[Frontiers in Bioscience 14, 1661-1683, January 1, 2009]

Bacteriophages of *Lactobacillus*

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1. ABSTRACT

In this review, we are listing *Lactobacillus* phages that have been reported in peer-reviewed articles published since 1960. Putative phages that are defective or have not been shown to be infectious, such as phage-like particles, are not discussed. Our literature searches led to the identification of 231 *Lactobacillus* phages, 186 of which have been observed by electron microscopy, with 109 belonging to the *Siphoviridae* family, 76 to the *Myoviridae* family, and 1 to the *Podoviridae* family. Model phages infecting *Lb delbrueckii*, *casei*, *rhamnosus*, *plantarum*, and *gasseri* are highlighted, as well as prophages of *Lactobacillus* hosts. To date, nine complete *Lactobacillus* phage genomes are available for comparisons and evolution studies. Features such as phage receptors and endolysins are also reviewed, as well as phage-derived genetic tools. *Lactobacillus* phage research has progressed significantly over the past decade but a thorough understanding of their biology is still lacking. Because of the risks they represent and the knowledge gaps that need to be filled, the outlook for research on *Lactobacillus* phages is bright.

2. INTRODUCTION

Humans began consuming fermented dairy products in the Middle East at about the same time they began domesticating animals. Approximately ten years after the first bacteria was isolated (1878), defined starter cultures were already developed (1). Metchnikoff's studies on the diets of Bulgarian peasants later led to the probiotic hypothesis which fueled research on *Lactobacillus* (2). Factories manufacturing fermented milk products soon started to flourish, as did research on lactic acid bacteria. However, despite this, dairy plants had, and still have, to deal with the deadly enemy of lactic acid bacteria, namely virulent bacteriophages.

2.1. *Lactobacillus* species

Metchnikoff was one of the first researchers to be convinced of the health benefits of consuming yogurt on a regular basis. One hundred years later, it is becoming increasingly clear that lactic acid bacteria (LAB) have some beneficial effects (3). The genus *Lactobacillus* includes 106 validly described species (4). Perhaps because of their origins, people tend to associate *Lactobacillus* species with the dairy industry. However, *Lactobacillus* species are used in many other fermentation processes (5). For example, *Lb. fermentum* is used in sourdough (wheat and rye breads) and soy fermentation processes (6, 7) as well as in traditional sorghum beer by fermenting dolo and pito wort (8), and is a member of the microbial population in fermenting cocoa beans (9), caper berries (10), and cassava (11-14). *Lactobacillus* strains are also found in vegetable and meat fermentations as well as in sewage water and drains. Last, but not least, *Lactobacilli* can be found in human microbiota, including that of the vagina (5, 15).

2.2. *Lactobacillus* phages

One of the main problems encountered in food fermentations is the ubiquitous presence of virulent bacteriophages, which can alter the quality of fermented products or delay manufacturing processes. Even though a plethora of phage control measures have been introduced since the discovery of bacteriophages as the major cause of fermentation failures (16), phages remain a high risk for the dairy industry (17). Since the first *Lactobacillus* phage was isolated from New York City sewage water (18), other phages have been characterized from different species. In 1981, Sozzi *et al.* published the first review on *Lactobacillus* phages, which was limited to morphological information (19). A few years later, Sechaud *et al.* (20) published a review with additional information on genetic and growth characteristics, which was quickly followed by a general review of lactic acid bacteria phages (21). More recently, one book chapter highlighted phages released from vaginal *Lactobacillus* (22) and a second one insisted on the genomic aspects of *Lactobacillus* phages (23). The major aim of this review was to retrieve most of the peer-reviewed papers on *Lactobacillus* phages that were published mainly in English since 1960.

3. *LACTOBACILLUS* PHAGE OVERVIEW

3.1. Habitats

Because of the risk that represents phage infections to dairy fermentation processes, many *Lactobacillus* phages have been isolated from milk products. However, for unknown reasons, *Lactobacillus* phage infections remains relatively low as compared to those affecting lactococci and *Streptococcus thermophilus* (23). Nevertheless, the isolation of *Lb. delbrueckii* subsp. *bulgaricus* phages from yogurt has been repeatedly documented (24-33), as well as phages infecting *Lb. helveticus* from various dairy factories (25, 34). *Lb. acidophilus* phages have been found in yogurts and acidophilus milks in the United States (35), Phages infecting *Lb. plantarum* were also found in dairy products, but also in fermented vegetables and meats, and plant materials such as silage (36-39). *Lb. fermentum* phages have been found in wheat bread sourdough, cheese whey, wheat meal (7), and Chinese yogurt (40), while *Lb. sanfranciscensis* phages were isolated from sourdough (41).

Lactobacilli are also part of the bacterial biota of the vagina (42) and likely play a beneficial role in vaginal health. In fact, phage infections may be involved in creating an ecological imbalance by decreasing the number of *Lactobacillus* cells in bacterial vaginosis, followed by "an increase in the number of anaerobic Gram-negative rods" (15, 22). In addition, chemicals such as activated form of benzo(alpha)pyrene found in cigarettes smoke, may induce the release of prophages from *Lactobacillus spp.* in the vagina (43).

Indeed, lysogeny is relatively frequent in *Lactobacillus* strains (44). The first report of lysogeny involved two strains of *Lb. fermentum* (45). Following this pioneering study, a larger study on 148 *Lactobacillus* strains (15 species) revealed that 27% of them released phages following exposure to mitomycin C (46). Phage-like particles have also been found in *Lb. helveticus*, *Lb. casei*, *Lb. plantarum*, *Lb. brevis*, *Lb. buchneri*, *Lb. fermentum*, and *Lb. acidophilus*. The various sources of *Lactobacillus* phages are reported in Tables 1 to 3.

3.2. Morphology of *Lactobacillus* phages

Because of early advances in staining methods for electron microscopy (47), most *Lactobacillus* phages were first characterized at the morphological level. To date, all of them possess an isomeric capsid and a tail, and thus belong to the *Caudovirales* order. In 2007, Ackermann reported that 190 *Lactobacillus* phages have been observed with an electron microscope, including 120 from the *Siphoviridae* family (long noncontractile tail) and 70 from the *Myoviridae* family (contractile tail) (48). Our own searches retrieved 231 *Lactobacillus* phages, 186 of which have been observed with an electron microscopy, with 109 belonging to the *Siphoviridae* family, 76 to the *Myoviridae* family, and only 1 to the *Podoviridae* family (Tables 1 and 2). Of note, the phages listed in this review were shown to inhibit the growth of a least one *Lactobacillus* strain. Putative phages that are defective or have not been shown to be infectious, such as phage-like particles, are not listed.

3.2.1. *Myoviridae* family

The first *Lactobacillus* myophages were isolated in 1965 and they infected strains of the *fermentum* species (49). Two more *Lb. fermentum* phages with a contractile tail have since been isolated, while the others belong to the *Siphoviridae* family (7, 50, 51). Phages with contractile tails that infect *Lb. casei*, *Lb. brevis*, and *Lb. crispatus* strains have also been observed, but have not been as extensively studied as *Lb. plantarum* myophages LP65 and fri. Interestingly, to our knowledge, all reported *Lb. helveticus* phages belong to the *Myoviridae* family (Table 1) (25, 34, 52), with the possible exception of an inducible but defective *Siphoviridae* phage (phi lh60) (53).

Overall, the tails of *Lactobacillus* myophages range from about 120 to 272 nm (Table 1). A neck is also a common feature of all *Lactobacillus* myophages, while baseplates or double baseplates are found in phages infecting *Lb. plantarum* strains, but are barely seen or not reported in others (data not shown). The icosahedral capsids of these *Lactobacillus* myophages range in diameter from 50 to 115 nm (Table 1), likely reflecting the difference in the size of their genomes.

3.2.2. *Siphoviridae* family

Almost 60% of the known *Lactobacillus* phages belong to the *Siphoviridae* family (48). They have an icosahedral capsid (B1 morphotype) of 40 to 76 nm in diameter (Table 2) and a tail of 116 to 500 nm in length. A few of them have a prolate head (morphotype B2) of 120 to 150 nm long by 40 to 50 nm wide (Table 2). The prolate phages described to date infect *Lb. delbrueckii* subsp. *lactis* (phages JCL1032, 0235) and *Lb. acidophilus* (phi y8), *Lb. fermentum* (064 and 0209) and *Lb. salivarius* (phi223). Interestingly, with one exception, all the *Lb. delbrueckii* phages described to date belong to the *Siphoviridae* family. *Lb. plantarum* siphophage B2 has the longest tail (500 nm) and the largest isometric capsid (110 nm in diameter) of any *Lactobacillus* phage isolated to date (54, 55). *Lb. gasseri* phage phiadh also has a long tail (about 400-460 nm in length (56, 57)), while *Lb. sake* phage PWH2 has a 81-nm diameter capsid (58). *Lb. fermentum* phages isolated from Chinese yogurt have the smallest capsid, surprisingly reported at 40 nm in diameter (40). Other morphological characteristics such as the presence or absence of a collar and a baseplate have not always been reported in the literature for *Lactobacillus* siphophages and are thus not discussed in the present review.

4. *LACTOBACILLUS* PHAGE MODELS

In the following sections, we will summarize the most relevant characteristics of the best-characterized phages that infect industrially relevant *Lactobacillus* species.

4.1. *Lactobacillus delbrueckii* phages

4.1.1. LL-H and others

Lactobacillus delbrueckii phages have been widely studied by the group of Alatossava in Finland. The siphophage LL-H, which infects subsp. *lactis* strains, has become one of the few *Lactobacillus* phages model. Two reviews on this phage have already been published (59, 60).

The Valio Finnish Co-operative Dairies Association isolated this virulent phage in 1972 at a local dairy. It has a 47 ± 2 nm-diameter capsid and a 171 to 180-nm-long non-contractile tail (Table 2). The tail has approximately 45 cross-striations and a double-disk baseplate at the distal end. A 30-nm-long fiber appears to be attached to the lower baseplate structure (61-63). Like several other dairy phages, the lytic cycle of phage LL-H depends on the availability of divalent cations (Ca^{2+} and Mg^{2+}) (64, 65). The genome of LL-H was the first *Lactobacillus* phage genome to be fully sequenced (66-68). It contains 34,659-bp with a G+C content of 47.8% (68). The revised NCBI sequence now points to 51 *orf*s on one strand and three on the other. The genome is organized into four general modules (DNA packaging, morphogenesis, cell lysis and DNA replication (Figure 1). Genes encoding for proteins with related putative functions are grouped together on the genome and are expressed on the same transcripts. Temporal gene expression analysis has revealed an early phase of approximately 20 min during which DNA replication is triggered. This early gene expression is followed by a late phase 30-40 min post-infection, which leads to transcription of genes encoding for phage structural components and cell lysis (68). The genome of LL-H is packaged (in a headful mechanism, *pac*-type) from a concatemer that can fill as many as six capsids (69).

Interestingly, the remnants of an integrase gene and an *attP* site have been found on the LL-H genome (70), which suggest that this virulent phage was derived from a temperate phage (59, 68). In support of this hypothesis, several homologous genes were found in the genome of *Lb. delbrueckii* subsp. *bulgaricus* temperate phage mv4 (66). This latter phage, also called 0448 (26), was one of the first prophages described for this *Lactobacillus* species (26, 28). Phage mv4 can also infect and integrate its genome into the chromosome of *Lb. delbrueckii* subsp. *lactis* LKT (30), a strain sensitive to virulent phage LL-H. Beside phages LL-H and the *pac*-type mv4, other *Lactobacillus delbrueckii* phages belong to the same DNA homology group (named “a”, see Section 7) such as virulent phages LL-K and LL-S (previously called lv (25), or LL55 (71)), as well as the temperate phage lb539 (31). Phage lb539 was isolated with the host strain *Lb. delbrueckii* subsp. *bulgaricus* CRL539 but it can also infect *Lb. lactis* LKT (72).

Lb. delbrueckii phage JCL1032 is also reasonably well characterized, but, to our knowledge its complete genomic sequence is not yet available. Unlike LL-H, this *Siphoviridae* phage has a prolate capsid and packages its DNA via a *cos* site (73). It has been recently shown that JCL1032 can integrate its genome into two different sites in the chromosome of *Lb. delbrueckii* subsp. *lactis* ATCC 15808 (also a host strain for virulent phages LL-H and mv4), even though at low efficiency (73). JCL1032 is thus now considered a temperate phage. Interestingly, short genomic regions of JCL1032 are homologous to sequences found in the genomes of phages LL-K, mv4, and lb539 (73), but not in LL-H or LL-S (74). These observations reinforced the hypothesis that these phages share a common ancestor.

Table 1. *Lactobacillus Myoviridae* phages

#	Phage name	Virulent / Temperate	Host or lysogenic strain	Date	Country of isolation	Sources	Capsid diameter (nm)	Tail length (nm)	Latent period (min)	Burst size	Refs
1	phi7-E1	V	*Lb brevis* 7-E1	2000	USA	Sauerkraut	87±4	149±6			182
2	N-1		*Lb casei*	<1966	Japan		50-99	92-190			19, 183
3	300	V	*Lb casei* 300	<1960	South Africa	Sewage	82	123	220	20	49, 184, 185
4	316	V	*Lb casei* 316	<1960	South Africa	Sewage	82	123-127	220	6	49, 184, 185
5	780	V	*Lb casei* 780	<1963	South Africa	Sewage	82	123-127	220	20	185
6	phiPY4	V	*Lb casei / casei rhamnosus*	<2002	Japan	Silage	94	165			39
7	phi218	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	99	152	160	70	186, 187
8	FYc	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	87	149	170	70	186
9	NHc	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	90	150	140	80	186
10	NTc	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	79.6	131	140	70	186
11	TKc	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	87	151	190	70	186
12	TMc	V	*Lb casei* C1045	<1965	Japan	Sewage/feces	82	143	190	100	49, 186, 187
13	TZc	V	*Lb casei* C1045	<1969	Japan	Sewage/feces	91.5	168	150	150	186
14	SDL	V	*Lb casei* N-S	<1974	Japan	Soil	115	180	155	110	187
15	SG-T		*Lb casei* S-1	<1975	Japan	Environment	50-99	92-190			19, 188
16	356	V	*Lb casei rhamnosus* 356	<1960	South Africa	Sewage	82	127	180	33	49, 184, 185
17	kc12a	T	*Lb crispatus* KC12a	<2001	USA	Vagina	67	260			15, 22
18	kc5a	T	*Lb crispatus* KC5a	<2001	USA	Vagina					15, 22
19	lb2	V	*Lb delbrueckii bulgaricus*	<1974	USA	Cheese	50	175			52, 189
20	11-22		*Lb delbrueckii lactis*				50-99	92-190			19
21	206	V	*Lb fermentum* 206	<1960	South Africa	Sewage	72	138	72	100	49, 184, 185
22	222a	V	*Lb fermentum* 222a	<1960	South Africa	Sewage	69	138	97	30	49, 185
23	315	V	*Lb fermentum* 315	<1960	South Africa	Sewage	72	148	77	60	49, 184, 185
24	514	V	*Lb fermentum* 514	<1960	South Africa	Sewage	72	138	85	88	49, 184, 185
25	FE5-B2	V	*Lb fermentum*/*Lb brevis*	1993	Italy	Sourdough	80	150			190
26	FE5-B3	V	*Lb fermentum*/*Lb brevis*	1993	Italy	Sourdough	80	150			190
27	FE5-B4	V	*Lb fermentum*/*Lb brevis*	1994	Italy	Sourdough	80	170			190
28	FE5-B1	V	*Lb fermentum*/*Lb brevis*	<1995	Italy	Sourdough	83	170	30	100	50
29	FiLH3		*Lb helveticus*								191
30	foto 9	V	*Lb helveticus*	<1977	Italy	Cheese					192
31	hv	V	*Lb helveticus* ATCC15807 CNRZ328, HKT	1955	Finland	Cheese	56	230			25, 146
32	832-B1/ 15807-B1	V	*Lb helveticus* ATCC15807, CNRZ832	1987	France	Cheese	53	140	50	300	33, 34
33	01086	T	*Lb helveticus* CNRZ1086		France	Cheese					34
34	01117	T	*Lb helveticus* CNRZ1117	1987	France	Whey	50-54	160			34
35	0240	T	*Lb helveticus* CNRZ240		France	Cheese	50-54	160			34
36	0241	T	*Lb helveticus* CNRZ241	<1989	France	Cheese	53		60	100	34, 193
37	0243	T	*Lb helveticus* CNRZ243		France	Whey	50-54	160			34
38	0244	T	*Lb helveticus* CNRZ244		France	Whey	50-54	160			34

39	0303	T	*Lb helveticus* CNRZ303	1987	France	Cheese					34
40	032	T	*Lb helveticus* CNRZ32	1987	France	Whey	50-54	160			34
41	328-B1	V	*Lb helveticus* CNRZ328	1987	France	Whey	50-54	160			34
42	034	T	*Lb helveticus* CNRZ34		France	Cheese	56-60	260			34
43	035	T	*Lb helveticus* CNRZ35	1987	France	Whey	50-54	160			34
44	0465	T	*Lb helveticus* CNRZ465		France	Whey	50-54	160			34
45	0465	T	*Lb helveticus* CNRZ465		France	Whey	50-54	160			34
46	NCDO 01244	V	*Lb helveticus* CNRZ493	<1960	Finland	Cheese	56-60	260			34
47	065	T	*Lb helveticus* CNRZ65		France	Cheese	50-54	160			34
48	0762	T	*Lb helveticus* CNRZ762		France	Cheese	50-54	160			34
49	phi1	V	*Lb helveticus* CNRZ892	1975	France	Whey	50-54	160			34
50	phi2	V	*Lb helveticus* CNRZ892	1976	France	Whey	50-54	160			34
51	phi3	V	*Lb helveticus* CNRZ892	1976	France	Whey	50-54	160			34
52	phi4	V	*Lb helveticus* CNRZ892	1976	France	Whey	50-54	160			34
53	phi5	V	*Lb helveticus* CNRZ892	1978	France	Whey	50-54	160			34
54	phi6	V	*Lb helveticus* CNRZ892	1976	France	Whey	50-54	160			34
55	phi8	V	*Lb helveticus* CNRZ892	1973	France	Whey	50-54	160			34
56	phi9	V	*Lb helveticus* CNRZ892	1973	France	Whey	50-54	160			34
57	phi204	V	*Lb helveticus* CNRZ892	1976	France	Whey	50-54	160			34
58	223-B2	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
59	223-B3	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
60	834-B3	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
61	835-B11	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
62	1097-B12	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
63	1097-B14	V	*Lb helveticus* CNRZ892	1987	France	Whey	50-54	160			34
64	hb	V	*Lb helveticus* HB	1974	France	Whey	50	150			25
65	hw	V	*Lb helveticus* HW	1974	France	Whey	50	149			25
66	hw1	V	*Lb helveticus* HWL	1975	France	Whey	51	151			25
67	l112	V	*Lb helveticus* L112			Whey	50-99	92-190			191
68	b2	V	*Lb helveticus* LT3	1963	France	Whey	49	146			34
69	ATCC 25180		*Lb paracasei*				50-99	92-190			19
70	fri	V	*Lb plantarum* A	1979	Canada	Meat	90	190	75	200	36, 37, 54, 107
71	phiPY1	V	*Lb plantarum*/*Lb pentosus*	<2002	Japan	Silage	90	200			39
72	phiPY2	V	*Lb plantarum*/*Lb pentosus*	<2002	Japan	Silage	90	200			39
73	LP65	V	*Lb plantarum* LP65/ WCFS1	1992	Spain	Salami	61±3	193±8	100		106
74	phi22-D10	V	*Lb plantarum*/*Lb pentosus*	2000	USA	Sauerkraut	85±5	271±9			182
75	kc21T	T	*Lb sp.*	<2001	Turkey	Vagina	45	160			15
76	Y20	V	*Lb sp.* LA296	<2002	Korea	Sauerkraut	94±6	118±13	19±2	74±10	38

Many lactic acid bacteria phages have become models to study various aspects of phage biology. *Lactobacillus* phages are no exception. The first group I intron in a siphophage was found in the genome of phage LL-H (75). The intron (ORF168, Figure 1) is located in the *terL* gene that encodes the large terminase subunit (75) and contains an active endonuclease for self-splicing activity. Two similar introns have also been identified in phage JCL1032, one in the *terL* gene and the other in the gene encoding the putative tape measure protein (TMP). In

Table 2. *Lactobacillus Siphoviridae phages*

#	Phage name	Virulent / Temperate	Host or lysogenic strain	Date	Country	Sources	Capsid diameter (nm)	Tail length (nm)	Latent period (min)	Burst size	Refs
1	Ia12	T	*Lb acidophilus* CFM12, VPI11084, NCTC189, ATCC11975	<1990	USA		49	290			194
2	Ia13	T	*Lb acidophilus* CFM13, VPI 11759	<1990	USA			343			194
3	phi y8	T	*Lb acidophilus* Y8	<1996	USA	Yogurt	130x39	300	30	100	35
4	phiPY5	V	*Lb casei*	<2002	Japan	Silage	71	247			39
5	II-2 / II2	T	*Lb casei* 11-2	<1974	Japan		62	182			46
6	C782	T	*Lb casei* 1138	<1974	Japan		50-76	152-182			46
7	II-5	T	*Lb casei* 11-5	<1970	Japan		57	215			195
8	3793	T	*Lb casei* 3793	<1970	Japan		57	216			46, 195
9	PL-1	T	*Lb casei* ATCC334	<1967	Japan	Yakult	54-56	262-282	90-100	32-200	78, 89, 144, 196, 197
10	phiAT3	T	*Lb casei* ATCC393				53	200			88
11	A2	T	*Lb casei* ATCC393	<1994	Spain	Whey	55±3	239±8	140	180-200	79, 80
12	C-5	T	*Lb casei* C-5	<1970	Japan		58	210			195
13	YIT0001	T	*Lb casei* C782	<1974	Japan		48	152			46
14	G	V	*Lb casei* S-1	<1969	Japan	Sewage / feces	59	258	120	80	186
15	G_{10}	V	*Lb casei* S-1	<1969	Japan	Sewage / feces	56	253	150	50	186
16	NHs	V	*Lb casei* S-1	<1969	Japan	Sewage /feces	54	266	90	60	186
17	UZ	V	*Lb casei* S-1	<1969	Japan	Sewage / feces	54	269	140	60	186
18	phiFSV-A	V	*Lb casei* S-1 (ATCC 27139)	<1983	Japan	lactic beverage	57	156			130
19	phiFSV-B	V	*Lb casei* S-1 (ATCC 27139)	<1983	Japan	lactic beverage	57	156			130
20	phiFSV-C	V	*Lb casei* S-1 (ATCC 27139)	<1983	Japan	lactic beverage	57	156			130
21	J-1	V	*Lb casei* S-1 (ATCC 27139)	<1965	Japan	Yakult	55	290	45-110	35-160	77, 144, 198
22	phiFSW	T	*Lb casei* S-1 (ATCC27139*)*	<1982	Japan	Yakult	57±2	156-158			89, 130
23	phi393	T	*Lb casei casei* ATCC393	<1977	Germany	UV induction	50-76	200-290	130		19, 44
24	phi41k	T	*Lb casei pseudoplantarum* Elnaga 41k	<1977	Germany		50-76	200-290	130		19, 44
25	1088	V	*Lb delbrueckii bulgaricus*	<1977	England	Yogurt	56-62	205-215			24
26	ch2	V	*Lb delbrueckii bulgaricus*	1973	USA	Whey	50-52	160-170	40	130	25, 29
27	010	T	*Lb delbrueckii bulgaricus* CNRZ10	1986	France		52	180			199
28	01013^2	T	*Lb delbrueckii bulgaricus* CNRZ1013	1985	France		55	200			199
29	01014^2	T	*Lb delbrueckii bulgaricus* CNRZ1014	1985	France		55	200			199
30	11	V	*Lb delbrueckii bulgaricus* CNRZ1054	1975	France	Sourdough	52	190			199
31	13	V	*Lb delbrueckii bulgaricus* CNRZ1055	1980	France	Sourdough	52	190			199
32	15	V	*Lb delbrueckii bulgaricus* CNRZ1056	<1985	France	Sourdough	55	200			199
33	19	V	*Lb delbrueckii bulgaricus* CNRZ1057	<1985	France	Sourdough	55	200			199

34	112	V	*Lb delbrueckii bulgaricus* CNRZ1058	1980	France	Sourdough	52	190			199
35	01243	V	*Lb delbrueckii bulgaricus* CNRZ1059	<1958	Finland		52	190			199
36	c5h	V	*Lb delbrueckii bulgaricus* CNRZ1065	1985	France		52-55	150-170			199
37	011	T	*Lb delbrueckii bulgaricus* CNRZ11	1986	France		52	190			199
38	c31	V	*Lb delbrueckii bulgaricus* CNRZ449	1983	France		52-55	150-170			199
39	0494	T	*Lb delbrueckii bulgaricus* CNRZ494	1980	France		52	190			199
40	lb539	T	*Lb delbrueckii bulgaricus* CRL539	1997	Argentina	Yogurt, Cheese	47	159			31, 72
41	lb1	V	*Lb delbrueckii bulgaricus* LB1	<1974	USA	Whey	59.4	198			189
42	lb4	V	*Lb delbrueckii bulgaricus* LB4	1973	USA	Whey	53	128			25, 199
43	P1 (lb5)	V	*Lb delbrueckii bulgaricus* LB5		France		50-76	200-290			19, 26
44	lb6		*Lb delbrueckii bulgaricus* LB6				57	205			19, 200
45	c3	V	*Lb delbrueckii bulgaricus* LT1	1963	France	Yogurt	44	116			25
46	mv1 (0449)	T	*Lb delbrueckii bulgaricus* LT1 (0449)	1963	France	Yogurt	50	180			26, 28
47	c5	V	*Lb delbrueckii bulgaricus* LT4	1963	France	Yogurt	55	140-170			25
48	mv4 (0448)	T	*Lb delbrueckii bulgaricus* LT4 (0448)	1963	France	Yogurt	50	180			26, 28
49	y5	V	*Lb delbrueckii bulgaricus* Y5	1973	USA	Whey	52	160-190			25, 52
50	BYM	V	*Lb delbrueckii bulgaricus* YSD V	1997	Argentina	Yogurt	50±2	181±2	<40	23	32, 33
51	A-1	V	*Lb delbrueckii lactis*	<1966	Italy	Whey	55	200			19, 201
52	F1		*Lb delbrueckii lactis*				50-76	200-290			19, 200
53	F6		*Lb delbrueckii lactis*				50-76	200-290			19
54	foto 4	V	*Lb delbrueckii lactis*	<1977	Italy	Cheese					192
55	YAB	V	*Lb delbrueckii lactis* Ab1	1998	Argentina	Yogurt	55±2	251±2	<40	48	32, 33
56	JCL1032	T	*Lb delbrueckii lactis* ATCC15808	<1993	Switzerland	Dairy plant	120x40	270±5			172
57	BaA	V	*Lb delbrueckii lactis* CNRZ1011	<1970	Switzerland		55	200			199, 201
58	BaF1	V	*Lb delbrueckii lactis* CNRZ1012	<1970	Switzerland		55	200			199, 201
59	0235	T	*Lb delbrueckii lactis* CNRZ235	<1986	France		125x50	230-300			20, 199
60	0237[2]	T	*Lb delbrueckii lactis* CNRZ237	<1986	France		55	200			199
61	0252	T	*Lb delbrueckii lactis* CNRZ252	<1986	France		52	250			31, 199
62	lb$_3$	V	*Lb delbrueckii lactis* LB-lb3	2000	Argentina	Yogurt	57±2	273±2	<40	27	33
63	LL-S (LL-55, lv)	V	*Lb delbrueckii lactis* LKT	1953	Finland	Cheese plant	50±2	173±5	120	80-185	69, 25, 202
64	LL-K	V	*Lb delbrueckii* subsp. *lactis* LKT and LL23	1957	Finland	Cheese plant	51±2	171±4			69
65	LL-H	V	*Lb delbrueckii lactis* LL23 and LKT	1972	Finland	Whey	47±2	171-190	70	100-200	60, 61, 69
66	LL-Ku	V	*Lb delbrueckii lactis* LL78	1950	Finland	Cheese plant	49±3	132±6			69
67	phiPYB2 (B3,4,5,7,9,11)	T	*Lb fermentum*	2006	China	Yoghurt	40±1	130±3			40
68	535 (535/222a)	T	*Lb fermentum* 535	<1960	South Africa	Sewage	50	182	85	73	45, 49, 184, 185

69	OBU130	T	*Lb fermentum* BU130	1991	Italy	Whey	56±1	186±4			7
70	BU77-B1	V	*Lb fermentum* BU77	1994	Italy	Sourdough	55	198±2			7, 190
71	017	T	*Lb fermentum* CNRZ17	1999	Italy	Whey	59±1	198±9			7
72	0209	T	*Lb fermentum* CNRZ209	1999	Italy	Beets	119x41	293±5			7
73	Z63-B2	V	*Lb fermentum* CNRZ63	1994	Italy	Sourdough	54±2	169±5			51, 190
74	Z63-B3	V	*Lb fermentum* CNRZ63	1991	France	Whey	57±2	201±4			7
75	Z63-B1	V	*Lb fermentum* CNRZ63	<1995	Italy	Sourdough	60	160	20	10	50
76	064	T	*Lb fermentum* CNRZ64	1999	Italy	Human mouth	118x42	289±8			7
77	OFE129	T	*Lb fermentum* FE129	1991	Italy	Whey 1991	55±1	183±6			7
78	FEM	T	*Lb fermentum* FE3	1986	Italy	Wheat	50±1	201±5			7
79	phiadh	T	*Lb gasseri* ADH (NCK97)	1989	USA	Human	65	398			56, 57
80	Ia11 (19992)	T	*Lb gasseri* ATCC19992	<1974	Japan		60	256			46, 194
81	phi gaY	T	*Lb gasseri* ATCC33323	<2004	Japan		63	168			203
82	MLC-A	V	*Lb paracasei*	2005	Argentina	Ferm. milk	57±2	156±3	30	69±4	145
83	PL-2	T	*Lb paracasei* ATCC27092	<1998	Japan		45	150			204
84	phiPY3	V	*Lb plantarum / pentosus*	<2002	Japan	Silage	73	264			39
85	phiPY6	V	Lb plantarum / pentosus	<2002	Japan	Silage	71	188			39
86	phiPY7	V	*Lb plantarum / pentosus*	<2002	Japan	Silage	71	254			39
87	phiPY8	V	*Lb plantarum / pentosus*	<2002	Japan	Silage	75	235			39
88	phiPY9	V	*Lb plantarum / pentosus*	<2002	Japan	Silage	75	235			39
89	phiPY10	V	*Lb plantarum / pentosus*	<2002	Japan	Silage	75	235			39
90	B2	V	*Lb plantarum* ATCC8014	1971	USA	Sewage sludge	110	500	75	12-14	54, 55
91	phiLP2	T	*Lb plantarum* ATCC8014	<1994	Spain	Whey	52±2	289±10			37
92	phiLP1-A	V	*Lb plantarum* ATCC8014	<1994	Spain	Corn silage	67±3	251±10			37
93	phiLP1-B	V	*Lb plantarum* ATCC8014	<1994	Spain	Corn silage	67±3	251±10			37
94	phig1e	T	*Lb plantarum* G1e	<1996	Japan	Plant	63	260			94, 95
95	SC921	V	*Lb plantarum* LA0280	<1997		Kimchi	60	260			108
96	Y1	V	*Lb plantarum* LA280	<2001	Korea	Kimchi		?[1]	19-46	74-110	38, 108
97	phiJL-1	V	*Lb plantarum* MU45	2003	USA	Cucumber	59	182	35	22	104, 105
98	phi14-C8	V	*Lb plantarum* or *Lb pentosus*	2000	USA	Sauerkraut	70±2	292±10			182
99	PB	V	*Lb plantarum* P219	<1969	Japan	Sewage	76	251	70	40	186
100	PH	V	*Lb plantarum* P219	<1969	Japan	Sewage/feces	76	264	60	40	186
101	phi219	V	*Lb plantarum* P219	<1969	Japan	Sewage/feces	73	252	60	20	186
102	phi786	V	*Lb plantarum* P219	<1969	Japan	Sewage/feces	75	268	60	20	186
103	Lc-Nu	V	*Lb rhamnosus* strain Lc 1/3	<1993	Finland	Cheese plant	50±2	212±3			89
104	PWH2	T	*Lb sake* R4a	<1990	Germany	Sausage	81	270	90	110	58
105	227	T	*Lb salivarius* 227	<1972	Japan	Human feces	54	152			205
106	S171	T	*Lb salivarius* S171	<1970	Japan		63	230			195
107	223	T	*Lb salivarius* S-223	<1972	Japan	Human feces	107x53	176			205
108	S-9	T	*Lb salivarius* S9	<1970	Japan		59	220			195
109	PLS-1 (Sa-S)	T	*Lb salivarius* Sa-S	<1970	Japan		57	230	80	100-130	195, 206
110	EV3	V	*Lb sanfranciscensis* H2A	<2005	Italy	Sourdough	48±4	180±8	60	30	41
111	kc7a	T	*Lb sp.*	<2001	USA	Vagina	45	300			15
112	kc39	T	*Lb sp.*	<2001	USA	Vagina	67	250			15

[1]Phage Y1 tail was not seen or absent and the phage was considered as a Podoviridae by the authors, [2]Phages 237, 1013 and 1014 are probably the same phage according to restriction profiles

Table 3. Other *Lactobacillus* phages

#	Phage name	Virulent / Temperate	Host or lysogenic strain	Date	Country	Source	Refs
1	1138	T	*Lb casei* 1138 (species B)	<1974	Japan		46
2	C47	T	*Lb casei* C47 (species C)	<1974	Japan		46
3	IAM1043	T	*Lb casei* IAM1043 (species C)	<1974	Japan		46
4	NIRD DECP	T	*Lb casei* NIRD DECP (species B)	<1974	Japan		46
5	NIRDR094	T	*Lb casei* NIRDR094 (species C)	<1974	Japan		46
6	Unamed		*Lb casei* NLF	<1958	USA	Human mouth	207
7	phi37	T	*Lb delbrueckii* subsp. *bulgaricus* B06				170
8	phi38	T	*Lb delbrueckii* subsp. *bulgaricus* B29				170
9	P2 (lb9)	V	*Lb delbrueckii* subsp. *bulgaricus* LB9	1978	France		26
10	P3	V	*Lb delbrueckii* subsp. *bulgaricus* LB12	1982	France		26
11	P18	V	*Lb delbrueckii* subsp. *bulgaricus* LB42	1981	France		26
12	P19	V	*Lb delbrueckii* subsp. *bulgaricus* LB42	1981	France		26
13	P20	V	*Lb delbrueckii* subsp. *bulgaricus* LB42	1981	Morocco		26
14	P21	V	*Lb delbrueckii* subsp. *bulgaricus* LB42	1981	France		26
15	P22	V	*Lb delbrueckii* subsp. *bulgaricus* LB35	1981	France		26
16	P23	V	*Lb delbrueckii* subsp. *bulgaricus* LB35	1981	Morocco		26
17	phi50	V	*Lb delbrueckii* subsp. *lactis* LKT				170
18	phi51	V	*Lb delbrueckii* subsp. *lactis* LKT				170
19	phi52	V	*Lb delbrueckii* subsp. *lactis* LKT				170
20	1444	T	*Lb delbrueckii* subsp. *lactis* CNRZ 1444				31
21	Stl1	V	*Lb delbrueckii* subsp. *lactis* C2				170
22	phiy	V	*Lb delbrueckii* subsp. *lactis* LKT				170
23	41	V	*Lb fermentum* 41	<1960	South Africa	Sewage	184
24	69	V	*Lb fermentum* 69	<1960	South Africa	Sewage	184, 185
25	222	V	*Lb fermentum* 222	<1960	South Africa	Sewage	184, 185
26	276	V	*Lb fermentum* 276	<1960	South Africa	Sewage	184, 185
27	517	V	*Lb fermentum* 517	<1960	South Africa	Sewage	184, 185
28	544	T	*Lb fermentum* 544	<1960	South Africa	Sewage	45
29	547	V	*Lb fermentum* 547	<1960	South Africa	Sewage	184, 185
30	phi14	V	*Lb helveticus* LH14				170
31	phi10	V	*Lb helveticus* LH6				170
32	phi11	V	*Lb helveticus* LH6				170
33	phi12	V	*Lb helveticus* LH6				170
34	phi13	V	*Lb helveticus* LH6				170
35	ATCC 15807-B1	V	*Lb helveticus* ATCC15807 (CNRZ328)				146
36	14-F3	V	*Lb paraplantarum* 14-F3	2000	USA	Sauerkraut	182
37	14-H4	V	*Lb paraplantarum* 14-H4	2000	USA	Sauerkraut	182
38	7-C4	V	*Lb plantarum* 7-C4	2000	USA	Sauerkraut	182
39	9-B4	V	*Lb plantarum* 9-B4	2000	USA	Sauerkraut	182
40	14-A4	V	*Lb plantarum* 14-A4	2000	USA	Sauerkraut	182
41	14-E10	V	*Lb plantarum* 14-E10	2000	USA	Sauerkraut	182
42	22-A2	V	*Lb plantarum* 22-A2	2000	USA	Sauerkraut	182
43	22-E2	V	*Lb plantarum* 22-E2	2000	USA	Sauerkraut	182
44	60-E4	V	*Lb plantarum* 60-A4	2000	USA	Sauerkraut	182
45	60-E8	V	*Lb plantarum* 60-E8	2000	USA	Sauerkraut	182

Table 4. *Lactobacillus* phages for which the complete genome is available

Phage	Bacterial strain	Virulent / Temperate	Family	Lenght (bp)	Number of ORFs	DNA packaging system	G+C (%)	GenBank number	Reference(s)
A2	*Lb casei* ATCC393	T	*Siphoviridae*	43,411	61	*cos*	44.8	AJ251789	79-81
phiAT 3	*Lb casei* ATCC393	T	*Siphoviridae*	39,166	53	*cos*	44.6	AY605066	88
kc5a	*Lb crispatus* KC5a	T	*Myoviridae*	38,239	61	ND	36.9	DQ320509	NCBI
LL-H (llh)	*Lb delbrueckii lactis* LL23	V	*Siphoviridae*	34,659	52	*pac*	47.8	EF455602	66-68
phiadh	*Lb gasseri* ADH	T	*Siphoviridae*	43,785	62	*cos*	35.3	AJ131519	57
phig1e	*Lb plantarum* G1e	T	*Siphoviridae*	42,259	62	*pac*	43.1	X98106	95
LP65	*Lb plantarum* LP65	V	*Myoviridae*	131,573	165	ND	37.3	AY682195	106
phiJL-1	*Lb plantarum* MU45	V	*Siphoviridae*	36,677	52	*pac*	39.4	AY236756	105
Lc-Nu	*Lb rhamnosus* strain Lc 1/3	V	*Siphoviridae*	36,466	51	*cos*	44.2	AY131267	92

The reported data are from the references and may differ from the NCBI web site.

JCL1032, both introns belong to the IA1 group, but they do not contain an endonuclease (76). The exact role of these introns in the phage replication cycle remains unclear.

4.2. *Lactobacillus casei* phages

The first phage infecting an *Lb. casei* (or *paracasei*) strain was isolated in Japan in 1965. Phage J-1 caused an abnormal fermentation of the Yakult beverage (fermented from skim milk) (77). Interestingly, the host strain was originally isolated from human feces ("Shirota" strain). Phage PL-1, which infects the same strain, was isolated two years later (78). Both siphophages have a long non-contractile tail (about 290 nm in length for J-1 and about 265 to 280 nm for PL-1) and an icosahedral head (about 55 nm in diameter). PL-1 also has a fiber extending from the distal end of the baseplate.

4.2.1. A2

Phage A2 was isolated in Spain from a whey sample of a failed "Gamonedo" ("Gamoneu" in the Asturiaz dialect), a home-made blue cheese produced using *Lb. casei* 393 (79). The genome of this temperate phage of the *Siphoviridae* family can integrate into the genome of *Lb. casei* ATCC 27092 and is also spontaneously released from *Lb. casei* ATCC 393 (79). Its 42,411-bp genome has a G+C content of 44.8%, 61 *orfs* and cohesive ends (Table 4) (80, 81). Fifty-five *orfs* are oriented in one direction while six are transcribed in the opposite direction (80, 81) (Figure 1). Similar to other phage genomes with cohesive ends, phage A2 is organized in several modules that include in order packaging, head morphogenesis, head-tail joining, tail morphogenesis, lysis, integration, genetic switch region, and replication modules (82).

In the early-transcribed region, two promoters have been identified. While the promoter P_L directs the expression of gene *cI* (lytic cycle repressor), P_R mediates lytic functions and the transcription of the *cro* lysogenic repressor gene (82-84). The *attP* site is located between the lysis and lysogenic modules, close to *orf20*, which codes for the integrase (85). An interesting feature of this phage is the presence of two −1 frameshifts that are leading to the production of the major capsid and tail proteins (gp5 and gp10, respectively) as well as larger versions of these two proteins. The resulting four proteins were shown to be present in the virion structure (86, 87). Moreover, both forms of gp5 are essential for the phage progeny (86). Finally, on a global scale, the genomic comparisons showed similarities between A2 and *S. thermophilus* phage Sfi-21 and *Staphylococcus aureus* phage PVL (80), while its replication module shares homology with the corresponding module of *Lb. gasseri* phage phiadh (81) (Figure 1).

4.2.2. phiAT3

The complete genome sequence of *Lb. casei* temperate phage phiAT3, another *cos*-type siphophage, was reported in 2005 (88). The genome has 53 *orf*s and is organized into five functional clusters (DNA packaging, morphogenesis, lysis, lysogenic/lytic switch, and replication). The genes coding for the integrase, excisionase, and *c*I repressor are encoded on the complementary strand (Figure 1). A comparative analysis revealed that phiAT3 shares homology with *Lb. casei* phage A2, particularly in the replication region. As with phage A2, the *attP* locus of phage phiAT3 is located close to the 3' end of the integrase gene (88). However, the *attB* site of phage phiAT3 is located at the 3'end of the $tRNA^{Arg}$ gene locus in *Lb. casei* ATCC393 (85), while the A2 integration site is in the $tRNA^{Leu}$ gene locus. A distinctive feature of phiAT3 is the presence of an IS element (ISLC3) in a gene that encodes a putative structural protein (ORF14).

4.3. *Lactobacillus rhamnosus* phage Lc-Nu

Virulent phage Lc-Nu, a member of the *Siphoviridae* family, was isolated from a whey sample coming from a Finnish cheese plant (89) and can also infect an industrial probiotic *Lb. rhamnosus* strain (90). Of note, the host was originally identified as *Lb. casei* 1/3 (89, 91). Its 36,466-bp genome sequence has a 44.2% G+C content and 51 *orfs* (Table 4). Despite the absence of an *attP* site and an integrase gene, the genome contains the remnants of a repressor gene, suggesting a temperate origin for this phage (92). Several *Lb. rhamnosus* strains contain a number of phage-related DNA sequences (91, 93), although Lc-Nu cannot integrate in any of them (92). Other noticeable feature in this genome includes three putative methyltransferase genes that may be involved in methylation of newly synthesized DNA, likely to defend against host R/M systems. A signal peptide was also predicted in the endolysin-encoding gene suggesting exportation though a sec-dependent mechanism. Finally, Lc-Nu showed more homology with phiAT3 than with A2, mainly because over 90% identity was found in several structural proteins (Figure 1).

4.4. *Lactobacillus plantarum* phages

4.4.1. phig1e

This temperate pac-*type* siphophage lysogenizes *Lb. plantarum* G1e, which was isolated from plant materials in Japan (94). Its genome was the second *Lactobacillus* phage genome to be sequenced (95). Its 42,259-bp genome has a GC content of 43.1% and contains 62 *orfs*, 54 on the complementary strand and eight on the other strand (Table 4 and Figure 1). Putative functions were attributed to some ORFs. Ntp may be a terminase subunit while Hel is likely a putative DnaB-helicase involved in DNA replication. The major capsid protein (gpG, ORF32) was observed by SDS gel electrophoresis (94) while the major tail protein (gpP, ORF27) was confirmed by immunoelectron microscopy (96). The endolysin (97), holin (98, 99), and integrase proteins (100) were also purified and characterized for this phage. Among other *orfs* of particular interest, the *cpg* gene is expressed through the promoter P_L and encodes a 132-aa protein similar to SOS-related repressors, while *cng*, under the control of the promoter P_R oriented in the opposite direction, encodes a Cro-like repressor (88 aa). Both proteins can bind to operator-like GATAC boxes but in slightly different way (101, 102). As shown by footprint assays, Cng does not completely cover two of the seven boxes identified in the phig1e genome (namely Gb4 and Gb6). This difference could be involved in the lysogenic/lytic decision (103).

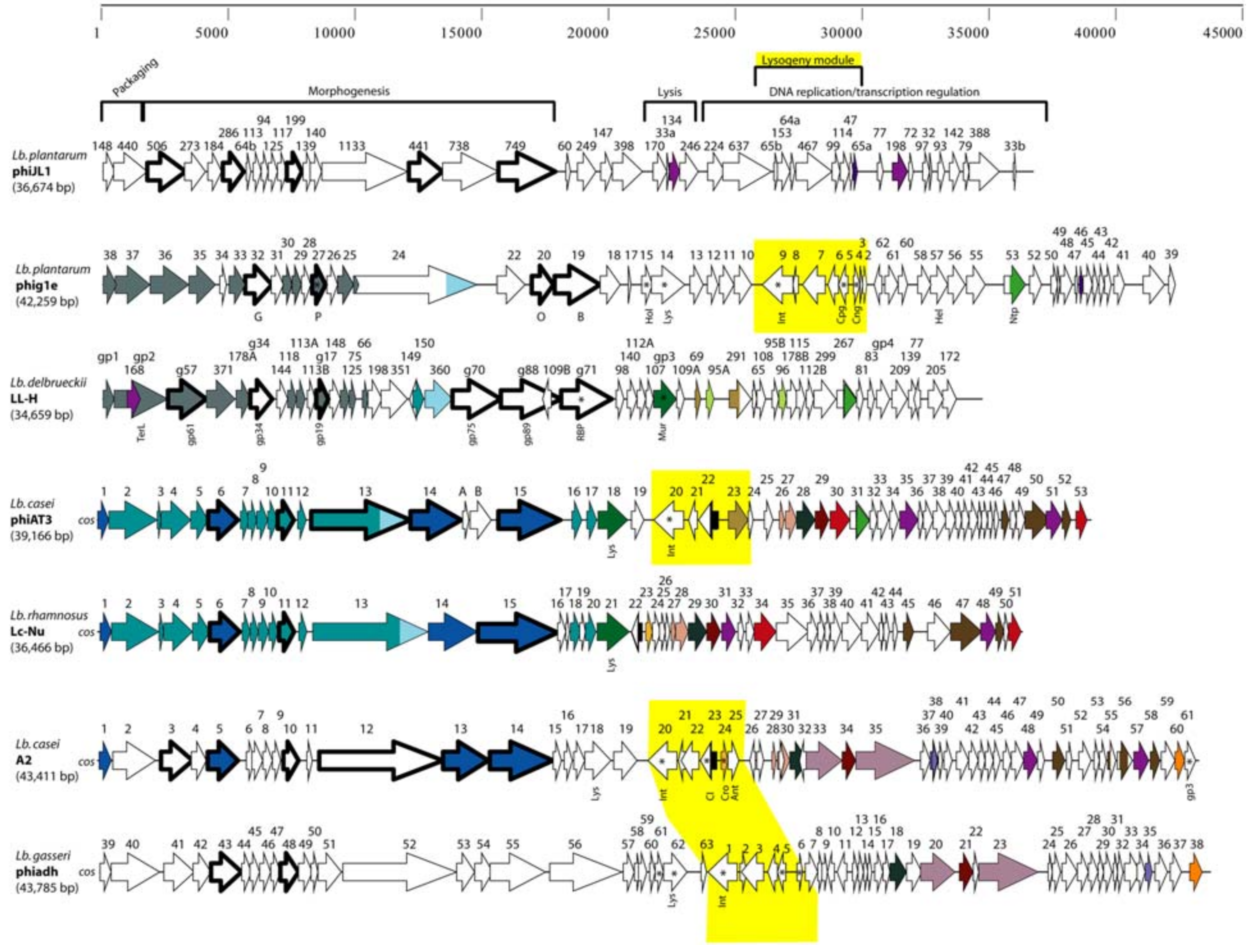

Figure 1. Genome comparison of *Lactobacillus* phages of the *Siphoviridae* family. The ORF numbers correspond to the names in GenBank (see accession numbers in Table 4), except for phig1e where numbers correspond to the locus tag numbers given by NCBI (accession number NC_004305). Arrows with a same color represent deduced proteins sharing more than 30% identity in amino acids. ORFs similar to ORF168 of LL-H (intron in gp2) were found twice in phages A2, Lc-Nu, phiAT3, and phiJL1. The ORFs previously confirmed either by LC/MS-MS or N-terminal sequencing are represented by bold arrows, and stars within the ORF indicate that a biochemical activity was reported. (The references are given through the text). Finally, proposed general modules are indicated above the map.

4.4.2. phiJL-1

The virulent *Lb. plantarum* siphophage phiJL-1 was isolated from a cucumber fermentation factory in the United States (104). It has a 36,700-bp linear, double-stranded DNA genome with a G+C content of 39.36% and 52 *orf*s (105). Seven functional modules have been proposed (DNA replication, transcription regulation, DNA packaging, head morphogenesis, head-tail joining, tail morphogenesis, and cell lysis) (105). On the 52 putative ORFs, five were experimentally determined to be part of the phage structure. Unlike other virulent *Lactobacillus* phages, no remnant of a lysogeny module was detected. Nonetheless, several deduced proteins (endonucleases, helicase, and a minor tail protein) are homologous with those of the *cos*-type temperate *Lb. casei* siphophage A2, and its genome organization is close to *Lactobacillus* phages phig1e (*Lb. plantarum*) and phiadh (*Lb. gasseri*) and to *S. thermophilus* temperate phage Sfi21 (105).

4.4.3. LP65

The virulent phage LP65 was isolated after a discoloration problem in a Spanish salami factory (106). Unlike other *Lactobacillus* phages for which the complete genome sequences are available, phage LP65 is a member of the *Myoviridae* family (Table 4). More specifically, it is included in the SPO1-like group of phages. LP65 has a very large genome of 131,573-bp with a G+C content of 37.3%, and 165 *orfs* (106). The genome was divided into three main regions. Region 1 contains *orf5* to *orf76*, which code for the species-specific proteins ORF5 through ORF52 as well as ORF53 through ORF73, which are involved in DNA replication. Many tRNA are also found upstream from *orf76*. Region 2 contains *orf88* through *orf119*, which code for structural genes. Lastly, region 3 contains *orf120* through *orf163,* which do not correspond to any genes in databases, except for two intron-associated HNH endonucleases. No lysogenic module or remnants were found in the genome. More specifically, phage LP65 was compared to *S. aureus* phage K and *Bacillus subtilis* phage SPO1 because they share the same overall organization. In total, 32 *orfs* of LP65 share sequence identity with K and SP01. They also have the same morphology, except for the fact that LP65 has a longer tail and a tail fiber. Finally. DNA-DNA hybridization assays have also revealed that LP65 shares homology with phage fri, another *Lb. plantarum* myophage. Phage fri was isolated in 1983 from a commercial meat starter culture (36). Unlike most phages isolated from dairy fermentations, phage fri does not significantly impair fermentation as the infected host strain generates enough acid to produce an acceptable final product (107).

4.4.4. Y1

Lb. plantarum phage Y1 was isolated from a sauerkraut fermentation in Korea. To our knowledge, this is the only *Lactobacillus* phage that belongs to the *Podoviridae* family (short tail) (38, 108). Unfortunately, no further details are available.

4.5. *Lactobacillus gasseri* phage phiadh

Phage phiadh was isolated after inducing the strain *Lb. acidophilus* ADH (56), which was later renamed *Lb. gasseri* (109). This *Lactobacillus* strain is a human isolate that produces bacteriocins, is resistant to bile, and adheres to human fetal intestinal cells (110). *Lb. gasseri* NCK102, a prophage-cured derivative, is sensitive to phage phiadh (56).

Altermann *et al.* (1999) reported the complete genome sequence of phage phiadh (57). The genome of phiadh has cohesive ends (*cos*-type) flanking its 62 *orfs* (57), of which many are homologous with *orf*s of *Lb. casei* phage A2 (81) and, to a less extent, *Lb. plantarum* phage phiJL-1 (105). Based on transcriptional studies, the genome of phiadh has been divided into three groups (111). The early-expressed genes (mRNA expressed approximately 10 min after the beginning of infection) included those involved in the lytic/lysogenic module and in DNA replication. The middle-expressed class of transcripts appeared approximately 30 min after the infection and were probably involved in DNA packaging, while the late-expressed group of transcripts were transcribed 40 to 50 min after the infection and include the genes involved in morphogenesis and cell lysis (111). The integration and lysis systems of phiadh have also been characterized (112-114) (see section 6.3).

4.6. *Lactobacillus crispatus* phages

Another phage genome is available on the NCBI website, namely the *Lb. crispatus* temperate myophage kc5a (Table 4). This phage was isolated during a large study on vaginal biota in the United States and Turkey (15). It can be spontaneously released from strain *Lb. crispatus* KC5a by the addition of BPDE, a compound found in cigarette smoke (22). To our knowledge, its genome sequence has not been published. This small phage genome (38,239-bp) for a myophage contains 61 *orfs*, including *orf45,* which encodes a putative tail sheath protein.

5. *LACTOBACILLUS* PROPHAGES

Lysogeny, and even poly-lysogeny, is a common feature in several bacterial species (115) and *Lactobacillus* is no exception. At the time of writing this review, eleven *Lactobacillus* genome sequences were available on the NCBI web site (116). Prophage sequences are usually identified by the presence of an integrase gene as well as a seemingly morphogenesis module (117). Not all the genomes have been analyzed for the presence of prophages, but a few were retrieved from *Lb. johnsonii*, *Lb. plantarum*, *Lb. salivarius* subsp. *salivarius*, *Lb. gasseri*, and *Lb. casei* (118-122). Based on their genome organization, *Lactobacillus* prophages appear to belong to the *Siphoviridae* family, although many await confirmation. For example, two seemingly complete prophages (and one remnant) were detected in the genome of *Lb. johnsonii* NCC533 (123), but none of them can be induced with mitomycin C or UV (119). Prophage remnants as well as a few orfs showing similarities with phage genes have been identified in the genome of *Lb. acidophilus* NCFM (124). Similarly, one prophage remnant has been detected in the genome of *Lb. sakei* 23K, which was isolated from a sausage (125). *Lb. salivarius* UCC118 has two complete prophages (Sal1 and Sal2) as well as two remnants (Sal3 and Sal4) (126). An identical pattern was found in *Lb. plantarum* WCFS1 with two complete prophages (Lp1 and Lp2) and two remnants (R-Lp3 and R-Lp4) (118). Transcripts covering the lysogeny modules of Sal1 and Sal2 (120) and Lp1 (118) have been identified but none for Sal3 genes. Only a few genes of Sal4 are transcribed (120). Interestingly, a 10-kb circular DNA from Sal4 can observed following exposition of *Lb. salivarius* UCC118 to mitomycin C.

As mentioned previously, virulent phages can arise from prophages, particularly when the lysogeny module is inactivated (127). Virulent phages can also acquire new DNA from the gene pool available through prophages (128, 129). Indeed, the genome of the *Lb. casei* phage FSV contains extensive sequences also found in the temperate phage FSW (130, 131). *Lb. delbrueckii* subsp. *lactis* virulent phage LL-H is also related to temperate phage mv4 (66).

5.1. Lysogenic conversion genes

Prophages represent a significant part of the strain-specific DNA in many bacteria (23). Moreover, they carry genes that are expressed under lysogenic state and thus may provide a selective advantage to the host. These genes are often referred to lysogenic conversion genes when their presence change or provide a new characteristic/advantage to the host, but are not usually related to phage function. Candidates for lysogenic conversion genes have been found in the prophages of *Lb. johnsonii* NCC533 (119) and *Lb. plantarum*, both isolated from human oral cavity (132, 133), as well as in *Lb. casei* phage A2 and others. Those candidates were localized close to the prophage genome ends (121) either in the lysis or the lysogeny modules (118). For example, phage A2 genes possibly involved in lysogenic conversion are *orf19* (located between the lysin and the integrase genes) and *orf22* (upstream from the integrase gene) (Figure 1). The *orf22* showed homology to a gene found in a pathogenic island of *Clostridium difficile* while the ORF19 presents similarity with a putative protein found in *Listeria monocytogenes*. In *Lb. plantarum* phage phig1e, four genes have been hypothesised to be lysogenic conversion genes (named 10 to 13 ; see Figure 1), mainly due to their localization and according with alignments with other prophages form various species (122). Further analyses and studies are still needed to determine if these genes indeed contribute to the fitness of *Lactobacillus* hosts.

6. OTHER CHARACTERISTICS OF *LACTOBACILLUS* PHAGES

6.1. Comparative genome analyses

As indicated previously, others have already reviewed in great details the genomic aspects of *Lactobacillus* phages (23). Comparative genome analyses have mainly focused on *Lactobacillus* siphophages because the genomes of only two *Lactobacillus* myophages are currently available (23). Here, we are providing an updated figure representing the comparative analyses of siphophage genomes (Figure 1). Considerable genetic polymorphism is found in the relatively small *Lactobacillus* phage genomes, which is in agreement with the diversity also found in their host genomes. However, the organization is similar with the general modules found in the same order in the genomes, including the lysogeny module when present (Figure 1). Interestingly, similarities are also found between *cos*- and *pac*-type *Lactobacillus* phages. Nonetheless, *cos*-type phages (*Lb. casei* phiAT3, *Lb. rhamnosus* Lc-Nu, *Lb. casei* A2, *Lb. gasseri* phiadh) are more related to each other than *pac*-type phages (*Lb. plantarum* phiJL-1, *Lb. plantarum* phig1e, *Lb. delbruekii* LL-H) (Figure 1). In particular, the morphogenesis module of *Lb. rhamnosus* phage Lc-Nu is highly similar to the one of *Lb. casei* phage phiAT3. Similarly, *Lb. casei* phage A2 is also related to *Lb. casei* phiAT3, suggesting a common ancestor. On the other hand, the two *Lb. plantarum* phage genomes suggest the presence of at least two lineages of siphophages in this species (Figure 1). The analyses of additional *Lactobacillus* phage genomes is certainly warranted to obtain in much better comprehensive dataset, which will eventually lead to a better understanding of their origin and evolution.

6.2. Identification of receptors

The first step in the tailed-phage infection process is the adsorption of the phage, through the receptor binding protein (RBP) located at the distal part of its tail, to the host cell surface receptor. The host recognition process is one of the most important in phage biology because mutation in either the phage RBP or the host receptors will prevent phage infection. It is thus not surprising that *Lactobacillus* phage adsorption and host-recognition processes have been investigated. The RBP protein of the virulent siphophage LL-H, which infects *Lb. delbrueckii* subsp. *lactis* strains, is encoded by gene *g71*. Amino acid changes in the C-terminal end of RBP affect adsorption. Moreover, most of the residues in the C-terminus of the protein are conserved in ORF474 of phage JCL1032, which infects the same host strain as phage LL-H. Since the N-terminal domain of the two proteins is different, the C-terminus is likely the protein interaction domain (134). The crystal structures of a few *Lactococcus lactis* phage RBPs have been solved and have confirmed that the C-terminal part (head domain) is responsible for host recognition (135-138).

The phage LL-H receptor on the host surface has also been investigated. Purified lipoteichoic acid (LTA) prevented the adsorption of phage LL-H to *Lb. delbrueckii* host cells, indicating that LTA is a component of the phage receptor (139). The degree of dealanylation of LTA also appears to play a role in phage adsorption (140). Interestingly, another study has suggested that *Lb. delbrueckii* subsp. *lactis* strains possess three types of phage receptors, two of which are recognized by phage LL-H and one by phage JCL1032 (134). LTA is not a component of *Lb. delbrueckii* phage LL-Ku and c5 receptors (140).

Rhamnose residues of the polysaccharide on the cell surface of *Lb. casei* have also been linked to the adsorption of phages PL-1 and J-1 (141-143). The virulent *Lb. casei* phage MLC-A, which has the same host range as J-1 and PL-1, likely uses the same receptor (144, 145), while *Lb. delbrueckii* phages YAB, lb3, and BYM attach to a cell surface polysaccharide-peptidoglycan complex (33). On the other hand, rhamnose (and several other sugars) have no effect on the adsorption of *Lb. helveticus* phages hv and ATCC 15807-B1 (146). The S-layer protein of various *Lb. helveticus* strains may also act as a receptor for phage adsorption (33, 147). Clearly, phage receptors are highly diverse in *Lactobacillus* and need to be studied on a case-by-case to better comprehend each phage-host system and to develop phage-resistant strains.

6.3. Endolysin studies

Cell lysis is another critical step in phage biology as it indicates the successful completion of the phage infection process. In most phages, the lytic process depends on the combined action of two proteins, namely the holin and the endolysin. The holin creates holes in the cell membrane to allow access of the endolysin to its substrate, the cell wall. One possible exception in *Lactobacillus* may be the endolysin of *Lb. plantarum* phig1e which possesses a signal peptide, suggesting secretion through a SecA-dependent mechanism (97, 148). Of the four main classes of bacterial endolysins, muramidase-like (also called lysozyme) and amidase-like endolysins have been found in *Lactobacillus* phages (149). While muramidase-like endolysins target the N-acetylmuramic acid backbone of the cell wall, amidase-like enzymes break down the peptidoglycan by acting on the amide bond linking a sugar to a peptide (148, 150). *Lactobacillus* phages LL-H, phiadh, and mv1 possess a muramidase-like endolysin (113, 151, 152), while phage PL-1 has an amidase-like endolysin (N-acetylmuramoyl-L-alanine amidase) (153). The endolysins of these phages have been expressed in *E. coli*, purified, and briefly characterized. Interestingly, the LL-H phage Mur protein has a broad activity as it hydrolyzes the cell walls of various *Lactobacillus* species and *Pediococcus damnosus* (151). Similarly, the endolysins of *Lb. helveticus* phage phi0303 (154) and *Lb. gasseri* phage phigaY are active against the cell walls of many Gram-positive bacteria (155). These cell-wall degrading enzymes have generally two domains. For example, the catalytic domain of phigaY endolysin is at the N-terminal, while the C-terminal domain binds to various Gram-positive bacteria (155). The catalytic domains of the LL-H and mv1 endolysin are also located at the N-terminal (151, 152). Phage endolysins are of particular interest for a better knowledge of the phage biology but also for biotechnological applications. Endolysin can be used to control flavor development (59, 156), to restrain various microflora (108) or used in molecular biology studies (157, 158).

6.4. Genetic tools developed from *Lactobacillus* phages

A number of genetic tools have been developed from *Lactobacillus* phages (reviewed in (159)). For example, the *int* gene from *Lb. delbrueckii* subsp. *bulgaricus* phage mv4 and its *attP* have been used to construct an integration vector (160). Interestingly, this vector can integrate into a conserved tRNA^{Ser} gene found in the chromosome of *Lb. delbrueckii* subsp. *bulgaricus* strains as well as in *Lb. plantarum*, *Lb. casei*, *Lactococcus lactis* subsp. *cremoris*, *Enterococcus faecalis,* and *Streptococcus pneumoniae* strains (161). The characterization of the integrase gene and the *attP* site of the temperate *Lb. gasseri* phage phiadh (112) has also led to the construction of a site-specific integration vector (162-164). Similar studies have been performed with the integrases of *Lb. casei* phages A2 (85) and phiAT3, which were integrated into the chromosome of *Lb. rhamnosus* strains (88). Expression vectors have also been designed using *Lactobacillus* phage promoter and repressor (165, 166).

The analysis of the DNA replication module of *Lb. casei* temperate phage A2 DNA led to the construction of a vector containing the replication origin (*ori*) of A2. The presence of the vector into *Lb. casei* strains confers partial resistance to phage A2 (167). Origin-derived phage-encoded resistance (PER) is a system whereby multi-copies of phage *ori* sequences are supplied *in trans* on a plasmid carried by the host (168). Upon phage infection, the plasmid-based phage *ori* presumably segregates phage-encoded replication factors, thereby limiting phage development while leading to an increased plasmid replication. The same research group also constructed a food-grade *Lb. casei* strain resistant to phage A2 through the development of a "delivery and clearing" system using the A2 integrase, the *attP* site, and a cI-like repressor combined with a second vector containing a beta-resolvase gene to remove undesired DNA on the first vector such as an antibiotic resistance gene (169).

7. TOWARDS A SPECIFIC CLASSIFICATION SCHEME FOR *LACTOBACILLUS* PHAGES

Prior to the availability of genomic sequences, the classification of *Lactobacillus* phages was based mainly on morphological observations and DNA homology. Phages infecting *Lb. delbrueckii* strains were the first to be catalogued in the mid-1980s (26, 170). Phages classified within group "a" included phages LL-H, mv4, and LL-S (LL-55 or lv) because they shared homology in the morphogenesis and cell lysis genes as well as two major structural proteins (35 and 19 kDa). Group "b" included three virulent phages (lb4, c3, and c5) with two homologous structural proteins (23 and 31 kDa) (171), while *Lb. delbrueckii* group "c" included siphophages JCL1032 and 0235, which had a prolate capsid as compared to an isometric capsid for phages of groups "a" and "b". However, Forsman (1993) suggested that phage JCL1032 be classified in a different group because it still shared DNA homology with several phages from groups "a" and "b" (172). Finally, group "d" included only phage 0252, which possess a longer tail (20).

By the year 2000, complete genome sequences were available for five *Lactobacillus* siphophages. While they do not share significant DNA homology, the organization of their structural gene module was well conserved (173). This observation led to a proposed classification scheme for *Siphoviridae* phages (122) in which *Lb. casei* phage A2 and *Lb. gasseri* phage phiadh were assigned to the Sfi-21 supergroup whereas *Lb. delbrueckii* phages LL-H and mv4 as well as *Lb. plantarum* phage phig1e were classified within the Sfi11-like group (122). The genome organization of *Lb. rhamnosus* phage Lc-Nu was later shown to be similar to that of Sfi21-like phages (92).

This latter classification scheme has the merit of grouping several phages infecting distinct bacterial genera. For example, most Sfi-21-like phages possess a genome with cohesive ends and a characteristic capsid module, which includes a protease. Phages of the Sfi-11 group package their DNA via a headful mechanism and possess an additional gene coding for a capsid protein as well as a distinct scaffolding protein (122). Another proposal for phage classification was put forward and gave rise to the proteomic tree (174). This classification scheme also goes beyond host boundaries and is mainly based on the deduced proteome without taking into account the morphological characteristics. Finally, a classification system based on the presence of specific modules in phage genomes was also proposed (174). One particular phage could belong to several groups according to their module composition. A similar reticulate approach was also presented recently (175).

The mosaic nature of tailed phage genomes appear to be the main characteristic highlighted by many comparative studies (176). This mosaicism is likely reflecting lateral transfers that occurred (and are still occurring) between different phages (121). The polythetic nature of phages is obviously a problem when desiring to adopt a new classification system for phages (177). Another problem appears with the desire of grouping phages for which there is no possibility to get any morphological and host data, such as those from metagenomic studies (178). Finally, it is recognized that phylogenetic trees can be distorted by uneven representation. Dairy phages in general and *Lactobacillus* phages in particular are often under represented in these schemes. Therefore, it is our opinion that, at this time, such tree is currently not meaningful and certainly not practical. Much more data are needed before settling on a new phage classification. Similarly, the lack of standardized information on most *Lactobacillus* phages suggests that it is risky exercise to attempt to classify them by singling out one method.

8. OUTLOOK

Lactobacillus phage research has progressed significantly over the past decade. However, our knowledge of *Lactobacillus* phage biology is limited and certainly lags behind that of other phages. Phages with similar morphologies have been isolated from a wide variety of *Lactobacillus* species. From a practical standpoint, grouping *Lactobacillus* phages based on their host range and morphology is arguably the easiest way to currently classify them. Unlike phages from other lactic acid bacterial species such as *Lactococcus lactis* (179) and *Streptococcus thermophilus* (180), *Lactobacillus* phages are much more diverse, which is likely a reflection of the relatively high number of species in the *Lactobacillus* genus. It is valuable to observe, though, a relatively well-conserved genome organization (Figure 1).

Because of this diversity, the current gaps in our understanding of these phages and their ubiquity, the outlook for research on *Lactobacillus* phages is bright. It is likely that phage-associated fermentation/production difficulties will grow in the future, especially with the increased production of probiotic *Lactobacillus* strains. The on-going studied of the human *Lactobacillus* biota may also lead to the isolation of new phages. It remains to be seen which groups of phages will emerge with these new applications. A thorough characterization of these phages will be needed to shed light on their origins, evolution, and relationships with other phages (181).

9. ACKNOWLEDGEMENTS

We are very grateful to H.W. Ackermann and T. Alatossava for providing numerous articles on *Lactobacillus* phages. We also would like to thank Simon Labrie, Helene Deveau, and Genevieve Rousseau for their help and comments on the genomic analyses. This work was funded by the Natural Sciences and Engineering Research Council of Canada.

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Key Words *Lactobacillus sp.*, Bacteriophage, Prophage, *Lactococcus*, *Streptococcus*, Genome, Review

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