BACTERIOPHAGE
2016, VOL. 6, NO. 1, e1145782 (9 pages)
http://dx.doi.org/10.1080/21597081.2016.1145782

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REVIEW

Bacteriophage P2

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ABSTRACT
P2 is the original member of a highly successful family of temperate phages that are frequently found in the genomes of gram-negative bacteria. This article focuses on the organization of the P2 genome and reviews current knowledge about the function of each open reading frame.

ARTICLE HISTORY
Received 13 October 2015
Revised 13 January 2016
Accepted 14 January 2016

KEYWORDS
capsid; DNA replication; lysis; lysogenic conversion; lysogeny; regulation; tail

Introduction

Temperate enterobacteriophage P2 is the best-studied example of a class of temperate phages that are commonly found in γ-proteobacteria. In 1951 Giuseppe Bertani isolated P2[1] from the *Escherichia coli* strain in which lysogeny was discovered by Bordet and Reneaux.[2] Interest in the P2-like phages was increased by Erich Six's discovery of helper-dependent or "satellite" phage P4, which depends upon P2 late genes for its propagation.[3] Since P2-like prophages are so widespread, we have written this article to assist investigators in identifying the functions of P2-like prophages found in the sequence analysis of bacterial genomes. This article summarizes briefly what is known about the P2 genome and gene function, pointing out salient differences with the related and also well-studied phage 186 as well as other P2-related phages of interest. P2 is a member of the subfamily *Peduovirinae*, which has been further divided into the P2-like viruses and the more distantly related (based on sequence similarity) HP1-like viruses.[4] In this review, members of these 2 genera will be referred to as P2-like and HP1-like, and the group collectively as P2-related. A more extensive review by Nilsson and Haggård-Ljungquist can be found in The Bacteriophages.[5]

Virion and genome structure

P2 belongs to the family *Myoviridae*, with an icosahedral capsid 60 nm in diameter and a 135 nm contractile tail (Fig. 1). The P2 genome (NC_001895) consists of a linear dsDNA molecule of 33574 bp, with 19 base, 5′ phosphoryl-terminal, cohesive ends.[6,7] There are 42 open reading frames, organized into 10 transcription units. The physical genetic map of P2, depicted in the prophage orientation beginning at the left attachment site (*att*L), is illustrated in Figure 2. It should be noted, however, that nucleotide numbering of the genome, as reported in the reference sequence in Genbank, is from the left cohesive end rather than from *att*L. Table 1 summarizes the properties of the genes and their products.

The lysogeny region

The genes necessary for phage integration/excision and the lysogeny decision lie at the left end of the prophage genome. P2 integrase is a member of the tyrosine recombinase family and promotes the site-specific recombination between the phage and host *att* sites required for integration of the phage genome.[8] The P2 regulatory region contains 2 face-to-face promoters, P_e and P_c, and encodes 2 transcriptional regulators (Fig. 3). The P2 immunity

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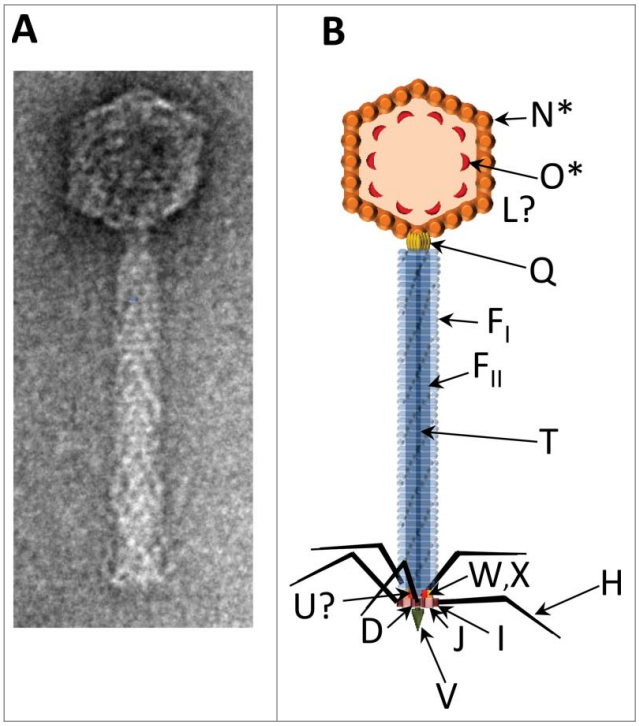

Figure 1. The P2 virion. (A) Electron micrograph of P2, negatively stained with uranyl acetate. This image was generously provided by Dr. Terje Dokland. (B) Schematic illustration of the P2 virion. Arrows indicate the known locations of virion proteins. GpN* is the cleaved form of gpN that constitutes the major capsid protein; gpO* is the fragment of scaffold that remains in the capsid after cleavage. The location in the capsid of the head completion protein gpL is unknown. The dodecameric connector or portal protein, gpQ, lies at the head/tail junction. The tail tube gpF_I and tail sheath gpF_{II} are polymerized around the tape measure protein gpT. Arrangement of baseplate components gpW, gpX, gpI, gpJ, gpU, gpD is based on EM studies, known protein-protein interactions, and the location of homologous proteins in the baseplate of bacteriophage T4; assignment for the location of gpU is still tentative. The tail spike is a trimer of gpV, and gpH makes up the tail fibers.

repressor, C, is a small, slightly basic protein of only 99 amino acids that contains an N-terminal helix-turn-helix DNA binding domain.[9] Dimers of C protein bind 2 direct repeats, separated by 2 helical turns, which span the −10 region of the early promoter P_e to repress transcription of *cox* and the replication genes.[10] The Cox protein binds to and represses the P_c promoter, which is needed for transcription of the C and *int* genes.[11,12] Cox is a winged HTH protein that oligomerizes as a helical filament and wraps DNA around its outside.[13] As is the general case for temperate phages, C also stimulates its own transcription from P_c while Cox represses it. Thus, expression of C leads to lysogenization, whereas Cox expression leads to the lytic cycle. In addition to its role in regulation of lysogenization, Cox also serves as the directionality factor that allows the Int protein to cause prophage excision.[14] Many P2-like phages have this arrangement of genes and sites to control the lysis-lysogeny switch.[15] However, some P2-like phages and all HP1-like phages characterized thus far have the more complicated arrangement found in the P2-like phage 186.[16-18] In this 186-type regulatory switch, there is an additional promoter (P_e) and an additional regulatory protein (CII) involved in expression of the repressor during the establishment of lysogeny[19] (Fig. 3). CII is a potent transcription activator that positively regulates transcription from P_e, binding as a dimer to 2 inverted repeat 7-mer half-sites.[20] P_e expression is subsequently turned down by the binding of the immunity repressor.

The immunity repressor in phages with the 186-type regulatory region is quite different from that in phages with the P2-type region. The 186 repressor, at 192 amino acids, is nearly twice as large as the P2 repressor. It forms an unusual wheel-like heptamer of dimers that provides extended cooperative binding to both adjacent and distant operators.[18,21] Like P2 Cox, 186 Apl functions as both a repressor and a directionality factor for excision.[17] However, the Cox and Apl proteins from P2-related phages cluster into 2 phylogenetically distinct groups that appear to have co-evolved with the P2-type or 186-type repressor and integrase, respectively.[15]

The difference in structure between the P2-type and 186-type immunity repressors affects the prophage response to SOS induction. Neither family of repressors contains the LexA cleavage motif commonly found in the repressors of temperate phages. However, while P2 is noninducible,[1] 186 is induced during the SOS response.[22,23] A small accessory gene in 186, *tum*, is expressed from a LexA-regulated promoter and functions as an antirepressor to effect SOS induction of 186.[22-24] The difference in repressor structure also affects the interaction of these 2 phages with the satellite element P4. P4 encodes a protein, Epsilon, which can bind to the P2 C protein to derepress a P2 prophage and allow it to serve as a helper for P4 growth.[25,26] In contrast, P4 cannot derepress a 186 prophage and therefore cannot propagate on a 186 lysogen.[27]

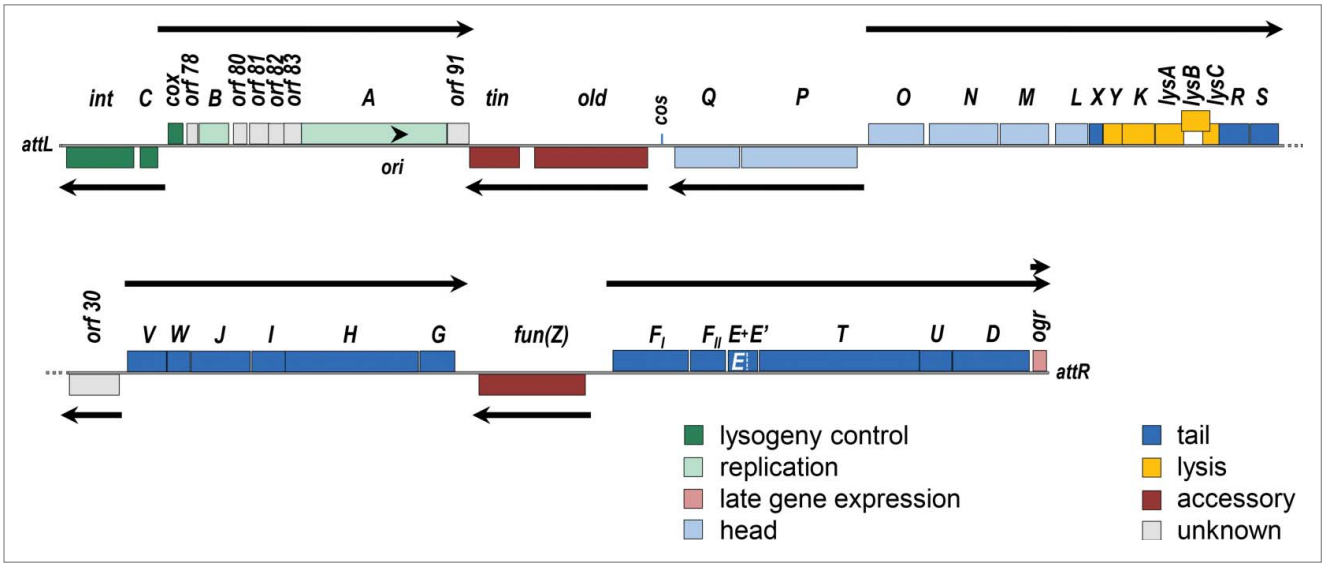

Figure 2. P2 genetic map. The P2 genome is displayed in prophage orientation, beginning at the leftward attachment site (*attL*). Genes are color coded by function, as indicated, and genes above the line are read rightwards while those below the line are read leftwards. Arrows indicate the direction and extent of each transcription unit. The arrowhead indicates the location of the replication origin (*ori*) and direction of replication. The *lysB* gene is offset to illustrate the overlap with *lysC*; the dotted white line indicates the end of gene *E* within the longer *E*+*E*′ coding sequence generated by a-1 frameshift.

The DNA replication module

The P2 replication genes, *A* and *B*, lie in an operon with the *cox* gene and are flanked by several small open reading frames of unknown function. Following the entry of linear P2 DNA into host cells, the 19 base pair cohesive ends allow the genome to circularize. P2 replicates as circular monomers, unidirectionally from a defined origin.[28] The product of gene *A* nicks the circular DNA at the replication origin, which lies within the *A* gene.[29] GpA binds to the 5′-phosphate, and allows the 3′-hydroxyl to serve as a primer for the leading strand.[30] The product of gene *B* loads the *E. coli dnaB* helicase onto the replicating fork.[31] At the end of a round of replication, the P2 A protein causes the formation of closed circular, daughter DNA molecules.[30]

The capsid genes

The capsid genes lie in 2 divergently transcribed gene clusters. Gene *Q* encodes the dodecameric portal protein, which is thought to act as the initiator for capsid assembly, and provides the docking site for the tail proteins and the entry and exit portal for the DNA.[32-34] Genes *P* and *M* encode the large and small subunits, respectively, of the terminase complex, required for DNA packaging.[35] In contrast to the arrangement found in many dsDNA phages, these 2 genes are not adjacent in the P2 genome. Another unusual feature of P2 DNA packaging is that the packaging substrate is closed circular monomeric P2 DNA.[36] The M protein is thought to carry the endonuclease activity responsible for converting circular P2 DNA to the linear form with cohesive ends in the presence of empty P2 procapsids and ATP, [37] and the 55 base pair cohesive end site (*cos*) is also required for this process.[38] Gene *O* encodes a bifunctional 284 amino acid protein. The N-terminal half of gpO functions as a serine protease that cleaves gpO, and a 15.5 kDa N-terminal cleavage product of gpO, O*, remains in the finished capsids.[39] The carboxyl terminal 90 amino acids of gpO contain the scaffolding function that causes gpN to form the T =7 prohead.[39] The gpO protease also cleaves off the N-terminal 31 amino acids of the major capsid protein, gpN, to yield N*, the protein of the mature capsid.[40,41] The product of gene *L* is not needed for DNA maturation or packaging.[42] Instead, gpL is needed to make the finished capsid, and it is found in the capsid.

The lysis genes

The lysis module includes 2 essential genes *Y*, and *K*, and 3 accessory genes – *lysA, lysB* and *lysC* - which are dispensable under certain conditions of growth. Gene *Y* encodes a holin, which allows the P2 lysozyme, the

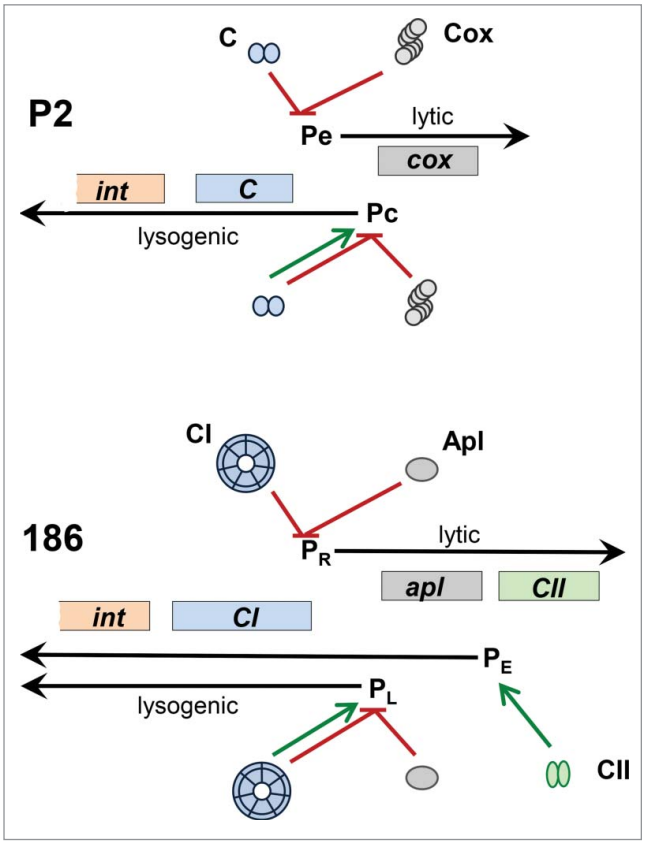

Figure 3. Comparison of the P2 and 186 lysogeny control regions. Black arrows designate the divergent lytic and lysogenic transcripts from the indicated promoters. Genes in the two phages encoding regulatory proteins with equivalent functions are colored the same, as are their corresponding gene products. The promoter targeted by each protein is indicated with a red line if the protein inhibits expression and with a green arrow if the protein activates expression.

product of gene *K*, to access the peptidoglycan.[43,44] The *lysA* gene product functions as an antiholin, needed to delay the action of gpY until the optimal lysis time.[43,44] Amber mutants in *lysB* exhibit delayed lysis in non-permissive cells.[43] The *lysC* gene, which overlaps the *lysB* gene, was originally identified by a mutation that overcomes the P2 growth defect conferred by a temperature-sensitive mutation in the *β*' subunit of RNA polymerase.[45] LysB and LysC are functional homologues of lambda Rz and Rz1, which make up the spanin complex that fuses the inner and outer membranes to complete host cell lysis.[46]

The tail genes

There are 16 essential P2 tail genes, found within 3 transcription units. Genes *X*, *R* and *S* are at the end of the operon that begins with gene *O*, and flank the lysis module. Gene *X* encodes a tail function, according to *in vitro* complementation studies,[43] and gpX has recently been localized to the top of the baseplate.[47] Nonsense mutants in gene *R* make abnormally long tails lacking the head-tail connector, and giant naked tail tubes.[48] There is some similarity between gpR and part of T4 phage gp15, which is the connector required for T4 tails to bind to T4 capsids.[49] Mutants in gene *S* produce predominantly normal-appearing but inactive tails, as well as a small number of extended, empty tail sheaths.[48] Therefore, gpR and gpS have been proposed to play a role in tail completion and head joining. Tail genes *VWJIHG* are expressed in a single transcription unit.[50-52] In phage 186, however, these genes are cotranscribed with the upstream capsid-lysis-tail gene operon.[53] The product of gene *V* makes up the small spike at the tip of the tail; it is a trimeric iron-binding protein involved in membrane penetration.[54-57] The *W* gene product is homologous to the T4 phage gp25, which is part of the T4 baseplate; it has been localized to the top of the baseplate, [47] and copurifies with gpV.[57] The *J* gene product lies at the edge of the baseplate; [57] gpJ and gpI are believed to make up the baseplate wedges.[58] Gene *H* encodes the tail fiber protein, and gene *G* is required for tail fiber assembly.[59] The tail genes F_I, F_{II}, *E, T, U* and *D* comprise a single transcription unit.[50,52] Gene F_I encodes the tail sheath, and F_{II} encodes the tail tube.[60] Gene E contains a programmed translational frameshift, allowing it to make a shorter (E) and a longer (E+E') protein, both of which are essential for phage growth.[61] These proteins likely function as chaperones for tail assembly, analogous to the G and G-T proteins of phage lambda.[62,63] Because of its exceptional length, gene *T* is presumed to determine tail length.[61] Gene *U* is likely to encode the tail tube initiator and gene *D* is believed to encode the central baseplate hub.[58] GpD belongs to the same protein domain family (pfam05954: Phage_GPD) as Mu gp44, which forms a trimer with an overall structure like that of the T4 gp27 trimer that forms the central hub of the T4 baseplate.[64,65]

Control of late gene expression

P2 late promoters share a conserved DNA sequence that is centered 55 base pairs upstream of the transcription start [66,67] and required for late gene expression.[68,69] These sequences are recognized and bound

Table 1. P2 genes and gene products.

Gene	Temporal expression	Size of gene product (aa)	Accession #	Function
int	early	337	NP_046786	integrase
C	early	99	NP_046787	immunity repressor
cox	early	91	NP_046788	repressor of C expression; directionality factor required for excision
orf78	early	56	NP_046789	unknown; highly conserved
B	early	166	NP_046790	DNA replication; lagging strand synthesis
orf80	early	74	NP_046791	unknown; highly conserved, DUF2732
orf81	early	100	NP_046792	unknown; highly conserved
orf82	early	74	NP_046793	unknown; C4 type zinc finger protein, DksA/TraR family
orf83	early	91	NP_046794	unknown; highly conserved
A	early	761	NP_046795	DNA replication; site-specific nick at ori
orf91	early	109	NP_046796	unknown, conserved ASCH superfamily domain - possible RNA binding protein
tin	constitutive	253	NP_046797	blocks growth of T-even phages
old	constitutive	586	NP_046798	nuclease; blocks growth of phage λ
Q	late	344	NP_046757	portal
P	late	590	NP_046758	terminase lg subunit; DNA-dependent ATPase
O	late	284	NP_046759	capsid scaffold; prohead protease
N	late	357	NP_046760	major capsid precursor
M	late	247	NP_046761	terminase sm subunit
L	late	169	NP_046762	capsid completion protein
X	late	67	NP_046763	baseplate
Y	late	93	NP_046764	holin
K	late	165	NP_046765	endolysin
lysA	late	141	NP_046766	antiholin
lysB	late	141	NP_046767	lysis control, Rz-like spanin component
lysC	late	96	NP_757382	lysis control, Rz1-like spanin component
R	late	155	NP_046768	tail completion - sheath terminator?
S	late	150	NP_046769	tail completion - tube terminator?
orf30	constitutive	261	NP_046770	unknown; highly conserved
V	late	211	NP_046771	tail spike
W	late	115	NP_046772	baseplate
J	late	302	NP_046773	baseplate
I	late	176	NP_046774	baseplate
H	late	669	NP_046775	tail fiber
G	late	175	NP_046776	tail fiber assembly
fun(Z)	constitutive	528	NP_046777	FudR sensitivity; blocks phage T5
F_I	late	396	NP_046778	tail sheath
F_{II}	late	172	NP_046779	tail tube
E	late	91	NP_046781	tail assembly chaperone
E+E′	late	142	NP_046780	tail assembly chaperone; −1 frameshift extension of gpE
T	late	815	NP_046782	tail tape measure
U	late	159	NP_046783	tail - tube initiator?
D	late	387	NP_046784	baseplate hub
ogr	middle/late	72	NP_046785	activator of late transcription; C4 Zn-finger protein

by the 72 amino acid P2 Ogr protein, a zinc-binding transcription factor [70] which interacts with the C-terminal domain of the α subunit of *E. coli* RNA polymerase to stimulate late transcription.[71,72] The *ogr* gene is expressed at middle times after infection from its own promoter and also cotranscribed with the *FETUD* gene cluster late in infection.[73] Unlike *ogr*, the homologous *B* gene in 186 is under direct control of the phage immunity repressor.[74]

Accessory genes ("morons")

Just to the left of the *cos* site are 2 genes that are expressed from the prophage and interfere with the growth of 2 other classes of phages. The P2 *old* gene product interferes with the growth of λ phage and kills *E. coli* cells that lack the *recBCD* nuclease-helicase.[75] Induction of λ prophage in a P2 *old* $^+$-lysogenic strain results in partial degradation of many tRNA molecules.[76] Purified Old protein has been reported to have 5′ to 3′ exonuclease activity on DNA, as well as an uncharacterized ribonuclease activity.[77] The P2 *tin* gene product inhibits the growth of T-even bacteriophages.[78] Tin blocks the action of their single-stranded binding proteins (gp32), thus interfering with T-even phage DNA replication.[79]

The equivalent region of phage 186 encodes 2 different genes – orf 97, a conserved gene of unknown function, and the *tum* gene discussed above, required for SOS induction of a 186 prophage.[22]

The *Z/fun* gene lies between genes *G* and F_I. In the prophage state this gene causes sensitivity to 5-

fluorouracil[80] and resistance to bacteriophage T5.[81] Mutations in this gene can cause cell killing, eliminating the possibility of lysogenization.[82] The *Z/fun* gene is located at a site that appears to be a hotspot for site-specific insertion of foreign DNA into the genomes of P2-like phages. Ten unrelated sequences were found in this region in P2-like prophages in the *E. coli* reference collection (ECOR), inserted between a pair of highly conserved long inverted repeats.[83] The P2-related Salmonella phage sopEϕ encodes, at this same location, the type III effector SopE, a virulence factor injected into eukaryotic cells via the *Salmonella enterica* type III secretion system.[84]

Orf30 lies between genes S and V. It is nonessential, and transcribed constitutively from its own promoter at a low level.[49] Homologues of the predicted orf30 gene product are found in many *E. coli* genomes, but its function remains unknown. Some P2-like phages, such as 186, lack an accessory gene at this location, and the 2 flanking late gene operons are expressed as a single transcription unit.[53]

The wild type alleles of the *old, tin* and *Z/fun* genes provide a selective advantage to bacteria that are lysogenic for P2 by protecting them from infection with other unrelated bacteriophages. Known morons found in other P2-related phages play additional roles, contributing to bacterial virulence or SOS prophage induction. P2-like prophages found in bacterial genome sequences carry a wide variety of accessory genes; the advantages conferred by these genes to the phage or bacterial host and the role of P2-like prophages in the horizontal transfer of accessory genes is an attractive area for further investigation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Acknowledgments

This review is dedicated to the memory of Giuseppe Bertani and Erich Six. We thank Terje Dokland for the EM image used in Figure 1.

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