced by processing of the same transcript it controls [Pizza *et al*., 1996]. Phage P4, which was originally isolated from *E. coli* K-235, does not contain the genetic material to code for its capsid and tail proteins: these functions need to be provided by a so-called helper phage, such as P2. When phage P4 infects a sensitive *E. coli* host harboring the helper phage P2, it may enter either the lysogenic or the lytic pathway. However, in the absence of the helper phage, phage P4 may exist

either as a silent prophage integrated into the chromosome of the host cells, or as a multicopy plasmid. The retronphage phi R73 also uses an immunity mechanism similar to that of P4 [Sabbattini *et al.,* 1996]. The anti-immunity system of *E.coli* phage-plasmid N15 is also structurally and functionally similar to the immunity system of phage P4 [Ravin *et al.,* 1999] and anti-immunity system of bacteriophage P1 [Scott *et al*., 1978]. The bacteriophage sfV of *Shigella flexneri* [Allison *et al.*, 2002] contains a newly identified superinfection immunity region. This region not only produces a "typical" cI RNA but also encompasses *orf77*, which is located immediately downstream of the transcription termination region and inhibits the establishment of cI RNA-mediated immunity [Roberts *et al*., 2007].

Bacteriophage HK022 protects lysogens from superinfection through the production of a sequence-specific RNA-binding protein that prematurely terminates nascent transcripts of infecting phage [Weisberg *et al*., 1999]. This represents an RNA-based mechanism that terminates early transcription of bacteriophage genes. Besides the four superinfection immunity types summarized above, Cheng *et al*. [1999] proposed yet another superinfection immunity model found in bacteriophage cf, which is a temperate filamentous single-stranded DNA phage isolated from *Xanthomonas campestris* pv. *citri* [Dai *et al*., 1980]. The superinfection immunity of phage cf is shown to be mediated by a complex regulatory system that involves two counter-transcribed regulatory RNAs (cM1 and cM2) and a predicted repressor protein (ORF165). In this model, two hypothetical mechanisms were proposed to explain the control of the lytic-lysogenic switch. First, cM1 RNA could act as an enhancer of transcription of the major cf genes while the predicted repressor protein could direct its lysogenic effect through interactions with either cf DNA or cM1 and cM2 RNAs.

3.2. Other phage-encoded phage resistance mechanisms derived from bacteriophages

In the lysogenic state, it is not uncommon for prophage to specify additional functions which, by mechanisms unrelated to superinfection immunity, also prevent development of superinfecting phages. These prophage-encoded phage resistance systems do not play a key role in maintaining the lysogenic state and generally are not specific for homologous phage. For the purpose of this review they are summarized here as superinfection exclusion, restriction-modification, lysogenic conversion, and abortive infection even though conflicting definitions on their mode of action have appeared in the literature. Their conceptual and mechanistic differences are outlined in the following sections.

Lytic phages, which encode proteins to provide host cells with phage resistance (lytic conversion), have also been described [Decker *et al*., 1994; Lu & Henning, 1989]. Table 3 lists gram-negative bacteriophage-encoded proteins specifying phage resistance.

3.2.1. Superinfection exclusion

Superinfection exclusion is defined here as a resistance system that blocks the DNA injection process of a host cell-adsorbed (superinfecting) phage. To date, two temperate phage-encoded proteins (Table 3), represented by Sim and SieA, have been reported to confer phage resistance to gram-negative lysogens by this mechanism. Furthermore, the Glo protein encoded by the temperate *Vibrio cholerae* bacteriophage K139 was described to participate in phage exclusion at an early step infection [Nesper *et al.,* 1999]. In addition, two proteins of the virulent phage T4, named Imm and Sp, were also demonstrated to exclude other phages by direct or indirect inhibition of DNA injection. The Imm protein is produced within 1 to 2 min after infection of *E. coli* cells, blocks DNA transfer across the plasma membrane and partially inhibits the release of DNA from a superinfecting virion.

A *cor* orthologue from lambdoid phage mEp167 (cor_{mEP167}) accounts for the exclusion of FhuA-dependent lambdoid phages. This exclusion mechanism also appears to aperating at the level of phage DNA entry, as the phage adsorption, the production of phage particles after phage DNA transfection or the spontaneous induction of lysogens were shown to be unaffected in Cor^+ cells [Uc-Mass *et al*., 2004].

3.2.2. Restriction-modification (R-M system)

Restriction and Modification systems degrade superinfecting phage DNA. In a recent article Black and co-authors described the newly discovered GmrSD system [Bair *et al*., 2007]. In this system the *E. coli* isolate CT596 excludes infection by the Myoviridae T4$ip1^-$ phage that lacks the encapsidated IPI* protein normally injected into the host with phage DNA. Two proteins (GmrS and GmrsD) that are encoded by a cryptic prophage DNA form the enzyme GmrSD and degrade the superinfecting T4 phage lacking the encapsidated IPI* protein. More interestingly, this exclusion can be specifically overcome by the T4 IPI* protein.

3.2.3. Lysogenic conversion

As indicated above, lysogenic conversion can prevent adsorption of superinfecting phage to the host cell by modifying phage receptors [Kuzio & Kropinski, 1983; Wollin *et al.,* 1987] or by interacting with phage receptors [Vostrov *et al.,* 1996; Rybcin, 1984]. The mechanism of glycosyltransferase-mediated lysogenic/antigenic conversion has been well studied in *Shigella Flexneri* [Adams, 2001; Allison and Verma, 2000]. The bacteriophage-encoded factors involved in O-antigen modification in *S. flexneri* are O-acetyltransferses or glycosyltransferases. During lysogeny, the phage Sf6 expresses an O-acetyltransferase responsible for the conversion of unmodified serotype to serotype 3b. Other bacteriophages like Sf1, SfII, SfV, SfX, and the assumed cryptic SfIV express glycosyltransferases responsible for the conversion of the unmodified serotype Y to serotype 1a, 2a, 5a, X, and 4a, respectively [Markine-Goriaynoff *et al*., 2004]. The biological functions of serotype-converting glycosyltransferases encoded by proophages are diverse. Because they modify the O-antigen polysaccharide chains during lysogeny, and because these structures constitute the phage receptor; this mechanism provides to the infected bacteria an immunity against superinfection by other related phages [Vander Byl & Kropinski, 2000; Allison *et al*., 2002].

3.2.4. Lytic conversion

Virulent phages have also been shown to encode proteins that provide phage resistance to host cells [Decker *et al.,* 1994; Lu & Henning, 1989]. A lipoprotein (LIp) which is encoded by lytic phage T5, blocks the phage receptor FhuA, and, thus, prevents phage T5 adsorption [Decker *et al.,* 1994]. The mechanism is thought to limit inactivation of progeny phages by cell wall fragments from the lysed cells.

Table 3. Gram-negative bacteriophage-encoded genes participating in phage resistance

Bacteriophage	Gene	Molecular weight	Phage resistanse mechanism	Cellular location	Source
E. coli phage P1	*sim* (*orf1*)	9.3	Superinfection exclusion	Periplasm	Kliem & Dreiseikelmann, 1989
E. coli phage P1	*sim* (*orf2*)	29.5	Superinfection exclusion	Periplasm	Kliem & Dreiseikelmann, 1989; Maillou & Dreiseikelmann, 1990
E. coli phage P2	*old*	65.4	Abortive infection (degradation of foreign DNA)	Unknown	Lindahl *et al.,* 1970; Myung & Calendar, 1994
E. coli phage λ	*rexB*	16.0	Abortive infection	Unknown	Weigel *et al,.*1973
E. coli phage e14	*lit*	34	Abortive infection (inhibition of translation)	Inner membrane	Bingham *et al.,* 2000; Kao & Snyder, 1988
E. coli phage T4 (virulent)	*imm*	9.3	Superinfection exclusion	Inner membrane	Lu & Henning, 1989
E. coli phage T4 (virulent)	*sp*	11.0	Superinfection exclusion	Inner membrane	Lu & Henning, 1994; Obringer *et al.,* 1988
E. coli phage Φ80	*cor*	10.4	Lysogenic conversion (adsorption inhibiting)	Unknown	Vostrov *et al*., 1996; Matsumoto *et al*., 1985
E. coli phage mEP	cor_{mEP167}	Unkonown	Superinfection exclusion	Unknown	Uc-Mass *et al*., 2004
Salmonella typhimurium phage P22	*sieA*	18.8	Superinfection exclusion	Inner membrane	Hofer *et al.,* 1995
Salmonella typhimurium phage P22	*sie B*	22.4	Abortive infection	Membrane	Ranade & Poteete, 1993
Vibrio cholerae phage K139	*glo*	13.6	Superinfection exclusion or lysogenic conversion	Periplasm	Nesper *et al.,* 1999

3.2.5. Abortive infection

Abortive infection results in death of infected host cells and the parallel disruption of phage development via different mechanisms [Snyder, 1995; Chopin *et al*., 2005].

In addition to *sieA*, the temperate phage P22 of *Salmonella typhimurium* specifies another exclusion system, *sieB*, which aborts lytic development of some superinfecting phages [Susskind

et al., 1974; Ranade & Poteete, 1993]. The gene *sieB* encodes a 22.4 kDa protein, which is expected to be located in the membrane according to the deduced amino acid sequence. This gene is also conserved in phage lambda. In addition, *rex* of phage lambda and *old* of P2 have physiological similarities to the *sieB*-encoded system, and in all cases interference is accompanied by an abrupt cessation of DNA, protein, and RNA synthesis, causing death of the infected cell [Groman & Rabin, 1980]. However, the Rex defense system acts through a two-component mechanism. The RexA protein activates the formation of ion channels and the depolarization of the cytoplasmic membrane by RexB, a protein with four transmembrane domains. The Rex system has a large spectrum of activity as it aborts lytic growth of phages T1, T4, T5, and T7 [Duckworth *et al.,* 1981; Parma *et al*., 1992; Schinedling *et al.,* 1987].

The Lit (Late Inhibitor of T4) protein is a protease encoded by the defective prophage e14 in *E. coli* K-12. Following T4 infection of a Lit-containing cell, the translation elongation factor (EF-TU) is specifically cleaved by an activated Lit, resulting in the inhibition of translation [Bergsland *et al.,* 1900; Bingham *et al.,* 2000; Georgiou *et al*., 1998; Yu and Snyder, 1994].

An interesting abortive infection mechanism was identified from the investigation of a phage T4-encoded inhibitor of DNA restriction [for a review, see Kaufmann, 2000]. Indeed, some *E. coli* strains carry the *prr* locus which prevents the infection of phage T4 [Chapman *et al*., 1988; Levitz et al., 1900; Meidler *et al.,* 1999]. The prr element carries a gene (*prrC*) that encodes a latent anticodon nuclease, specific for the host lysine tRNA. After T4 infection, the ribonuclease enzyme is activated (by the T4 product stp) and cleaves the $tRNA^{Lys}$ in the wobble position of the anticodon loop and thereby blocks the translation and the phage development.

3.3. Immunity systems and other phage-encoded phage resistance mechanisms of LAB phages

3.3.1. Immunity systems

In contrast to bacteriophages of gram-negative bacteria, very little is known about the immunity systems of LAB bacteriophages. This is partially attributed to the fact that the genetics and molecular biology of LAB bacteriophages lags behind that of models of Gram-negative bacteriophages. Nevertheless, several phage genes conferring immunity to LAB against its infecting phages have been characterized. Among these, the repressor-encoding gene (*cI*) of *Lactobacillus casei* temperate phage A2 [Garcia *et al.,* 1999; Ladero *et al.,* 1998] is well investigated. The 224-residue repressor of the phage A2 possesses DNA binding and RecA-

mediated autocleavage motifs, is expressed during lysogeny, and confers superinfection immunity to the host. The gene product CI (25.3 kDa) has been purified, and it binds specially to a 153-bp DNA fragment that contains two divergent promoters mediating transcription from *cI* and a putative *cro*, respectively. Furthermore, this protein can selectively interact with three operator sites. These data indicate that the CI protein of phage A2 regulates the lytic and lysogenic pathway in a way similar to that of the CI protein of *E. coli* phage lambda. Another well-characterized repressor gene (*rad*) is from *Lactobacillus gasseri* temperate phage Φadh [Engel *et al*., 1998]. The gene product Rad (12.1 kDa) functions as a repressor of *rad* and *tec* transcription, and confers immunity against superinfecting phage Φadh.

In *L. lactis*, the repressor-encoding gene *orf4* and putative *cro*-like gene (*orf5*) of lactococcal phage TP901-1 were demonstrated to be the components of the genetic switch [Madsen *et al.,* 1999]. ORF4 (180 amino acids) can repress early phage promoters P_R and P_L and confers immunity to the *L. lactis* host strain against TP901-1. ORF5 is an anti-repressor as it is able to counteract repression of the lytic promoter P_L by ORF4. Interestingly, CI/ORF4 does undergo oligomerization and, despite lacking the RecA-dependent autoproteolytic site, TP901-1 is inducible by mitomycin C [Johansen *et al*., 2003].

The regulatory region of the temperate *L. lactis* bacteriophage r1t encompasses the two divergently oriented genes *rro*, which is encoding the phage repressor, and *tec* (topologically equivalent of *cro*). Both genes, of which the transcription start sites have been mapped, are preceded by consensus -35 and -10 promoter sequences. The regulatory region contains three 21 bp direct repeats with internal dyad symmetry which act as operators. A *lacZ* gene was translationally fused with an open reading frame following *tec*. Expression of the *lacZ* fusion could be induced 70-fold by the addition of mitomycin C at a concentration, which promotes the switch of r1t from the lysogenic to the lytic life cycle [Nauta *et al*., 1996]. In a subsequent work thermolabile repressor mutants of *rro* were constructed for the controlled production of proteins in *L. lactis* [Nauta *et al*., 1997].

The DNA-binding pattern appears to be conserved among repressors of lactococcal and streptococcal phages. This binding pattern can be exemplified by the repressor CI_{2009} of temperate lactococcal bacteriophage Tuc2009 [van de Guchte *et al*., 1999], which binds to three inverted repeats, two within the intergenic region and one within the cro_{2009} gene [Kenny *et al*., 2006]. Binding sites for various repressors of LAB bacteriophages have been shown to vary in

number and position [Blatny *et al*., 2001; Johansen *et al*., 2003; Nauta *et al*, 1996; Boyce *et al.,* 1995; Bruttin *et al.,* 2002; Kakikawa *et al*., 2000; Kenny *et al*., 2006].

In most temperate LAB phages, a CI vs. Cro-type genetic switch seems to be in operation where these two proteins compete for binding to the operators, some of whom overlap crucial promoter sequences. However, exceptions to this genetic switch mechanism exist. The two regulatory proteins of phage Sfi21 interact directly, while the switch region of the *Lactobacillus gasseri* temperate phage Φadh deviates from the analogous region of other temperate LAB phages because of the presence of convergent promoters [Engel *et al*., 1998].

The temperate *S. thermophilus* phage Sfi21 and TP-J34 and some other LAB phages contain, in addition to putative *cI*-like and *cro*-like genes, a putative antirepressor-encoding gene showing significant homology to the antirepressor gene of phage P1. Therefore, these phages might code for a common immunity system, which bears similarity to those of phage P1 and P22 [Sternberg & Hoess, 1983].

In conclusion, it seems that many bacteriophages of gram-positive and gram-negative bacteria share similar immunity systems that represent components of their genetic switch. This similarity is probably due to the evolutionary success of this regulatory switch, which appears to have been acquired or retained by various temperate bacteriophage lineages, being facilitated by their simple and modular genetic lay-out.

3.3.2. Other phage-encoded phage resistance mechanisms

In *Lactococcus lactis*, many naturally occurring phage resistance mechanisms have been identified in wild-type strains [Allison & Klaenhammer, 1998]. These mechanisms are often plasmid-encoded and can be classified into four categories, (i) interference with phage adsorption, (ii) prevention of phage DNA injection, (iii) restriction and modification (R/M) systems which degrade incoming DNA molecules, (iv) abortive infection, encompassing a range of mechanisms, any of which may disturb phage development at any time after phage DNA injection. In this section, we will focus on phage-encoded phage-resistance mechanisms found in LAB.

Table 4. Lactic acid bacteriophage-encoded phage-resistance genes

Phage	Gene	Mol Mass (kDa)	Phage-resistance mechanism	Cellular location	Reference
S. thermophilus phage TP-J34	*ltp*	15.8	Superinfection exclusion	Cytoplasmic membrane	Sun *et al*. 2006
S. thermophilus phage Sfi21	*orf203*	21.9	unknown	unknown	Bruttin *et al*. 1997
L. lactis phage Tuc2009	*sie2009*	18.7	Superinfection exclusion	Cytoplasmic membrane	McGrath *et al*. 2002
L. lactis prophage	*sieIL409*	18.2	Superinfection exclusion	Cytoplasmic membrane	McGrath *et al*. 2002
L. lactis prophage	*sieF/2A*	20.5	unknown	Cytoplasmic membrane	McGrath *et al*. 2002
L. lactis prophage	*SieF/2B*	17.2	unknown	unknown	McGrath *et al*. 2002

Several genes located between the repressor and integrase genes in the lysogenic module of the temperate LAB phage were also recently reported to mediate phage resistance (Table 4). The *ltp* gene of temperate *Streptococcus thermophilus* phage TP-J34 was shown to mediate phage resistance in both *S. thermophilus* and *L. lactis* [Sun *et al*., 2002 & 2006]. The *ltp* gene codes for a lipoprotein and is located between the repressor and integrase genes in the lysogenic module of phage TP-J34. It was demonstrated that *ltp* was expressed during lysogeny and that the gene product (Ltp) was located in the cytoplasmic membrane of the lysogenic strain *S. thermophilus* J34. Expression of *ltp* leaves phage adsorption unaffected, but interferes with phage injection and, consequently, phage replication. Disruption of *ltp* in the prophage of strain J34 caused a delayed cell lysis phenotype upon induction with mitomycin C. However, a clear interpretation of this effect is complicated by a possible polar effect of the *ltp* disruption on the intergrase-encoding gene.

The sie_{2009} gene, which is situated between the genes encoding the repressor and integrase, on the lysogeny module of the temperate lactococcal bacteriophage Tuc2009, was also shown to mediate a phage resistance phenotype in *L. lactis* against a number of bacteriophages [McGrath *et al*., 2002]. The Sie_{2009} protein is membrane-bound and its expression does not affect phage adsorption, transfection and plasmid transformation, but interferes with plasmid transduction and phage replication. Taken together, these results indicate that the observed phage resistance results

from DNA injection blocking. By a polymerase chain reaction (PCR)-based strategy, several additional, but mostly unrelated *L. lactis* prophage genes (i.e., sie_{IL409} and $sie_{F7/2A}$) were also identified and shown to mediate a phage-resistance phenotype similar to that conferred by sie_{2009}.

A phage gene located between *int* and *cI-like* in the lysogenic module of temperate *S. thermophilus* phage ΦSfi21 has also been reported to confer significant phage resistance to heterologous virulent phages when cloned onto a plasmid [Bruttin *et al*., 1997].

The discovery of different phage-encoded bacteriophage resistance systems in different LAB species indicate that such phage-encoded systems are widespread as proposed by van Sinderen and his colleagues [McGrath *et al.,* 2002]. Even though these phage resistance-conferring genes do not share sequence homology they do share the same topology in the lysogenic module of respective phages. Another common feature of these genes appears to be that they all encode membrane proteins, which may be a requirement for their common mode of action in disrupting phage DNA entry, as demonstrated by the Ltp protein [Sun *et al*. 2006]. Analysis of prophage sequences has revealed that many of them possess genes, situated between the integrase and repressor-encoding genes. For instance, two genes encoding lipoproteins were detected within the lysogeny module of two *Lactobacillus* prophages [Ventura *et al*., 2004a, 2004b]. Further charaterization of such genes will be needed to determine their contribution, if any, towards defending their host from superinfecting phages.

4. TRANSDUCTION

4.1. Overview of transduction

Phage-mediated transduction, first described in 1952 for *S. typhimurium* and the temperate bacteriophage P22 [Zinder and Lederberg, 1952], is one of three naturally occurring mechanisms, along with conjugation and transformation, whereby DNA is transferred from one bacterium to another (i.e., horizontal gene transfer). Transduction of host genes by phages occurs in two ways. In the case of generalized transduction random fragments of DNA are transferred by either a temperate or virulent bacterophage, resulting in a low transduction frequency of any genetic material. On the other hand, specialized transduction occurs only with temperate phages, thereby a specific portion of the host genome is accidentally excised together with prophage. Bacteriophages P22 and λ [Birge, 2000] are two classic examples of generalized and specialized transduction, respectively. Both types of transduction appear to result from mistakes made by the enzymatic systems involved in excising and packaging phage DNA. Generalized transducing

phages commonly encapsulate their DNA by the headful mechanism, generating permuted DNA molecules. If the enzymes responsible for packaging accidentally use bacterial DNA instead of phage DNA, generalized transduction occurs. In the case of specialized transduction, the enzymes responsible for prophage excision cut out a piece of DNA that does not belong to prophage, resulting in a DNA molecule containing both viral and bacterial DNA. Therefore, specialized transducing particles are usually defective in one or more functions.

4.2. The extent of temperate phage-mediated transduction and its impacts on bacteria

Temperate phage-mediated transduction has been described in various species such as *Bacillus subtilus* [Marrero *et al*., 1984; Deichelbohrer, 1985], *Lactobacillus gasseri* [Raya and Klaenhammer, 1992], *L. lactis* [Birkeland and Holo, 1993; Klaenhammer and McKay, 1976], *Listeria monocytogenes* [Hodgson, 2000], *Pseudomonas Aeruginosa* [Blahova *et al*., 1997], *Salmonella typhimurium* [Liagostera *et al*., 1986; Schicklmaier and Schmieger, 1995], *Streptomyces* spp. [Mchenney and Baltz, 1988] and *Yersinia enterocolitica* [Hertwig *et al*., 1999].

To date, the most detailed study on the frequency of temperate transducing phages was performed by Schicklmaier and Schmieger [1995] using *S. typhimurium*. From 85 natural isolates of the *S. typhimurium* complex, 65 strains (76.5%) released 71 different temperate phages. Forty-three (93.5%) of 46 tested phages were able to transduce the chromosomal markers his^+ and trp^+, as well as the plasmid pBR325. Later, Schicklmaier *et al.* [1998] showed that 99% of the investigated *Salmonella* phages were capable of generalized transduction of chromosomal host markers and plasmids.

Hertwig *et al*. [1999] studied temperate phage-mediated gene transfer in *Yersinia*. The transduction experiments were performed with a temperate phage and small plasmids isolated from a pathogenic *Y. enterocolitica* strains. A transduction frequency of 10^{-5} to 10^{-7} transductants/PFU was achieved under laboratory conditions.

In a natural microbial community, transduction of *Pseudomas aeruginosa* plasmid Rm149 by the generalized transducing bacteriophage ΦDS1 was shown to occur during a 9-day incubation of environmental test chambers in a freshwater reservoir [Saye *et al*., 1987]. Temperate phage-mediated transductions between different species [Zahrt *et al*., 1994] or genera [Neal *et al*., 1993] have also been reported.

Through generalized transduction, temperate phages can package and transmit any chromosomal locus among bacterial cells. From a medical perspective, transmission of chromosomally encoded virulence genes by bacteriophage has been described. For instance, staphylococcal phage 80α can at high frequency transduce the *Staphylococcus aureus* pathogenicity island SapI1, which contains the gene for toxic shock syndrome toxin (*tst*) [Ruzin *et al*., 2001]. In *Corynebacterium diphtheriae*, it has been suggested that the *tox* gene, which encodes diphtheria toxin, was acquired by an ancestral form of phage ß, through transduction [Holmes 2000], because this gene was localized to one end of the integrated phage genome adjacent to the *attP* site. Transductions of antibiotic resistance by temperate bacteriophages have also been reported [Blahova *et al*., 1997 & 1999].

On the other hand, transduction of plasmids by temperate phage can be exploited as efficient gene transfer system especially for species which are poorly transformable. For example, plasmid pSA-COS1 which carries the cohesive end region from temperate lactococcal bacteriophage ΦLC3 was shown to be packaged *in vivo* by ΦLC3, allowing transfer into host strain *L. lactis subsp. cremoris* NCDO 1201 with a transduction frequency between 10^{-4} and 10^{-3} transductants per PFU [Birkeland and Holo, 1993]. A plasmid containing the *pac* site of phage P22 was also efficiently transduced by phage P22 [Schmidt and Schmieger, 1984]. Phage hybrids constructed by Yamamoto *et al*. [1985], which carry all the late genes of coliphage Φ80 and most of the *Salmonella* phage P22 early region including the *immC* and *immI* bipartite immunity loci, could transfer the *argF* and *proA* markers at high frequency (21% for *argF* and 12% for *proA*).

From the above reports and considering that some lytic phages are also spontaneously derived from prophages, it can be assumed that the potential for prophage-mediated gene transfer (i.e., transduction) is much higher than expected. Morever, transduction as a means of gene exchange during evolution and especially as a mechanism for the spread of plasmids in bacterial populations is likely to happen much more frequently.

4.3. Temperate phage-mediated transduction in LAB

Among the LAB temperate phage-mediated transduction has been demonstrated in lactococci and *Lactobacillus*. McKay *et al.* [1973] demonstrated the transduction of the genetic properties for lactose utilization (*lac*) by UV-induced lysogenic phage from wild-type *L. lactis* subsp. *lactis* C2 to a Lac^- derivative [McKay *et al*., 1973] as well as the intermittent co-transduction of the *prt* (protease-encoding gene) marker with *lac* [McKay and Baldwin, 1974; Klaenhammer and McKay, 1976]. It was later shown that both the *lac* and *prt* loci were plasmid-linked [Molskness

et al., 1974; McKay *et al*., 1976]. The ability of temperate phage BK5-T from *L. lactis* subsp. *cremoris* BK5 to transduce both plasmid and chromosomal markers has also been demonstrated [Davidson *et al*., 1990].

Although lysogenic bacteriophages of *Lactobacillus* species have been described, there have been very few reports of transduction in this genus. Temperate phage PLS-1 could transduce auxotropic markers between *Lactobacillus salivarius* strains [Tohyama *et al*., 1971]. Raya *et al*. [1989] reported the transfer of vector plasmids in *Lb. gasseri* by temperate phage Φadh. Luchansky *et al*. [1989] described that plasmid pGK12 was transduced from phage Φadh lysogen into a recipient strain of *L. acidophilus* ADH at an average frequency of 3.4 x 10^{-8} transductants/PFU. In a subsequent study, the transduction frequency of plasmid pGK12 could be increased by 10^2-10^5-fold by inserting restriction fragments of bacteriophage into this vector [Raya and Klaenhammer, 1992].

Transduction between different LAB species has recently been reported [Ammann *et al*., 2008], supporting the hypothesis that some *S. thermophilus* and *L. lactis* bacteriophages have evolved by direct exchange of genetic modules.

5. CONCLUSION

It has become clear that lysogenic bacteriophages can provide their hosts with a number of phenotypic attributes, ranging from increased virulence to enhanced resistance against a diverse phage population. This is likely to be one of the main evolutionary drivers for the abundance of prophages in bacterial genomes, in addition to their contribution to horizontal transfer. However, we are likely to have only scratched the surface with regards to the identification of such fitness enhancers. It has been suggested that temperate phages reserve certain sections of their genome for such functions, specifically between the genes encoding the repressor and the integrase as well as between the lysis module and the attachment site (Desiere *et al*., 2001). Examination of these variable genomic regions would indicate that the vast majority of lysogenic phages encode at least one function that could contribute to increased fitness of the host. The challenge for future research in this area would be the unravelling of these functions and the investigation of the molecular details as to the mechanisms by which lysogens have improved their chances of survival.

ACKNOWLEDGEMENTS

Douwe van Sinderen is the recipient of a Science Foundation Ireland Principal Investigator award (02/IN1/B198). S.M. would like to acknowledge the support of the Natural Sciences and Engineering Research Council (NSERC) of Canada.

REFERENCES

Adams, M.M., G. E. Allison and N. K. Verma. (2001). Type IV O antigen modification genes in the genome of *Shigella flexneri* NCTC 8296. Microbiology 147:851-860.

Allison, G. E., and T. R. Klaenhammer. (1998). Phage resistance mechanisms in lactic acid bacteria. Int. Dairy J. 8:207-226.

Allison, G. E., and N. K. Verma. (2000). Serotype-converting bacteriophages and O-antigen modification in *Shigella flexneri*, Trends Microbio. 8:17-23.

Allison, G. E., D. Angeles, N. Tran-Dinh, & N. K. Verma. (2002). Complete genomic sequence of SfV, a serotype-converting temperate bacteriophage of *Shigella flexneri*. J Bacteriol 184:1974–1987.

Ammann, A., H. Neve, A. Geis, K. J. Heller. (2008). Plasmid transfer via transduction from *Streptococcus thermophilus* to *Lactococcus lactis*. J Bacteriol. 190:3083-3087.

Arendt, E. K., A. Lonvaud, and W. P. Hammes. (1991). Lysogeny in *Leuconostoc oenos*. J. Gen. Microbiol. 137:2135-2139.

Bail, O. (1925). Der Kolistamm 88 von Gildemeister und Herzberg, Med. Klin. (Munich), 21:1271-1273.

Bair, C. L., D. Rifat, and L. W. Black. (2007). Exclusion of Glucosyl-Hydroxymethylcytosine DNA Containing Bacteriophages Is Overcome by the Injected Protein Inhibitor IPI*. J Mol Biol. 366:779-89.

Baldwin, K. A., and L. L. McKay. (1987). Spontaneous release of temperate phage by relysogenized lactose-positive transduction of *Streptococcus lactis* C2. J. Dairy Sci. 70:2005-2012.

Barnet, Y. M., and J. M. Vincent. (1970). Lysogenic conversion of *Rhizobium trifolii*. J Gen Microbiol. 61:319-325.

Barondess, J. J., and J. Beckwith. (1995). *Bor* gene of phage λ, involved in serum resistance, encodes a widely conserved outer membrane lipoprotein. J. Bacteriol. 177:1247-1253.

Bergsland, K.J., C. Kao, Y.N. Yu, R. Gulati, and L. Snyder. (1990). A site in the T4 bacteriophage major head protein gene that can promote the inhibition of all translation in *Escherichia coli*. J. Mol. Biol. 213:477-494.

Bertani, G. (1958). Lysogeny. Adv. Virus Res. 5:151-193.
Bertani, G. (2004). Lysogeny at mid-twentieth centry: P1, P2, and other experimental systems. . J. Bacteriol 186:595-600.

Bertani, L. E., and E. W. Six. The P2-like phages and their parasite P4. In: R. Calendar (Ed.), *The Bacteriophages.* New York, USA: Plenum Press; 1988; pp.73-143.

Biere, A. L., M. Citron, and H. Schuster. (1992). Transcriptional control via translational repression by *c4* antisense RNA of bacteriophages P1 and P7. Genes Dev 6:2409-2416.

Bingham, R., S. I. N. Ekunwe, S. Falk, L. Snyder, and C. Kleanthous. (2000). The major head protein of bacteriophage T4 binds specifically to elongation factor Tu. J Biol Chem 275:23219-23226.

Birge, E.A. Genetics of temperate bacteriophages. In: E. A. Birge (Ed.), *Bacterial and bacteriophage genetics*. New York, USA: Springer; 2000; pp.253-292.

Birge, E.A. Transduction. In: E. A. Birge (Ed.), *Bacterial and bacteriophage genetics*. New York. USA: Springer; 2000; pp.293-313.

Birkeland, N. K., and H. Holo. (1993). Transduction of a plasmid carrying the cohesive end region from *Lactococcus lactis* bacteriophage ΦLC3. Appl. Environ. Microbiol. 59:1996-1968.

Blahova, J., K. Kralikova, V. Krcmery SR., D. Mlynarcik, J. Trupl. (1997). Transduction of antibiotic resistance including imipenem resistance by type phages from nosocomial strains of *Pseudomonas Aeruginosa*. Acta virologica 41:293-296.

Blahova, J., K. Kralikova, V. Krcmery, and A. Mikovicova. (1999). High-frequency transduction (HFT) of resistance to ceftazidime and other antibiotics by a wild-type *Pseudomonas aeruginosa* phage. Zent.bl. Bakteriol. 289:179-183.

Blatny, J.M., P.A. Risoen, D. Lillehaug, M. Lunde and I.F. Nes. (2001). Analysis of a regulator involved in the genetic switch between lysis and lysogeny of the temperate *Lactococcus lactis* phage phi LC3. *Mol. Genet. Genomics* 265:189–197.

Bordet, J. (1925). Le problême de l'autolyse microbienne transmissible ou du bactêriophage. Ann. Inst. Pasteur. 39: 711-763.

Boyce, J., B. E. Davidson, and A. J. Hiller. (1995). Identification of prophage genes expressed in lysogens of the *Lactococcus lactis* bacteriophage BK5-T. Appl. Environ. Microbiol. 61:4099-4104.

Broudy, T.B. and V. A. Fischetti. (2003). In vivo lysogenic conversion of Tox(-) Streptococcus pyogenes to Tox(+) with Lysogenic Streptococci or free phage. Infect Immun. 71:3782-6.

Brown, K. L., G. J. Sarkis, C. Wadsworth, and G. F. Hatfull. (1997). Transcriptional silencing by the mycobacteriophage L5 repressor. EMBO J. 16:5914-5921.

Brüssow, H., C. Canchaya, and W. Hardt. (2004). Phages and the evolution of bacterial pathogens: from genomic rearrangements to lysogenic conversion. Microbiol Mol Biol Rev. 68:560-602.

Bruttin, A., S. Foley and H. Brussow. (2002). DNA-binding activity of the *Streptococcus thermophilus* phage Sfi21 repressor, *Virology* 303:100–109.

Bruttin, A., F. Desiere, S. Lucchini, S. Foley, and H. Brüssow. (1997). Characterization of the lysogeny DNA module from the temperate *Streptococcus thermophilus* bacteriophage ΦSfi21. Virology 233:136-148.

Canchaya, C., F. Desiere, W. M. McShan, J. J. Ferretti, J. Parkhill and H. Brüssow. (2002). Genome analysis of an inducible prophage and prophage remnants integrated in the *Streptococcus pyogenes* strain SF370. Virology. 302:245-58.

Canchaya, C., C. Proux, G. Fournous, A. Bruttin, and H. Brüssow. (2003). Prophage genomics. Microbiol Mol Biol Rev. 67:238-276.

Canchaya, C., G. Fournous, and H. Brüssow. (2004). The impact of prophages on bacterial chromosomes. Mol. Microbiol. 53:9-18.

Casjens, S. (2003). Prophages and bacterial genomics: what have we learned so far? Mol. Microbio. 49:277-300.

Chapman, D., I. Morad, G. Kaufmann, M.J. Gait, L. Jorissen, and L. Snyder. (1988). Nucleotide and deduced amino acid sequence of stp: the bacteriophage T4 anticodon nuclease gene. J. Mol. Biol. 199:373-377.

Cheng, C-M., H-J. Wang, H-J. Bau, and T-T. Kuo. (1999). The primary immunity determinant in modulating the lysogenic immunity of the filamentous bacteriophage cf. J. Mol. Biol. 287:867-876.

Cheong, J. P. E., and J. D. Brooker. (1998). Lysogenic bacteriophage M1 from *Selenomonas ruminantium*: isolation, characterization and DNA sequence analysis of the integration site. Microbiology 144:2195-2202.

Chopin, A., A. Bolotin, A. Sorokin, S. D. Ehrlich, and M. C. Chopin. (2001). Analysis of six prophages in *Lactococcus lactis* IL1403: different genetic structure of temperate and virulent phage populations. Nucleic Acids Res. 29:644-651.

Chopin, M.-C., A. Chopin and E. Bidnenko. (2005). Phage abortive infectionin lactococci: variations on a theme. Curr. Opin. Microbiol. 8: 473-479.

Christiansen, B., M. G. Johnsen, E. Stenby, F. K. Vogensen, and K. Hammer. (1994). Characterization of the lactococcal temperate phage TP901-1 and its site-specific integration. J. Bacteriol. 176:1069-1076.

Csiszovszki, Z., B. Zsuzsanna, S. Semsey, T. Ponyi, P. P. Papp, and L. Orosz. (2003). ImmX immunity region of rhizobium phage 16-3: two overlapping cistrons of repressor function. J Bacteriol. 185:4382-92.

Cluzel, P. J., J. Serio, and J. P. Accolas. (1987). Interactions of *Lactobacillus bulgaricus* temperate bacteriophage 0048 with host strains. Appl. Environ. Microbiol. 53:1850-1854.

Coleman, D., J. Knights, R. Russell, D. Shanley, T. H. Birkbeck, G. Dougan, and I. Charles. (1991). Insertional inactivation of the *Staphylococcus aureus* beta-toxin by bacteriophage phi 13 occurs by site- and orientation-specific integration of the phi 13 genome. Mol. Microbiol. 5:933-939.

Coleman, D. C., D. J. Sullivan, R. J. Russell, J. P. Arbuthnott, B. F. Carey, and H. M. Pomeroy. (1989). *Staphylococcus aureus* bacteriophages mediating the simultaneous lysogenic conversion of ß-lysin, staphylokinase and enterotoxin A: molecular mechanism of triple conversion. J. Gen. Microbiol. 135:1679-1697.

Coombes, B. K., M. E. Wickham, N. F. Brown, S. Lemire, L. ossi, W. W.L. Hsiao, F. S.L. Brinkman and B. B. Finlay. (2005). Genetic and molecular analysis of GogB, a phage-encoded type III-secreted substrate in *Salmonella enterica* serovar *typhimurium* with autonomous expression from its associated phage. J Mol Biol. 348:817-30.

Coetzee, J. N., H. C. De Klerk. (1962). Lysogeny in the genus Lactobacillus. Nature. 194:505.

Dai, H., K. S. Chiang and T. T. Kuo. (1980). Characterization of a new filamentous phage cf from *Xanthomonas citri*. J. Gen. Virol. 46 :277-289.

Davidson, B. E., I. B. Powell, and A. J. Hiller. (1990). Temperate bacteriophages and lysogeny in lactic acid bacteria. FEMS Microbiol. Rev. 87:79-90.

Decker, K., V. Krauel, A. Meesmann, and K. J. Heller. (1994). Lytic conversion of *Escherichia coli* by bacteriophage T5: blocking of the FhuA receptor protein by a lipoprotein expressed early during infection. Mol. Microbiol. 12:321-332.

De Klerk, H. C., and N. Hugo. (1970). Phage-like structures from *Lactobacillus acidophilus*. J. Gen. Virol. 8:231-234.

Deichelbohrer, I., J. C. Alonso, G. Luder, T.A. Trautner. (1985). Plasmid transduction by *Bacillus subtilis* bacteriophage SPP1: effects of DNA homology between plasmid and bacteriophage. J Bacteriol. 162:1238-43.

Desiere, F., S. Lucchini, and H. Brüssow. (1998). Evolution of *Streptococcus thermophilus* bacteriophage genomes by modular exchanges followed by mutations and small deletions and insertions. Virology 241:345-356.

Desiere, F., McShan, W.M., Van Sinderen, D., Ferretti, J.J. and H. Brüssow. (2001). Comparative genomics reveals close genetic relationships between phages from dairy bacteria and pathogenic streptococci: Evolutionary implications for prophage-host interactions. Virology 288: 325-341.

Dhaese P, M. R. Dobbelaere, M. Van Montagu. (1985). The temperate *B. subtilis* phage phi 105 genome contains at least two distinct regions encoding superinfection immunity. Mol Gen Genet. 200:490-2

Duckworth, D.H., J. Glenn, and D.J. McCorquale. (1981). Inhibition of bacteriophage replication by extrachromosomal genetic elements. Microbiol. Rev. 45:52-71.

Engel, G., E. Altermann, J. R. Klein, and B. Henrich. (1998). Structure of a genome region of the *Lactobacillus gasseri* temperate phage Φadh covering a repressor gene and cognate promoters. Gene 210:61-70.

Faruque, S. M., Asadulghani, M. N. Saha, A. R. M. A. Alim, M. J. Albert, K. M. N. Islam, and J. J. Mekalanos. (1998). Analysis of clinical and environmental strains of nontoxigenic *Vibrio cholerae* for susceptibility to CTXΦ: Molecular basis for origination of new strains with epidemic potential. Infect Immun. 66: 5819-5825.

Faruque, S. M., M. M. Rahman, Asadulghani, K. M. N. Islam, and J. J. Mekalanos. (1999). Lysogenic conversion of environmental *Vibrio mimicus* strains by CTXΦ. Infect Immun. 67:5723-5729.

Felis, G. E. and F. Dellaglio. (2007). Taxonomy of Lactobacilli and Bifidobacteria. Curr. Issues Intest. Microbiol 8: 44-61.

Figueroa-Bossi, N. and L. Bossi. (1999). Inducible prophages contribute to *Salmonella* virulence in mice. Mol. Microbiol. 33:167-176.

Forti, F., S. Polo, K. B. Lane, E. W. Six, G. Sironi, G. Dehó, and D. Ghisotti. (1999). Translation of two nested genes in bacteriophage P4 controls immunity-specific transcription termination. J. Bacteriol. 181:5225-5233.

Garcia, P., V. Ladero, J. C. Alonso, and J. E. Suarez (1999). Cooperative interaction of CI protein regulates lysogeny of *Lactobacillus casei* by bacteriophage A2. J. Virol. 73:3920-3929.

Gautier, M., A. Rouault, C. Hervė, P. Sommer, V. Leret, G. Jan, J. M. Fraslin, F. Prėvot, and A. Coste. (1999). Bacteriophages of dairy propionibacteria. Lait 79:93-104.

Georgiou, T., Y.N. Yu, S. Ekunwe, M.J. Buttner, A. Zuurmond, B. Kraal, C. Kleanthous, and L. Snyder. (1998). Specific peptide-activated proteolytic cleavage of *Escherichia coli* elongation factor Tu. Proc. Natl. Acad. Sci. USA. 95:2891-2895.

Goshorn, S. C., and P. M. Schlievert. (1989). Bacteriophage association of strptococcal pyrogenic exotoxin type C. J. Bacteriol. 171:3068-3073.

Greene, J., and R. B. Goldberg. (1985). Isolation and preliminary characterization of lytic and lysogenic phages with wide host range within the Streptomycetes. J Gen Microbiol. 131:2459-2465.

Groman, N. B., and M. Rabin. (1980). Superinfection exclusion by heteroimmune corynebacteriophages. J. Virol. 36:526-532.

Groman, N. B. (1984). Conversion by corynephages and its role in the natural history of diphtheria. J. Hyg. 93:405-17.

Hayashi, T., H. Matsumoto, M. Ohnishi, and Y. Terawaki. (1993). Molecular analysis of a cytotoxin-converting phage, ΦCTX, of *Pseudomonas aeruginosa*: structure of the *attp-cos-ctx* region and integration into the serine tRNA gene. Mol.Microbiol.7:657-667.

Hertwig, S., A. Popp, B. Freytag, R. Lurz, and B. Appel. (1999). Genralized transduction of small *Yersinia enterocolitica* plasmids. Appl. Environ. Microbiol. 65:3862-3866.

Hodgson, D. A. (2000). Generalized transduction of serotype ½ and serotype 4b strains of *Listeria monocytogenes*. Mol. Microbiol. 35:312-323.

Hofer, B., M. Ruge, and B. Dreiseikelmann. (1995). The superinfection exclusion gene (*sieA*) of bacteriophage P22: identification and overexpression of the gene and localization of the gene product. J. Bacteriol. 177:3080-3086.

Holzmayer, T. A., G. I. karataev, M. N. Rozinov, I. L. Moskvina, Y. L. Shumakov, V. L. Motin, S. M. Mebel, V. N. Gershanovich, and I. A. Lapaeva. (1988). Bacteriophage of Bordetella sp.: features of lysogeny and conversion. Zbl. Bakt. Hyg. A 269:147-155.

Holmes, R. K. (2000). Biology and molecular epidemiology of diphtheria toxin and the *tox* gene. J Infect Dis 181 Suppl 1:156-167.

Howe, M. M. Phage Mu: an overview. In: N. Symonds, A. Toussaint, P. van de Putte, and M. M. Howe, (Eds.), *Phage Mu*. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory; 1987; pp. 25-39.

Husson-Kao, C., J. Mengaud, J. C. Gripon, L. Benbadis, and M. P. Chapot-Chartier. (2000). Characterization of *Streptococcus thermophilus* strains that undergo lysis under unfavorable environmental conditions. Int. J. Food Microbiol. 55:209-213.

Inoue, K., and H. Iida. (1971). Phage-conversion of toxigenicity in *Clostridium botulinum* type C and D. Jpn J Med Sci Biol 24:53-56.

Ivånovics, G., V. Gaål, and B. Prågai. (1974). Lysogenic conversion to phospholipase A production in *Bacillus cereus*. J. Gen. Virol. 24:349-358.

Jarvis, A. W. (1989). Bacteriophages of lactic acid bacteria. J. Dairy. Sci. 72:3406-3428.

Jarvis, A. W., V. R. Parker, and M. B. Bianchin. (1992). Isolation and characterization of two temperate phages from *Lactococcus lactis* ssp. *cremoris* C3. Can. J. Microbiol. 38:398-404.

Johansen, A. H., L. Brondsted and K. Hammer (2003). Identification of operator sites of the CI repressor of phage TP901-1: evolutionary link to other phages. Virology 311:144–156.

Johnson, L. P., P. M. Schlievert, and D. W. Watson. (1980). Transfer of group A streptococcal pyrogenic exotoxin production to nontoxigenic strains by lysogenic conversion. Infect Immun. 28:254-257.

Johnson, L. P., M. A. Tomai, and P. M. Schlievert. (1986). Bacteriophage involvement in group A streptococcal pyrogenic exotoxin A production. J. Bacteriol. 166:623-627.

Josephsen, J., and H. Neve. Bacteriophages and lactic acid bacteria. In: S. Salminen & A. von Wright (Eds.). *Lactic acid bacteria (microbiology and functional aspects).* New York: Marcel Dekker, Inc.; 1998; pp.385-436.

Kakikawa M, S. Ohkubo, T. Sakate, M. Sayama, A. Taketo, K. Kodaira. (2000). Purification and DNA-binding properties of the cro-type regulatory repressor protein cng encoded by the *Lactobacillus plantarum* phage phi g1e. Gene 249:161-9

Kao, C., and L. Snyder. (1988). The lit gene product which blocks bacteriophage T4 late gene expression is a membrane protein encoded by a cryptic DNA element, e14. J. Bacteriol. 170:2056-2062.

Karaolis, A.K.R., S. Somara, D. R. Maneval, J. A. Johnson, and J. B. Kaper. (1999). A bacteriophage encoding a pathogenicity island, a type-IV pilus and a phage receptor in cholera bacteria. Nature, 399: 375-379.

Kaufmann, G. (2000). Anticodon nucleases. Trends Biochem 25:70-74.

Kenny, J.G., S. Leach, A. B. De la Hoz, G. Venema, J. Kok, G. F. Fitzgerald, A. Nauta,, J. C. Alonso, and D. van Sinderen. (2006) Characterisation of the lytic-lysogenic switch of the lactococcal bacteriophage Tuc2009. Virology 347: 434-446.

Kętyi, I. (1974). Role in virulence of *Shigella flexneri* antigens derived from lysogenic conversion. Infect Immun 9:931-933.

Klaenhammer, T. R., and L. L. McKay. (1976). Isolation and examination of transducing bacteriophage particles from *Streptococcus lactis* C2. J. Dairy Sci. 59:396-404.

Kliem, M., and B. Dreiseikelmann. (1989). The superimmunity gene *sim* of bacteriophage P1 causes superinfection exclusion. Virology 171:350-355.

Kuzio, J., and A. M. Kropinski. (1983). O-antigen conversion in *Pseudomonas aeruginosa* PAO1 by bacteriophage D3. J. Bacteriol. 155:203-212.

Labrie, S.J., and S. Moineau. (2007). Abortive infection mechanisms and prophage sequences significantly influence the genetic make-up of emerging lytic lactococcal phages. J. Bacteriol. 189:1482-1487.

Lamont, I., B. Kalionis, and J. B. Egan. (1989). Control of gene expression in the P2-related temperate coliphages. V. The use of sequence analysis of 186 Vir mutant to indicate presumptive repressor binding sites. J. Mol. Biol. 199:379-382.

Ladero, V., P. Garcia, V. Bascarán, M. Herrero, M. A. Alvarez, and J. E. Suarez. (1998). Identification of the repressor-encoding gene of the *Lactobacillus* bacteriophage A2. J. Bacteriol. 180:3474-3476.

Langley, R., D.T. Kenna, P. Vandamme, R. Ure and J. R. W. Govan. (2003). Lysogeny and bacteriophage host range within the *Bukholderia cepacia* complex. J Med Microbiol. 52:483-490.

Lawton, W. D., and D. M. Molnar. (1972). Lysogenic conversion of *Pasteurella* by *Escherichia coli* bacteriophage P1 CM. J Virol.9:708-709.

Lee, C. Y., and J. J. Iandolo. (1986). Lysogenic conversion of Staphylococcal lipase is caused by insertion of the bacteriophage L54a genome into the lipase structural gene. J. Bacteriol. 166:385-391.

Le Marrec, C., Van Sinderen, D., Walsh, L., Stanley, E., Vlegels, E., Moineau, S., Heinze, P., Fitzgerald, G., and B. Fayard. (1997). Two groups of bacteriophages infecting *Streptococcus thermophilus* can be distinguished on the basis of model of packaging and genetic determinants for major structural proteins. Appl. Environ. Microbiol. 63: 3246-3253.

Levin, M. (1972). Replication and lysogeny with phage P22 in *Salmonella typhimurium*. Curr. Top. Microbiol. Immunol. 58:135-156.

Levitz, R., D. Chapman D, M. Amitsur M, R. Green R, L. Snyder L, and G. Kaufmann. (1990). The optional *E. coli* prr locus encodes a latent form of phage T4-induced anticodon nuclease. EMBO J. 9:1383-1389.

Liagostera, M., J. Barbe, R. Guerrero. (1986). Characterization of SE1, a new general transducing phage of *Salmonella typhimurium*. J. Gen Microbiol.132:1035-41.

Lindahl, G., G. Sironi, H. Bialy, and R. Calendar. (1970). Bacteriophage lambda: abortive infection of bacteria lysogenic for phage P2. Proc. Natl. Acad. Sci. USA 66:587-594.

Lindqvist, B., G. Dehó, and R. Calendar. (1993). Mechanisms of genome propagation and helper exploitation by satellite phage P4. Microbiol. Rev. 57:683-702.

Losick, R. (1969). Isolation of a trypsin-sensitive inhibitor of O-antigen synthesis involved in lysogenic conversion by bacteriophage ϵ^{15}. J. Mol.Biol. 42:237-246.

Luchansky J. B., E. G. Kleeman, R. R. Raya, and T. R. Klaenhammer. (1989). Genetic transfer systems for delivery of plasmid deoxyribonucleic acid to *Lactobacillus acidophilus* ADH: conjugation, electroporation, and transduction. 72:1408-1417.

Lu, M. J., and U. Henning. (1989). The immunity (*imm*) gene of *Escherichia coli* bacteriophage T4. J. Virol. 63:3472-3478.

Lu, M. J., and U. Henning. (1994). Superinfection exclusion by T-even-type coliphages. Trends Microbiol. 2:137-139.

Lwoff, A. (1953). Lysogeny. Bacteriol. Rev.17:269-337.

Madigan, M. T., J. M. Martinko, and J. Parker. *Brock: Biology of microorganisms (9th).* New Jersey. USA.: Prentice Hall International, Inc.; 2000.

Madsen, P. L., A. H. Johansen, K. Hammer, and L. Brondsted. (1999). The genetic switch regulating activity of early promoters of the temperate lactococcal bacteriophage TP901-1. J. Bacteriol. 181:7430-7438.

Maillou, J., and B. Dreiseikelmann. (1990). The *sim* gene of *Escherichia coli* phage P1: nucleotide sequence and purification of the processed protein. Virology 175:500-507.

Markine-Goriaynoff, N., L. Gillet, J. L. Van Etten, H. Korres, N. Verma, and A. Vanderplasschen. (2004). Glycosyltransferases encoded by viruses. J Gen Virol. 85:2741–2754

Matsumoto, M., N. Ichikawa, S. Tanaka, T. Morita, and A. Matsushiro. (1985). Molecular cloning of phi-80 adsorption-inhibiting cor gene. Jpn. J. Genet. 60:475-483.

Maurelli, A. T., R. E. Fernandez, C. A. Bloch, C. K. Rode, and A. Fasano. (1998). "Black holes" and bacterial pathogenicity: a large genomic deletion that enhances the virulence of *Shigella* spp. and enteroinvasive *Escherichia coli*. Proc. Natl. Acad. Sci. USA 95:3943-3948.

Marrero, R., F. E. Young, and R. E. Yasbin. (1984). Characterization of interspecific plasmid transfer mediated by *Bacillus subtilis* temperate bacteriophage SPO2. J. Bacteriol. 160:458-461.

Martinez-Molina, E., and J. Olivares. (1979). Antibiotic production by *Pseudomonas reptilovara* as a phage conversion. Can. J. Microbiol. 25:1108-1110.

Mason, R., and W. E. Allen. (1975). Characteristics of *Staphylococcus aureus* associated with lysogenic conversion to loss of beta-hemolysin production. Can. J. Microbiol. 21:1113-1116.

McGrath, S., G. F. Fitzgerald, and D. van Sinderen. (2002). Identification and characterization of phage-resistance genes in temperate lactococcal bacteriophages. Mol. Microbiol. 43:509-520.

Mchenney, M. A., and R. H. Baltz. (1988). Transduction of plasmid DNA in *Streptomyces* spp. And related genera by bacteriophage FP43. J. Bacteriol. 170:2276-2282.

McKay, L. L., and K. A. Baldwin. (1974). Simultaneous loss of proteinase- and lactose-utilizing enzyme activities in *Streptococcus lactis* and reversal of loss by transduction. Appl. Environ. Microbiol. 36:360-367.

McKay, L. L., B. R. Cords, and K. A. Baldwin. (1973). Transduction of lactose metabolism in *Streptococcus lactis* C2. J. Bacteriol. 115:810-815.

McKay, L. L., K. A. Baldwin, J. D. Efstathiou. (1976). Transductional evidence for plasmid linkage of lactose metabolism in *Streptococcus lactis* C2. Appl. Environ. Microbiol. 32:45-52.

Meidler, R., I. Morad, M. Amitsur, H. Inokuchi, and G. Kaufmann. (1999). Detection of anticodon nuclease residues involved in tRNALys cleavage specificity. J. Mol. Biol. 287:499-510.

Miao, E. A., & S. I. Miller. (1999). Bacteriophage in the evolution of pathogen-host interactions. Pro. Natl. Acad. Sci. USA 96:9452-9454.

Mirold, S., W. Rabsch, M. Rohde, S. Stender, H. Tschäpe, H. Rüssmann, E. Igwe, and W. D. Hardt. (1999). Isolation of a temperate bacteriophage encoding the type III effector protein SopE from an epidemic *Salmonella typhimurium* strain. Proc. Natl. Acad. Sci. USA 96:9845-9850.

Molskness, T. A., W. E. Sandie, and L. R. Elliker. (1974). Characterization of Lac^+ transductants of *Streptococcus lactis.* Appl. Environ. Microbiol. 28:753-758.

Myung, H., and R. Calendar. (1994). The old exonuclease of bacteriophage P2. J. Bacteriol. 177:497-501.

Nauta A, D. van Sinderen, H. Karsens, E. Smit, G. Venema, J. Kok..(1996). Inducible gene expression mediated by a repressor-operator system isolated *from Lactococcus lactis* bacteriophage r1t. Mol Microbiol. 19:1331-41.

Nauta A, B. van den Burg, H. Karsens, G. Venema, J. Kok. (1997). Design of thermolabile bacteriophage repressor mutants by comparative molecular modeling. Nat Biotechnol. 15:980-3.

Neal, B. L., P.K. Brown, and P. R. Reeves. (1993). Use of *Salmonella* phage P22 for transduction in *Escherichia coli.* J. Bacteriol. 175:7115-7118.

Neve, H., K. I. Zenz, F. Desiere, A. Koch, K. J. Heller, and H. Brüssow. (1998). Comparison of the lysogeny modules from the temperate *Streptococcus thermophilus* bacteriophages TP-J34 and Sfi21: implication for the modular theory of phage evolution. Virology 241:61-72.

Neve, H., W. Freudenberg, F. Diestel-Feddersen, R. Ehlert and K. J. Heller. (2003). Biology of the temperate *Streptococcus thermophilus* bacteriophage TP-J34 and physical characterization of the phage genome. Virology. 315:184-94.

Nesper, J., J. Blaß, M. Fountoulakis, and J. Reidl. (1999). Characterization of the major control region of *Vibrio cholerae* bacteriophage K139: immunity, exclusion, and integration. J. Bacteriol. 181:2902-2913.

Obringer, J., P. McCreary, and H. Bernstein. (1988). Bacteriophage T4 genes sp and 40 apparently are the same. J Virol. 62:3043-3045

Osburne, M. S., and A. L. Sonenshein. (1976). Behavior of a temperate bacteriophage in differentiating cells of *Bacillus subtilis*. J Virol. 19:26-35.

O'Sullivan, D. J., C. Hill, and T. R. Klaenhammer. (1993). Effect of increasing the copy number of bacteriophage origins of replication, in *trans*, on incoming phage proliferation. Appl. Environ. Microbiol. 59:2449-2456.

Pacheco, S. V., O. G. Gonzalez, and G. L. P. Contreras. (1997). The *lom* gene of bacteriophage λ is involved in *Escherichia coli* K12 adhesion to human buccal epithelial cells. FEMS Microbiol. Lett. 156:129-132.

Parma D.H., M. Snyder, S. Sobolevski, M. Nawroz, E. Brody, and L. Gold. (1992). The rex system of bacteriophage lambda: tolerance and altruistic cell death. Genes Dev. 6:497-510.

Paul, J. H., and C. A. Kellogg. Ecology of bacteriophages in nature. In:C. A. Suttle, J. H. Paul, and C. A. Kellogg (Eds.). *Viral ecology*. Academic Press; 2000; pp.211-247.

Pizza, F., M. Zappone, M. Sana, F. Briani, and G. DehÒ. (1996). Polynucleotide phosphorylase of *Escherichia coli* is required for the establishment of bacteriophage P4 immunity. J. Bacteriol. 178:5513-5521.

Poblet-Icart, M., A. Bordons, and A. Lonvaud-Funel. (1998). Lysogeny of *Oenococcus oeni* (syn. *Leuconostoc oenos*) and study of their induced bacteriophages. Curr. Microbiol. 36:365-369.

Ptashne, M. A genetic switch: phage λ and higher organisms (2nd). Massachusetts. USA.: Cell Press and Blackwell Scientific Publications; 1992.

Pruzzo, C., E. A. Debbia, and G. Satta. (1980). Identification of the major adherence ligand of *Klebsiella pneumonite* in the receptor for coliphage T7 and alteration of *Klebsiella* adherence propertites by lysogenic conversion. Infect Immun 30:562-571.

Ranade, K., and A. R. Poteete. (1993). Superinfection exclusion (*sieB*) genes of bacteriophages P22 and lambda. J. Bacteriol. 175:4712-4718.

Ravin, N. V., A. N. Svarchevsky and G. Dehó. (1999). The anti-immunity system of phage-plasmid N15: identification of the antirepressor gene and its control by a small processed RNA. Mol. Microbiol. 34:980-994.

Raya, R. R., E. G. Kleeman, J. B. Luchansky, and T. R. Klaenhammer. (1989). Characterization of the temperate bacteriophage Φadh and plasmid transduction in *Lactobacillus acidophilus* ADH. Appl. Environ. Microbiol. 55:2206-2213.

Raya, R. R., and T. R. Klaenhammer. (1992). High-frequency plasmid transduction by *Lactobacillus gasseri* bacteriophage Φadh. Appl. Environ. Microbiol. 58:187-193.

Reiter, B. (1949). Lysogenic strains of lactic streptococci. Nature 164:667-668.

Roberts, R., G. E. Allison and N. K. Verma.(2007). Transcription-termination-mediated immunity and its prevention in bacteriophage SfV of *Shigella flexneri*. J Gen Virol. 88:3187-97.

Ruzin, A., J. A. Lindsay, and R. P. Novick. (2001). Molecular genetics of SaPII – a mobile pathogenicity island in *Staphylococcus aureus*. Mol. Microbiol. 41:365-377.

Rybchin, V. N. (1984). Genetics of bacteriophage Φ80 – a review. Gene 27:3-11.

Sabbattini, P., E. Six, S. Zangrossi, F. Briani, D. Ghiotti, and G. Dehó. (1996). Immunity specificity determinants in the P4-like retronphage phi R73. Virology 216:389-396.

Satta, G., C. Pruzzo, E. Debbla, and L. Calegari. (1978). Lysogenic conversion in *Klebsiella pneumoniae*: system which requries active immunity regulation for expression of the conversion phenomenon. J Virol. 28:786-794.

Saye, D. J., O. Ogunseitan, G. S. Sayler, and R. V. Miller. (1987). Potential for transduction of plasmids in a natural freshwater environment: effect of plasmid donor concentration and a natural microbial community on transduction in *Pseudomonas aeruginosa*. Appl. Environ. Microbiol. 53:987-995.

Schinedling, S., D. Parma, and L. Gold. (1987). Wild-type bacteriophage T4 is restricted by the lambda *rex* genes. J. Virol. 61:3790-3794.

Schicklmaier, P., and H. Schmieger. (1995). Frequency of generalized transducing phages in natural isolates of the *Salmonella typhimurium* complex. Appl. Environ. Microbiol. 61:1637-1640.

Schicklmaier, P., E. Moser, T. Wieland, W. Rabsch, and H. Schmieger. (1998). A comparative study on the frequency of prophages among natural isolates of *Salmonella* and *Escherichia coli* with emphasis on generalized transducers. Antonie Van Leeuwenhoek 73:49-54.

Schmidt, C., and H. Schmieger. (1984). Selective transduction of recombinant plasmids with cloned *pac* sites by *Salmonella* phage P22. Mol. Gen Genet 196:123-128.

Schnaitman, C. A., D. Smith, and M. F. De Salsas. (1975). Temperate bacteriophage which causes the production of a new outer membrane protein by *Escherichia coli*. J. Virol. 15:1121-1130.

Scott, J. R., B. W. West, J. L. Laping. (1978). Superinfection immunity and prophage repression in phage P1. Virology 85:587-600.

Shearwin, K. E., A. M. Brumby, and J. B. Egan. (1998). The Tum protein of coliphage 186 is an antirepressor. J. Biol. Chem. 273:5708-5715.

Sjogren, R., R. Neil, D. Rachmilewitz, D. Fritz, J. Newland, D. Sharpnack, C. Colleton, J. Fondacaro, P. Gemski, and E. Boedeker. (1994). Role of Shiga-like toxin I in bacterial enteritis: comparison between isogenic *Escherichia coli* strains induced in rabbits. Gastroenterology 106:306-317.

Snyder, L. (1995). Phage-exclusion enzymes: a bonanza of biochemical and cell biology reagents? Mol Microbiol 15:415-420.

Stanley, E., G. F. Fitzgerald, C. Le Marrec, B. Fayard, and D. van Sinderen. (1997). Sequence analysis and characterization of ΦO1205, a temperate bacteriophage infecting *Streptococcus thermophilus* CNRZ1205. Microbiology 143:3417-3429.

Sternberg, N., and R. Hoess. (1983). The molecular genetics of bacteriophage P1. Ann. Rev. Genet. 17:123-154.

Stetter, K. O. (1977). Evidence for frequent lysogeny in lactobacilli: temperate bacteriophages within the subgenus *Streptobacterium*. J. Virol. 24:685-689.

Strockbine, N.A., L. R. M. Marques, J. W. Newland, S. H. Williams, R. K. Holmes, and A. D. O'Brien. (1986). Two toxin converting phages from Escherichia coli O157:H7 strain 933 encodes antigenically distinct toxins with similar biologic activities. Infect Immun 53:135-140.

Sun, X. and K. J. Heller. (2002). Molecular and functional characterization of a temperate *Streptococcus thermophilus* phage TP-J34 gene (*ltp*) encoding a membrane-bound lipoprotein (edition 1). Aachen, Germany: Shaker Verlag GmbH.

Sun, X, A. Göhler, K. J. Heller, and H. Neve. (2006). The *ltp* gene of temperate *Streptococcus thermophilus* phage TP-J34 confers superinfection exclusion to *Streptococcus thermophilus* and *Lactococcus lactis*. *Virology* 350: 146-157.

Susskind, M. M., A. Wright, and D. Botstein. (1974). Superinfection exclusion by P22 prophage in lysogen of *Salmonella typhimurium*. IV. Genetics and physiology of *sieB* exclusion. Virology 62:367-384.

Tohyama, K., T. Sakurai, and H. Arai. (1971). Transduction by temperate phage PLS-1 in *Lactobacillus salivarius*. Jpn. J. Bacteriol. 26:482-487.

Tohyama, K., T. Sakurai, H. Arai, and A. Oda. (1972). Studies on temperate phages of *Lactobacillus salivarius*. I. Morphological, biological, and serological properties of newly isolated temperate phages of *Lactobacillus salivarius*. Jpn. J. Microbiol. 16:385-395.

Tsubokura, M., K. Otsuki, and Y. Kawaoka. (1982). Lysogenicity and phage typing of Yersinia enterocolitica isolated in Japan. Jpn. J. Vet. Sci. 44:433-438.

Uc-Mass, A., E. J. Loeza, M. de la Garza, G. Guarneros, J. Hernández-Sánchez and L. Kameyama. (2004). An orthologue of the *cor* gene is involved in the exclusion of temperate lambdoid phages. Evidence that Cor inactivates FhuA receptor functions. Virology 329:425-433.

Vaca-Pacheco, S., G. L. Paniagua-Contreras, O. GarcÍa-Gonzålez, M. de la Garza. (1999). The clinically isolated FIZ15 bacteriophage causes lysogenic conversion in *Pseudomonas aeruginosa* PAO1. Curr Microbiol. 38:239-243.

Van de Guchte, M., C. Daly, G. F. Fitzgerald, and E. K. Arendt. (1994). Identification of the putative repressor-encoding gene *cI* of the temperate lactococcal bacteriophage Tuc2009. Gene 144:93-95.

Vander Byl, C. and A. M. Kropinski. (2000). Sequence of the genome of *Salmonella* bacteriophage P22. *J Bacteriol* 182, 6472–6481.

Van der Vijver, J. C. M., M. van ES-Boon, and M. F. Michel. (1972). Lysogenic conversion in *Staphylococcus aureus* to Leucocidin production. J Virol . 10:318-319.

Ventura, M., C. Canchaya, D. Pridmore, B. Berger, and H. Brüssow. (2003). Integration and distribution of *Lactobacillus johnsonii* prophages. J. Bacteriol. 185:4603-4608.

Ventura, M., C. Canchaya, M. Kleerebezem, W. M. de Vos, R. J. Siezen, and H. Brüssow. (2004a). The prophage sequences of *Lactobacillus plantarum* strain WCFS1. Virology 316: 245-255.

Ventura, M., C. Canchaya , R. D. Pridmore and H. Brüssow. (2004b). The prophages of *Lactobacillus johnsonii* NCC 533: comparative genomics and transcription analysis. Virology 320:229-242.

Ventura, M., A. Zomer, C. Canchaya, M. O'Connell-Motherway, O. Kuipers, F. Turroni, A. Ribbera, E. Foroni, U. Wegmann, C. Shearman, M. J. Gasson, G. F. Fitzgerald, J. Kok, and D. van Sinderen. (2007). Comparative analysis of prophage-like elements present in two *Lactococcus lactis* strains. Appl. Environ. Microbiol. 73: 7771-7780.

Ventura, M., C. Canchaya, V. Bernini, E. Altermann, R. Barrangou, S. McGrath, M. J. Claesson, Y. Li, S. Leía, C. D. Walter, R. Zink, E. Neviani, J. Steele, J. Broadbent, T. R. Klaenhammer, G. F. Fitzgerald, P. O'Toole, and D. van Sinderen. (2006). Comparative genomics and transcriptional analysis of prophages identified in the genomes of *Lactobacillus gasseri*, *Lactobacillus salivarius* and *Lactobacillus casei*. Appl. Environ. Microbiol. 72: 3130-3146.

Verhoef, C., R. Benz, A. P. W. Poon, and J. Tommassen. (1987). New pore protein produced in cells lysogenic for *Escherichia coli* phage HK253hrk. Eur. J. Biochem. 164:141-145.

Voelker, L. L., and K. Dybvig. (1998). Characterization of the lysogenic becteriophage MAV1 from *Mycoplasma arthritidis*. J. Bacteriol. 180:5928-5931.

Vostrov, A. A., O. A. Vostrukhina, A. N. Svarchevsky, and V. N. Rybchin. (1996). Proteins responsible for lysogenic conversion caused by coliphages N15 and Φ80 are highly homologous. J. Bacteriol. 178:1484-1486.

Waldor, M. K., and J. J. Mekalanos. (1996). Lysogenic conversion by a filamentous phage encoding cholera toxin. Science 272:1910-1914.

Weigel, P. H., P. T. Englund, K. Murray, and R. W. Old. (1973). The 3'-terminal nucleotide sequences of bacteriophage lambda DNA. Proc Natl Acad Sci USA 70: 1151-1155.

Weisberg, R. A., M. E. Gottesman, R. W. Hendrix, and J. W. Little. (1999). Family values in the age of genomics: comparative analyses of temperate bacteriophage HK022. Annu. Rev. Genet. 33:565-602.

Wollin, R., B. A. D. Stocker, and A. A. Lindberg. (1987). Lysogenic conversion of *Salmonella typhimurium* bacteriophages A3 and A4 consists of O-acetylation of rhamnose of the repeating unit of the O-antigenic polysaccharide chain. J. Bacteriol. 169:1003-1009.

Yarmolinski, M. B., and N. Sternberg. (1988). Bacteriophage P1, In: R. calendar (Ed.), *The bacteriophages* (vol. 1. pp. 291-438). New York, Plenum Press.

Yokokura, T., S. Kodaira, H. Ishiwa, and T. Sakurai. (1974). Lysogeny in lactobacilli. J. Gen. Microbiol. 84:277-284.

Yoshizawa, Y., J. Sakurada, S. Sakurai, K. Machida, I. Kondo, S. Masuda. (2000). An exfoliative toxin A-converting phage isolated from *Staphylococcus aureus* strain ZM. Microbiol Immunol 44:189-191.

Yamamoto, N., M. L. Droffner, S. Yamamoto, P. Gemski, and L. S. Baron. (1985). High frequency transduction by phage hybrids between coliphage Φ80 and *Salmonella* phage P22. J. Gen Virol. 66:1661-1668.

Yu, C. E., and J. J. Ferretti. (1991). Molecular characterization of new group A streptococcal bacteriophages containing the gene for streptococcal erythrogenic toxin A (*speA*). Mol Gen Genet. 231:161-168.

Yu, Y.T.N., and L. Snyder. (1994). Translation elongation factor Tu cleaved by a phage exclusion system. Proc. Natl. Acad. Sci. 91: 802-806.

Żabicka, D., A. Mlynarczyk, B. Windyga, and G. Mlynarczyk. (1993). Phage-related conversion of enterotoxin A, Staphylokinase and beta-toxin in *Staphylococcus aureus*. Acta Microbiologica Polonica 42:235-241.

Zahrt, T. C., G. C. Mora, and S. Maloy. (1994). Inactivation of mismatch repair overcomes the barrier to transduction between *Salmonella typhimurium* and *Salmonella typhi*. J. Bacteriol. 176:1527-1529.

Zinder, N. D., and J. Lederberg. (1952). Genetic exchange in *Salmonella*. J. Bacteriol. 64:679-699.