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Listeria phages
Genomes, evolution, and application

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Listeria is an important foodborne pathogen and the causative agent of Listeriosis, a potentially fatal infection. Several hundred *Listeria* bacteriophages have been described over the past decades, but only few have actually been characterized in some detail, and genome sequences are available for less than twenty of them. We here present an overview of what is currently known about *Listeria* phage genomics, their role in host evolution and pathogenicity, and their various applications in biotechnology and diagnostics.

Listeria are Gram-positive, rod-shaped members of the *Firmicutes*, currently divided into nine species, namely *L. innocua*, *L. ivanovii*, *L. monocytogenes*, *L. grayi*, *L. seeligeri*, *L. welshimieri*, *L. marthii*, *L. rocourtiae*, and *L. fleischmannii*.[1-5] Only *L. monocytogenes* are human pathogens, causing the rare, but life-threatening disease Listeriosis, which mainly affects young, old, pregnant and immunocompromized individuals, and is associated with mortality rates of up to 30%. The disease can manifest as septicemia, meningitis or meningoencephalitis; or result in stillbirth or abortion in pregnant women.[5] *Listeria* is ubiquitously found in the environment, and transmission usually occurs via contaminated food and water. The organism can grow at low temperatures and in high-salt environments, and is also known to readily form biofilms.[6,7] These properties render it a high-risk organism for food producers.

Listeria Bacteriophages

Bacteriophages are the natural enemies of bacteria. Recently, they have again moved into the focus of research interest, with respect to biocontrol of pathogenic bacteria as well as offerering tools for novel and effective separation technologies and diagnostics. In fact, bacteriophages present ideally suited means to control and detect *Listeria* cells in foods. *Listeria* phages can be isolated with relative ease from various environmental sources by the soft agar overlay method.[8] First reports on bacteriophages specific for *Listeria monocytogenes* date back to the 1940s and 1960s.[9-12]

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To date, more than 500 *Listeria* phages have been isolated and characterized to a certain extent, most of them in the course of phage typing studies. All *Listeria*-specific bacteriophages found to date are members of the *Caudovirales*, featuring the long, non-contractile tails of the *Siphoviridae* family, or the complex contractile tail machines of the *Myoviridae* family. Interestingly, no podoviruses have ever been isolated for *Listeria* spp. The reason for this is unknown, but might be associated with the structure of the *Listeria* cell; yet, morphological diversity in the *Listeria* phages seems limited. The *Siphoviridae* are currently grouped into six species, depending on tail length. The presence of intact or cryptic prophages has been confirmed in many *Listeria* strains, e.g., phage A118 in *L. monocytogenes* WSLC 1118 or PSA in *L. monocytogenes* ScottA.[2,13-15] Bacteriophages have been found in all major *Listeria* species and serovars, except the unusual *L. grayii*, the newly proposed species *L. rocourtii* and *L. marthii,* as well as in serovar 3 strains. In general, serovar 3 strains are highly refractory to phage infection, whereas serovar 4 strains are very sensitive. Interestingly, strains of both serovars 4b and 4c also seem to lack any intact prophage genome.[16] Prophage absence in serovar 4 seems to be attributable to differences in teichoic acid composition.[16] Although being very sensitive to phage infection, also no prophages have been found in strains of *L. ivanovii* subsp *ivanovii*.[17]

Temperate *Listeria* phages feature a generally rather limited host range, partially due to homoimmunity, since the majority of *Listeria* strains carries prophages or prophage remnants. This is in contrast to the broad host range *Listeria Myoviridae,* which can be grouped in two clusters, the A511-like phages of the newly formed subfamily *Spounavirinae*, and the B054 and 01761-like phages, both of which feature a slightly larger genome (48.5 kb) then the *Siphoviridae* members.

Table 1 presents an overview of the best characterized *Listeria* bacteriophages. Many more have been isolated but are poorly characterized (if at all), including 25 phages from the international typing set, seven "experimental" phages,[18] fourty-two previously not described phages used by Hodgson during a transduction study[19] and 114 *Listeria* phages from silage of two dairy farms in New York State, USA.[20] Vongkamjan et al. report a host-range for all phages. Serovar groups 4 and 1/2 were found to be particularly susceptible to phage infection, while the other *Listeria* serovars were lysed to a varying degree. No phages have been reported for Serovar 3 strains, confirming earlier observations. Surprisingly, a very large proportion of the isolated phages feature genome sizes between 57–68 kb, in range of the 67 kb

Table 1. Synopsis of characterized *Listeria* bacteriophages

Phage name	Family (EM-confirmed)	Dimensions (head × tail)	Genome size (bp)	Lifestyle (host name)	Host serovar	Remarks	Refs.
01761	*Myoviridae*	66 × 270	48306	Temperate (PS1803)	1/2		84, unpublished data
11355C	*Siphoviridae*	63 × 320			1/2		84
11711A	*Siphoviridae*	63 × 320			1/2		84
02971A	*Siphoviridae*	64 × 307			1/2		84
02971C	*Siphoviridae*	64 × 306			1/2		84
90666	*Siphoviridae*	60 × 311			4		19, 84
907515	*Siphoviridae*	60 × 295			1/2		84
10072	*Siphoviridae*	61 × 292			1/2		84
12981	*Siphoviridae*	63 × 302			1/2		84
13441	*Siphoviridae*	61 × 315			1/2		84
00241	*Siphoviridae*	64 × 300			1/2		84
00611	*Siphoviridae*	63 × 301			1/2		84
90861	*Siphoviridae*	61 × 173			4		19, 84
910716	*Siphoviridae*	60 × 179			4		19, 84
93253	*Siphoviridae*	61 × 171			4		19, 84
A005		62 × 280			1/2		84
A006	*Siphoviridae*	62 × 280	38124	Temperate (WSLC 1006)	1/2	Transducing	19, 30, 31, 33
A020	*Siphoviridae*	63 × 248		Temperate (WSLC 1020)	4, 5		30, 50
A118	*Siphoviridae*	61 × 298	40834	Temperate (WSLC 1118)	1/2	Transducing	13, 19, 30
A500	*Siphoviridae*	62 × 274	38867	Temperate	4	ATCC 23074-Bl, transducing	19, 30, 31, 33, 50
A502	*Siphoviridae*	62 × 302	~39000	Temperate	1/2	Isolation from sewage, transducing	19, 30–32, 50
A511	*Myoviridae*	87 × 199	137619[a]	Virulent	1/2, 4, 5, 6	Isolation from sewage	19, 27, 30, 32, 50
A640	*Siphoviridae*	62 × 305		Temperate	4		19, 84
B012	*Siphoviridae*	61 × 286	41464	Temperate (WSLC 2012)	5, 6		30–32, 50
B021	*Siphoviridae*	61 × 302		Temperate	4		19, 84
B024	*Siphoviridae*	59 × 239	~37000	Temperate (WSLC 2024)	5, 6		30–32, 50
B025	*Siphoviridae*	63 × 252	42653	Temperate (WSLC 2025)	5, 6		30–33, 50
B035	*Siphoviridae*	63 × 294	38881	Temperate (WSLC 2035)	5, 6		30–32, 50
B051 (4211)[c]	*Siphoviridae*	62 × 245		Temperate (WSLC 2051)	5, 6		30, 32
B053	*Siphoviridae*	59 × 244	43471	Temperate (WSLC 2053)	5, 6		30–32, unpublished data
B054 (4286)[c]	*Myoviridae*	64 × 244	48172	Temperate (WSLC 2054)	5, 6		30–33
B055 (4295)[c]	*Siphoviridae*	62 × 242		Temperate (WSLC 2055)	5, 6		30, 32
B056 (5337)[c]	*Siphoviridae*	59 × 285	~35000	Temperate (WSLC 2056)	5, 6		30–32
B101	*Siphoviridae*	61 × 280	40862	Temperate (WSLC 2101)	5, 6		30–32, unpublished data
B110	*Siphoviridae*	57 × 288	39390	Temperate (WSLC 2110)	4, 6		30–32, unpublished data

Table 1. Synopsis of characterized *Listeria* bacteriophages (continued)

Phage name	Family (EM-confirmed)	Dimensions (head × tail)	Genome size (bp)	Lifestyle (host name)	Host serovar	Remarks	Refs.
B545	*Siphoviridae*	62 × 258		Temperate (WSLC 2545)	5, 6		30, 32
B620		61 × 299					84
B640	*Siphoviridae*	62 × 305		Temperate (WSLC 2640)	4	Transducing	19, 84
B653	*Siphoviridae*	61 × 260	37943	Temperate (WSLC 2653)	1/2, 4, 5, 6		30, 32, unpublished data
C707	*Siphoviridae*	60 × 243			5	Isolation from sewage	30, 32, 50
D441	*Siphoviridae*	63 × 247	~37000	Temperate (WSLC 4441)	4, 5		30–32
P35	*Siphoviridae*	58 × 110	35822	Virulent	1/2	Transduction experimentally proven	19, 33
P40	*Siphoviridae*	56 × 108	35638	Virulent	1/2, 4, 5, 6		33
P70	*Siphoviridae*	(128 × 57) × 141	67170	Virulent	1/2, 4, 5, 6		21
P100	*Myoviridae*	90 × 198	131384[b]		1/2, 4, 5, 6		26, 27
PSA	*Siphoviridae*	61 × 180	37618	Temperate	4		14, 19, 84

[a]Including terminal redundancy of 3125 bp. [b]Unit genome size, probably features a 6 kb terminal redundancy. [c]Numbers in parentheses are designations by Rocourt et al.[85]

found for the recently reported novel phage species P70, featuring an elongated head morphology.[20,21] This would suggest that the novel phage species is abundant in environmental samples, possibly possessing a selection advantage over their smaller genome siphovirus relatives. A similar, although smaller-scale study reported the isolation of 12 *Listeria* phages from a Turkey processing plant in the United States.[22] Arachchi et al. reported isolation of three phages active against *L. monocytogenes* from seafood[23]; Zhang et al. described phage FWLLm3, of which only the endolysin sequence is known[24]; and Anany et al. introduced three new *Listeria* phages (LmoM-AG8, 13, and 20).[25] The LmoM-AG20 genome is very similar to A511 and P100 (H. Anany, personal communication). Many more preliminary descriptions of *Listeria* phages and their isolation exist, highlighting their ubiquitous distribution and underlining the tremendous interest in these bacterial viruses.

Listeria Phage Genomics and Implications for Phage Evolution

Almost all *Listeria* phage genomes described today feature sizes between 30 and 65 kb, with only a handful of larger genomes (125–140 kb), featured by the broad-host-range myoviruses.[26-28] All *Listeria* bacteriophage genomes are composed of dsDNA and are organized in a modular fashion, usually comprising a module which encodes structural proteins, a module of early genes, encoding functions for DNA recombination, replication and repair, a lysis cassette featuring a holin and an endolysin gene and, in case of temperate phages, a lysogeny control region. Open reading frames of the latter are usually transcribed in opposite direction compared with the other genes. As it is the case with many other sequenced bacteriophage genomes, a large fraction of open reading frames encode products with weak or no homology to any other proteins. Approximately 50% of predicted phage proteins have no known function, and have been postulated to assume roles in host takeover, nucleotide metabolism, and transcription regulation.

Two large myoviruses infecting *Listeria* cells have been characterized in molecular detail, A511 and P100. Their genomes are very similar, with P100 featuring a 3 kb smaller unit genome, but a larger terminal redundancy of approximately 6 kb, compared with the 3.1 kb termini of A511.[27] P100 and A511 are morphologically indistinguishable, which is also reflected by a highly similar genome organization and strong sequence homologies among structural proteins. Both phages feature a baseplate structure which during tail contraction undergoes a structural rearrangement into a double-ringed organelle, a hallmark of the Twort-like phages of the *Spounavirinae* subfamily.[28] Both short and long tail fibers are present and involved in host recognition and adsorption. The A511 baseplate is among the most complex contractile injection systems known in nature,[29] and current research in our lab aims to elucidate the fine details of this superstructure. The major components of the adsorption apparatus feature strong sequence and secondary structure homologies to other phages of the *Spounavirinae* (Habann et al., submitted). Interestingly, two temperate myoviruses of *Listeria* have been described, namely B054[30-33] and 01761.[34] Both feature genes responsible for host genome integration and maintenance of a temperate lifestyle (ref. 33 and unpublished data).

Almost all known *Listeria* phages belong to the *Siphoviridae,* while no members of the short-tailed *Podoviridae* have been found or described. Most *Listeria* phages are classical lambda-type

siphoviruses, such as A118 or PSA, which feature a long, flexible tail and an isometric head. Typical genome sizes range from 35 to 40 kb. All members of this type of phages are temperate, i.e., they encode a lysogeny control region, including an integrase gene in their genome and host strains can be lysogenized, or the phage has been be induced from lysogenic carrier strains.[13,14,33,35] Still, morphology and genomes can be strikingly different even among the siphoviruses. The morphologically similar, but distinct phages P35 and P40 feature a lytic lifestyle and have a relatively broad host range among specific serovar groups. We also found that they do not possess the highly complex adsorption apparatus of myoviruses, their tail is not flexible but also not contractile, and their genomes lack genes associated with in lysogeny control.[19,33] They have been proposed to possibly represent archetype phages in evolutionary transition from a lytic (i.e., virulent) to a temperate lifestyle.

The newest addition to the *Siphoviridae* group are phages featuring the B2 capsid morphotype, such as the recently described phage P70.[21] The elongated head holds a larger genome of about 65 kb, and the phage features no relationship to the other known *Listeria* phages. Vongkamjan et al. also reported isolation of *Listeria* phages with similar sized genomes, suggesting that they could possibly fall into this new species.[20] As described for P35 and P40 above, P70 also features a virulent lifestyle and an unusually broad host range. This is in agreement with the lack of genetic determinants indicative of a lysogeny control module.[21]

Lysogeny is widespread in *Listeria*[17] and the presence of prophage does not correlate with epidemic clones. Some strains, such as *L. innocua* CLIP11262 can harbor up to six prophage(-like) elements, whereas *L. monocytogenes* EGD-e harbors only two prophage elements, and other strains (such as serovar 3 strains, WSLC1001 and WSLC1042) seem to be free of intact prophage sequences.[2,36-38] Temperate phages can be induced from lysogens using UV light or mitomycin C,[35] and lysogens are resistant to infection by the same or related phage.[36] Many of the temperate *Listeria* phages are capable of generalized transduction,[19] where random fragments of host DNA are packaged into the phage head during assembly. These particles are infective and can inject the bacterial DNA into susceptible cells, but can obviously not complete the infection cycle. However, genes for virulence factors, toxins and antibiotic resistance can be transferred. The ability to perform generalized transduction is dependent on the physical genome structure of the phage. Phages with circularly permuted genomes, such as A118,[13] can perform transduction because the terminase enzyme exhibits no or only low sequence specificity and packs the proheads using a "headful" mechanism. In contrast, phages with fixed invariable genome structures, such as PSA or A511,[14,27] are unable to transduce DNA because the terminase recognizes a specific sequence on the DNA, and this recognition event is crucial for DNA packaging. The absence of transduction is an important prerequisite for biotechnological application of phage preparations to kill viable bacteria (see below). The majority of known *Listeria* phages features a circularly permuted genome structure (**Table 1**), a simple structure which allows loss-free DNA replication by circularization upon cell entry.[39]

Temperate *Listeria* phages encode integrase enzymes which mediate integration of the phage genome into the host chromosome, and excision of the phage genome under inducing conditions.[40] Depending on the specific catalytic amino acid residue present, phage integrases are classified as serine or tyrosine recombinases.[41] Phage A118 features a serine integrase, which recognizes a sequence with only three basepairs homology between phage and bacterial attachment site.[13] In contrast, the PSA integrase is of the tyrosine type, and recognizes a 15 bp site located at the 3′ end of a $tRNA_{Arg}$ gene.[14] Phages A006, B025, and B054 also encode recombinase enzymes, recognizing 16–17 nt core sequences, whereas the attachment and recombination sequence required for the recombinase from phage A500 is 45 bp long. All four of these enzymes are presumably of the tyrosine type. Both B025 and PSA integrate in the same locus, a $tRNA_{Arg}$, excluding simultaneous presence of both prophages in the same host cell. A006 and A500 target other tRNA genes.[33] It was recently speculated that tRNA genes represent "anchoring elements" for prophage uptake in *Listeria*.[38] In contrast, the recombinase recognition site for B054 is different and quite unique, since it integrates into a transcription elongation factor.[33]

Albeit the availability of approximately 50 *Listeria* phage genomes and a growing number of host genomes, no clear indication for an influence of bacteriophage on *Listeria* pathogenicity or virulence has been found. Recently, however, an A118-like[13] prophage of *Listeria monocytogenes* integrated into the *comK* gene has been shown to play a role in the regulation of phagolysosome escape of the organism during infection.[42] Until then, no function could be assigned to the *Listeria comK*, a homolog of the natural competence regulator in *Bacillus subtilis*. Phage integration disrupts the *comK* gene, whereas phage excision restores the reading frame.[13,43] An earlier study suggested a role of a *comK*-integrated prophage in the persistence of *L. monocytogenes* in food processing plants, attributing higher cell densities after 48 h incubation on meat to *comK*-prophage- containing lysogens.[44] However, this observation has never been supported by studying possible underlying mechanisms, such as the increased formation of biofilms due to a higher fraction of lysed cells and better availability of nutrients, and other effects.

Recently, genome and transcriptome studies of *L. monocytogenes* found prophage gene expression to be a hallmark of intracellular gene expression. The expression of phage-derived genes is upregulated when *Listeria* proliferates intracellular. In contract, deletions in a single shared prophage (the "monocin locus"—see below) of two lineage II strains led to severe virulence attenuation.[38] Unfortunately, the underlying mechanism(s) leading to this attenuation remain yet unclear.

Last, but not least, a putative CRISPR system[45] has also been identified in *Listeria* and its phages. It is composed of two adjacent loci with a considerable difference in the number of repeats; locus II is only present in serovar 4b strains, while locus I is conserved in serovar 1/2a and 4b strains, and in *L. innocua*. Not all strains feature identifiable *cas* genes,[38] and only locus II seems to be functional.[16] A third repeat locus was recently identified in serovar 1/2a, 1/2b, 3b, and 7 strains and contains *cas* gene homologs.[16] However, the presence or absence of such typical CRISPR

elements does not correlate with the presence of a certain type or number of prophages in *Listeria,* and it can therefore only be speculated if CRISPR/Cas systems provide defense against bacteriophage infection in *Listeria*.[16]

Applications of *Listeria* Phages

Listeria poses a severe health threat to the consumer. Its unique ability to survive high salt concentrations and proliferate at refrigeration temperatures makes it especially difficult for food producers to eradicate *Listeria* from the production chain. Applicable law in most countries requires that *Listeria monocytogenes* is absent from 25 g of a food sample, which obviously is a challenge for any detection system. Given its sporadic occurrence on various types of food, its ubiquitous distribution in nature, the high mortality rate in infected individuals and its unknown infection dose, a strong need exists for highly sensitive and rapid diagnostics, as well as efficient and food-grade control strategies for *Listeria monocytogenes* in ready-to-eat foods. Initially, *Listeria* bacteriophages have been used for phage-typing *Listeria* isolates, either from foodborne outbreaks and epidemics, or for source tracking in contaminated production plants. The procedures to be used were devised more than 25 years ago. Several more or less defined typing sets were developed,[46,47] and subsequently supplemented and standardized.[18,30,48-50]

Attempts to harness the biological specificity of phages for *Listeria* host cell detection involved the construction of a luciferase reporter phage A511*::luxAB*,[51] and its testing in a food environment.[52] For this purpose, the *Vibrio harveyi* bacterial luciferase genes *luxAB* were inserted downstream of the A511 major capsid gene under the control of its own strong promoter. When a *Listeria* cell is infected, *luxAB* is transcribed, the luciferase enzyme produced in the infected cells, and in presence of its oxidizable aldehyde substrate (Nonanal) generates a strong and real-time detectable light emission. The assay is sensitive enough to detect one cell per gram of food after a shortened enrichment procedure, which provides a three day time advantage over conventional enrichment and plating protocols.[52]

The *Listeria* reporter phage concept has recently been further developed by the construction of A511::*celB.* The *celB* gene from *Pyrococcus furiosus* encodes a thermostable β-galactosidase, which can be used with various chromogenic, fluorescent or chemiluminescent substrates, also creating a detectable response upon phage infection.[53] The authors demonstrated the feasibility of the assay in detecting as low as 10 cfu/g/ml of food in chocolate milk and salmon[53] using an inexpensive substrate and a simple endpoint assay.

Quite naturally, bacteriophages also represent perfect tools for biocontrol of bacteria, in this case *Listeria*. In this case biocontrol is most effective by removal of the organisms from contaminated food material, since the pathogen prefers an intracellular lifestyle and phage-based product cannot reach the bacterium once inside the human host.

Biocontrol approaches for *Listeria* (and any other pathogen) require a number of specific characteristics from the phage(s) to be used: It must be strictly virulent, feature a broad host-range, unable to perform generalize transduction, and does not affect virulence or pathogenicity or result in lysogenic conversion of its host. Ideally, the phage can be propagated on a non-pathogenic host, to avoid handling large-scale pathogen cultures and to prevent any interference of phage preparation impurities with downstream pathogen detection systems.[54,55] Phage P100 was characterized by Carlton in 2005[26] and subsequently developed into a product, which has received GRAS-status by FDA/USDA for use in all food materials (2007). The phage has also been used in a number of studies showing its efficacy in removing *Listeria* contaminations from fish, removing *Listeria* biofilms from stainless steel surfaces,[56-58] and prevention of *Listeria* on cooked ham.[59]

A511, a close relative of P100,[27] was used in several proof-of-concept studies and was shown to very effectively reduce *Listeria* contaminations on various ready-to-eat foods by more than 5 log units.[60] Bigot et al. successfully used an A511-like phage for biocontrol of *Listeria* in ready-to-eat poultry products, demonstrating up to 7 log reductions in viable counts.[61]

Other anti-*Listeria* phage products exists, such as a cocktail of six phages, which has also been FDA- and USDA-approved for application on food and surfaces in food production facilities. The phage cocktail was used to reduce *Listeria* occurrence on fresh-cut produce,[62] and for spray application of phages on melons.[63]

Listeria phages have also been able to inhibit *Listeria* growth on artificially contaminated samples,[25] even when immobilized on cellulose membranes and used for packaging of ready-to-eat and raw meat products.

Zink and Loessner have described the presence of lytic particles in *Listeria* cultures, termed monocins.[64,65] These substances are produced from up to 70% of all *Listeria* cultures and they inhibit other *Listeria*. Monocins resemble phage tail structures and result from the presence of incomplete, cryptic prophages. The tail associated lytic proteins (used during infection for cell wall penetration) are toxic to certain *Listeria* species and act as biocins. The "monocin locus", a cryptic prophage region including the *lma* genes is conserved in all *L. monocytogenes* lineages and also present in *L. innocua*.[38,66] Many monocine-like substances are found in other genera of bacteria, e.g., the "pyocins" of Pseudomonads.[67] Currently, renewed interest in monocin/pyocin-like substances for biocontrol of pathogenic bacteria is evident.[68-70]

Another biocontrol and detection strategy is using recombinant phage-encoded peptidoglycan hydrolases (endolysins) instead of infective virus. The potential of bacteriophage-derived endolysins in controlling foodborne pathogens has been subject of several reviews, e.g., ref. 71. However, systematic studies are lacking. *Listeria* phage endolysins bear potential as disinfection agent, similar to what has been done in control of *Streptococcus equi*[72] and other Gram-positives.[73,74] The regulatory approval for protein based disinfectants may be less challenging than approval of a virus-based food additive.

Over the past decade, molecular details of *Listeria* phage endolysins have been elucidated. The crystal structure of two of them is known,[75,76] and their generally modular composition and binding ligands on target cells are intensively studied.[77-81] Cell wall binding domains of the endolysins have been used to decorate *Listeria* with fluorescent labels, in order to discriminate them in

mixed bacterial culture.[78] These CBD binding domains have also been used for immobilization of *Listeria* cells, following coating on paramagnetic beads and specific capture of *Listeria* cells from milk and other matrices, followed by plating or real-time PCR quantification.[82,83]

In conclusion, bacteriophages do not only play an important role in *Listeria* genome plasticity and evolution, but offer a large and versatile toolbox for development of novel detection and biocontrol methods for *Listeria*, based on infective viruses, genetically modified phage, and native or recombinant phage-encoded enzymes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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