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Bacteriophage T4 Genome†

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† Dedicated to the memory of Gisela Mosig, our friend, colleague, and mentor.

‡ Deceased.

T4 GENES TO GENOME

T-even phages (Fig. 1) have been major model systems in the development of modern genetics and molecular biology since the 1940s; many investigators have taken advantage of their useful degree of complexity and the ability to derive detailed genetic and physiological information with relatively simple experiments. Bacteriophages T2 and T4 were instrumental in the first formulations of many fundamental biological concepts. These include the unambiguous recognition of nucleic acids as the genetic material; the definition of the gene by fine-structure mutational, recombinational, and functional analyses; the demonstration that the genetic code is triplet; the discovery of mRNA; the importance of recombination in DNA replication; light-dependent and light-independent DNA repair mechanisms; restriction and modification of DNA; self-splicing introns in prokaryotes; translational bypassing; and others (506, 697). The advantages of T4 as a model system stemmed in part from the virus's total inhibition of host gene expression, which allows investigators to differentiate between host and phage macromolecular syntheses. Analysis of the assembly of the intricate T4 capsid and of the functioning of its nucleotide-synthesizing complex, its replisome, and its recombination complexes has led to important insights into macromolecular interactions, substrate channeling, and cooperation between phage and host proteins within such complexes. Indeed, the current view of biological "molecular machines" (15, 16) has its beginnings in T4 biology; the T4 replisome, late gene transcription complex and capsid assembly are paradigms of molecular machines.

The redundancies of protein functions and of pathways of DNA transactions probably allow T-even phages to exploit a broad range of potential hosts and environments while conferring substantial resistance against a wide range of antiviral mechanisms imposed by the host (4a, 599, 599a, 601, 786). T4 also produces several enzymes with widespread commercial applications, including its DNA and RNA ligase, polynucleotide kinase, and DNA polymerase. Many would argue that to know T4 is to know the foundations of molecular biology and the essential paradigms of genetics and gene expression.

There was a price to pay for all of the benefits provided by this highly tractable genetic system. Early efforts to clone T4 genes were largely thwarted by the glucosylated hydroxymethyl cytosine (HMC) DNA (which is central to the high expression and replication of the phage genome, the concurrent total inhibition of host transcription, and the eventual degradation of the host DNA). Most of the available restriction endonucleases failed to digest T4 DNA, delaying the gene-by-gene cloning analysis that rapidly advanced in other model organisms. Eventually, multiply mutant T4 strains defective in the nucleases that cleave unmodified DNA, in the enzymes leading to the synthesis of HMC-DNA, and in the protein blocking transcription of cytosine-containing DNA were constructed (1020). These T4dC (or T4C) strains permitted the construction of detailed restriction maps of T4 (137a, 139, 600, 814, 833a, 1214) and rapidly accelerated cloning and sequence analysis of T4 gene clusters. By the early 1990s, much of the genome had been sequenced, but extensive regions remained intractable. The uncloned DNA appeared to largely encode proteins involved in the transition from host to phage metabolism, nucleases, and other proteins toxic to the *Escherichia coli* cloning host. These regions were sequenced by different members of the T4 community, who closed the gaps by using PCR to carry out direct sequencing without cloning. Regions that have not otherwise been published include the *nrdC-tk* region (laboratory of E. Kutter), the *e-tRNA* region (laboratories of V. Mesyanzhinov and E. Kutter), the *34–35* region (laboratory of E. Goldberg), the *t-asiA*.5 region (laboratory of J. Drake) and the *ndd-rIIB* region (laboratories of K. Kreuzer and M. Uzan). The complete 168,903-bp sequence of the T4 genome is available as GenBank accession no. AF158101 and as entry NC_000866 at the NCBI *Entrez* Genome site (http://www.ncbi.nlm.nih.gov/Entrez). Among sequenced viruses in the database, only *Pseudomonas* phage ϕKZ (727), the African swine fever virus, herpesviruses, chlorella virus, and vaccinia virus have larger genomes.

The T4 genome is a rich arena for evaluating complete genomes in the context of a well-characterized biological system. Here, we demonstrate the use of some of the computational tools currently available for complete genome sequence

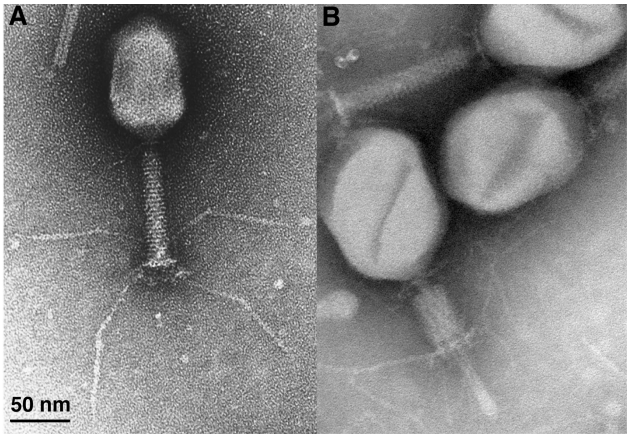

FIG. 1. Electron micrographs of bacteriophage T4. The well-recognized T4 morphology was nature's prototype of the NASA lunar excursion module. (A) Extended tail fibers recognize the bacterial envelope, and its prolate icosahedral head contains the 168,903-bp dsDNA genome. Reprinted with permission of M. Wurtz, Biozentrum, Basel, Switzerland. (B) The DNA genome is delivered into the host through the internal tail tube, which is visible protruding from the end of the contracted tail sheath. Courtesy of W. Rüger.

analysis and discuss the new insights gained from this analysis of the T4 genome and its nearly 300 genes.

NUCLEOTIDE SKEW IN THE T4 GENOME

T4 DNA has only 34.5% G+C, while its *E. coli* host has about 50% G+C. If T4 were assembled from "modules" of other genomes, as has been suggested for many phages (discussed below), different regions might be expected to have quite different G+C contents, particularly if they were recently acquired. However, only 18 of the known or predicted genes have less than 60% A+T and only 4 have less than 58%. Therefore, while some genes may have been more recently acquired, most of the T4 genome appears to have a lengthy, common history. Interestingly, it is the capsid proteins that have the lowest A+T contents, and these are the most widely conserved in the T4-related phages (701, 748, 919, 1069) and presumably among the earliest to have arisen. Gene *23*, encoding the major head protein, is the lowest, at 55% A+T. It also uses the highest proportion of codons that are translationally optimal for the host (65%), in keeping with its very high level of expression; about 1,000 copies of the protein are needed per phage particle synthesized.

A substantial skew toward G and against C in the coding strand is observed in translated regions. Only four genes have more than 20% C in the coding strand, while about 130 have more than 20% G and 37 have more than 22% G. A and T are more equitably divided between the strands. However, the AT bias is strong in the third position of codons, as expected with high-A+T genomes, and reflection points in the bias (Fig. 2) do correlate with changes in the direction of T4 transcription (499). Whether these biases are coupled to effects of transcription or replication on directional mutation pressure, as suggested previously (499), remains to be demonstrated. Variably used multiple origins of T4 DNA replication (see below) presumably preclude the use of nucleotide skew analysis to identify the origin of replication, as it is often used for microbial chromosomes (352). Overall, AT skew is a strong predictor of T4 coding regions and the transcribed strand, although in a few regions both strands are transcribed and, in at least one region, both are translated.

A genome of AT compositional bias presents issues of DNA structure that are worthy of brief consideration. Starting with a balanced 50% A+T genome, each GC replaced by an AT base pair eliminates one Watson-Crick hydrogen bond. This suggests that the evolution of HMC and glucosylation conferred a secondary selective advantage: it not only protects the DNA against degrading endonucleases but also improves double-strand stability. The OH and H side groups of the added glucose are able to form hydrogen bonds when in proximity with neighboring bases (456, 457). With only one hydrogen bond formed per glucose residue, the approximately 16% glucosylated HMC in T4 DNA could compensate for the 14% A+T bias above average in the genome.

The AT-rich T4 genome may also present features advantageous for a virus: a DNA structure different from the B-DNA of its host (809). On a local scale, the structure would approach D-form DNA: a polymer consisting of poly(dA-dT) double strands, overwound with only 8 bp per turn, a wider and shallower major groove, and a deeper and narrower minor groove (126, 127, 636). Close contacts of the glucosyl residues with side groups of neighboring bases could alter the preferred values of roll, slide, and twist angles of base pairs (258). Such forces and structural features can influence the outward appearance of the DNA in a way that may be recognized by proteins. Enzymes that melt DNA as part of their action (such as RNA polymerase and DNA polymerase) might transcribe and replicate AT-rich DNA faster than they would transcribe and replicate DNA with a balanced GC and AT content or might attract RNA polymerase and other host proteins in a competitive manner.

IDENTIFYING T4 GENES

On the basis of all available criteria, we conclude that T4 has about 300 probable genes packed into its 168,903-bp genome. The nucleotide positions of all probable genes, promoters, terminators, and the best characterized origins of replication are given in Table 1, along with several calculated properties for the genes and their encoded proteins. T4 has a total of 289 probable protein-encoding genes, 8 tRNA genes, and at least 2 other genes that encode small, stable RNAs of unknown function. Table 2 summarizes and references the functions and properties of the approximately 156 genes that have been characterized by mutation and/or by the properties of cloned gene products. Imprecision in the number of "genes" reflects ambiguities of genetic nomenclature, when some genes contain multiple coding regions (for instance, genes *16*, *17*, and *49* encode more than one protein).

Computational Strategies for Gene Assignment

The probability that an open reading frame (ORF) encodes a protein can be estimated by various computational methods that depend on observed patterns in the distribution of bases in known genes, along with such criteria as the presence of apparent translation initiation regions and the relationship to promoters and other genes. In the assembly and annotation of the T4 genome, the main tools used were the correlation coefficient, which compares the fractional use of each base at each of the three codon positions to those of a set of known T4 genes (971; T. Stidham, S. Peterson, and E. Kutler, Abstr. Evergreen Int. Phage Biol. Meet. p. 51, 1993), and the linguistics-based analysis, GenMark (99, 671). These methods were supplemented by identification of likely Shine-Dalgarno (SD) sequences for ribosome binding. As discussed below, such analyses indicate that virtually all the uncharacterized ORFs of T4 probably do encode proteins. Most known T4 genes have correlation coefficients above 0.85, as do most of the unassigned ORFs (Table 1). However, there appear to be constraints on the composition of some specific proteins that result in far lower values. This is seen for a few of the well-characterized but very small T4 genes, such as *stp* (−0.14), and for those that are predicted to encode integral membrane proteins, such as *imm* (0.31) and *ac* (0.51). Negative values are generally seen where a short but definitely expressed reading frame is superimposed on a different reading frame of another gene, such as *30.3′*, or in the complementary strand, as in *repEA* and *repEB.* Therefore, while a high correlation coefficient makes it very likely that an ORF does indeed encode a

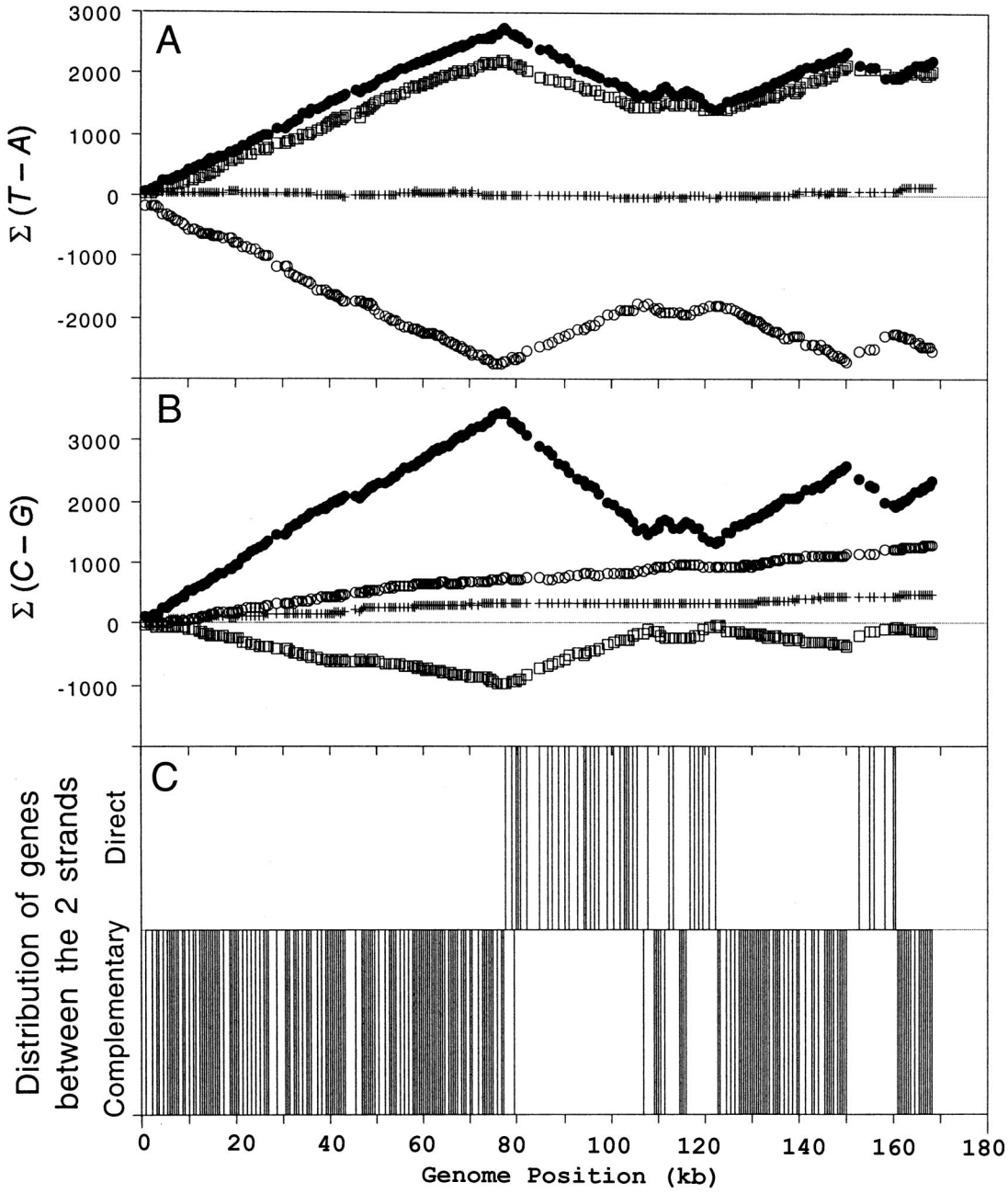

FIG. 2. Intrastrand biases (nucleotide skew) in the T4 genome. (A) Cumulative values of the number of T's minus the number of A's in a contiguous strand of the T4 genome for the first (●), second (□), and third (○) codon positions and for the intergenic regions (+), plotted against the genome position. The plus strand was used (5′ to 3′), from position 0 clockwise through the genome map, for the calculation. (B) Cumulative values of C's minus G's plotted as described for panel A. (C) Vertical lines show the distribution of genes in each strand, where "Direct" is the plus strand for which the analysis was performed and "Complementary" is the minus strand. Reprinted from reference 499, with permission from the publisher.

protein product, a low correlation coefficient cannot be used to exclude that possibility.

Work with T4 makes it clear that precisely identifying protein-coding regions can be complex, even in prokaryotes. (i) Five known T4 genes and several other ORFs have functional internal starts, with good experimental evidence for genes *17* and *49* that the shorter proteins have distinct functional roles (39, 286, 784, 788). In these two cases, separate but related gene names have been assigned (e.g., *17*, *17′*, and *17″*) to indicate this complex relationship. We expect that other examples of internal translational start sites will be identified.

(ii) Five other genes and ORFs have two closely spaced start codons with similarly strong values for the sequence information content (defined below) at their translation initiation sites

TABLE 1. Feature coordinates of the T4 genome

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
Start		1						
Pm	−	123						
Pm	−	377						
rIIA	−	2189	12	2,178	725	0.99	6.131	82,903
Pm	−	2263						
rIIA.1	−	2403	2200	204	67	0.89	7.156	8,129
Pe (1.4–3.9)	−	2422						
60+	−	2802	2458	345	160	0.93	8.738	18,600
60+	−	2990	2853	138				
60.1	−	3351	2971	381	126	0.96	9.364	14,651
mobA	−	3767	3654	114	37	0.78	9.54	4,192
Pe (3.6)	−	3847						
39	−	5328	3778	1,551	516	0.96	7.103	57,978
Pm	−	5349						
Term	−	5384						
39.1	−	5595	5398	198	65	0.79	7.997	7,156
39.2	−	5839	5702	138	45	0.86	8.497	5,107
goF = comCa	−	6267	5842	426	141	0.91	4.462	16,682
cef = mb	−	6482	6267	216	71	0.95	5.203	8,464
motB	−	7141	6653	489	162	0.98	9.205	18,219
Pe (5.9–7.3)	−	7179						
motB.1	−	7650	7291	360	119	0.84	4.993	13,804
motB.2	−	8161	7661	501	166	0.93	6.45	19,736
Pe (8.1)	−	8182						
dexA	−	8908	8225	684	227	0.98	4.763	25,966
dexA.1	−	9150	8908	243	80	0.90	5.31	9,392
dexA.2	−	9388	9143	246	81	0.93	4.184	9,518
dda	−	10729	9410	1,320	439	0.99	7.982	49,903
dda.1	−	11037	10726	312	103	0.84	9.776	12,104
srd	−	11785	11039	747	248	0.89	9.999	29,044
Pe (11.5)	−	11815						
modA	−	12510	11908	603	200	0.94	6.035	23,350
modB	−	13130	12507	624	207	0.91	5.306	24,244
Pe (12.8)	−	13150						
modA.2	−	13380	13198	183	60	0.83	4.11	7,024
modA.3	−	13859	13389	471	156	0.94	6.628	18,333
modA.4	−	14016	13852	165	54	0.91	5.852	6,162
srh	−	14216	14013	204	67	0.66	6.7	8,104
mrh	−	14676	14191	486	161	0.92	4.33	18,494
mrh.1	−	15026	14685	342	113	0.77	3.649	12,621
mrh.2	−	15232	15026	207	68	0.82	5.687	8,257
Pe (15.0)	−	15252						
Term	−	15305						
soc	−	15573	15331	243	80	0.95	6.361	9,117
Pl	−	15597						
Pl	−	16162						
segF = 69	−	16280	15606	675	224	0.78	10.148	26,218
Pl	−	16359						
56	−	16785	16270	516	171	0.78	4.734	20,425
oriA	−	16763						
Pm	−	16813						
dam	−	17625	16846	780	259	0.93	8.846	30,420
61 = 58	−	18963	17935	1,029	342	0.96	9.174	39,782
Pm	−	19122						
61.1	−	19130	18966	165	54	0.92	5.333	5,896
61.2	−	19758	19132	627	208	0.91	6.323	24,334
sp = rV	−	20051	19758	294	97	0.93	4.769	10,994
Pe (19.8)	−	20073						
61.4	−	20369	20112	258	85	0.75	9.828	10,187
dmd = 61.5	−	20553	20371	183	60	0.75	5.138	7,027
Pe (20.3)	−	20576						
41	−	22039	20612	1,428	475	0.98	5.439	53,602
Term	−	22347						
40	−	22393	22049	345	114	0.91	4.793	13,291
uvsX	−	23561	22386	1,176	391	0.98	5.310	43,999
Pm	−	23752						
segA	−	24235	23570	666	221	0.92	9.933	25,342

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TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
Pm	−	24460						
β-*gt*	−	25455	24400	1,056	351	0.97	9.079	40,670
42	−	26219	25479	741	246	0.98	5.933	28,492
Pm	−	26317						
imm	−	26624	26373	252	83	0.31	9.436	9,343
imm.1	−	27013	26636	378	125	0.96	6.486	14,074
Pe (26.4)	−	27044						
Term	−	27183						
43	−	29893	27197	2,697	898	0.97	6.087	103,622
Pm	−	29931						
Term	−	29967						
regA	−	30340	29972	369	122	0.77	8.939	14,620
62	−	30905	30342	564	187	0.93	8.592	21,364
44	−	31866	30907	960	319	0.98	7.016	35,790
Term	−	31912						
45	−	32603	31917	687	228	0.98	4.759	24,861
Pm	−	32626						
rpbA	−	33048	32659	390	129	0.98	7.283	14,712
45.2	−	33246	33058	189	62	0.85	5.671	7,477
Pm	−	33257						
46	−	34984	33302	1,683	560	0.98	8.263	63,588
Pm	−	35014						
46.1	−	35187	34981	207	68	0.73	4.068	8,153
46.2	−	35431	35168	264	87	0.85	4.288	10,268
Pe (35.3)	−	35662						
47	−	36447	35428	1,020	339	0.98	4.981	39,170
Pm	−	36576						
47.1	−	36584	36444	141	46	0.25	4.210	5,321
Term	−	36622						
α-*gt*	−	37826	36624	1,203	400	0.94	6.358	46,709
mobB	−	38679	37885	795	264	0.78	9.737	30,367
Pm	−	38681						
Term	−	38731						
α-*gt.2*	−	38922	38731	192	63	0.91	9.135	7,322
α-*gt.3*	−	39110	38907	204	67	0.91	9.609	7,931
α-*gt.4*	−	39396	39079	318	105	0.87	8.849	12,445
α-*gt.5*	−	39616	39398	217	72	0.95	4.22	8,548
55	−	40157	39600	558	185	0.94	5.45	21,537
Pm	−	40180						
55.1	−	40456	40193	264	87	0.79	4.114	9,846
55.2	−	40785	40459	327	108	0.88	9.717	12,727
Term	−	40836						
55.3	−	41038	40799	240	79	0.52	8.751	9,153
55.4	−	41170	41039	132	43	0.52	8.575	5,145
Pe (40.4)	−	41225						
55.5	−	41471	41178	294	97	0.75	9.821	11,809
55.6	−	41646	41464	183	60	0.71	9.581	6,962
Pe (41.0)	−	41670						
Term	−	41800						
nrdH	−	42113	41805	309	102	0.93	9.075	11,720
55.8	−	42328	42116	213	70	0.80	9.26	7,913
Pm	−	42805						
nrdG	−	42916	42446	471	156	0.78	8.312	18,248
Pm	−	43023						
mobC	−	43538	42906	633	210	0.88	9.852	23,978
nrdD+	−	44814	43535	1,280	605	0.99	6.889	67,964
I-TevII	−	45612	44836	777	258	0.98	9.808	30,371
Pl	−	45625						
nrdD+	−	46385	45848	538				
Pm	−	46441						
49′	−	46699	46382	318	105			11,888
49	−	46855	46382	474	157	0.79	8.618	18,145
Pl	−	46879						
Term	−	46884						
pin	−	47382	46897	486	161	0.98	4.369	18,817
Pe (46.7)	−	47416						
49.1	−	47521	47366	156	51	0.80	3.780	6,163

Continued on following page

TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
49.2	−	47826	47506	321	106	0.89	4.352	12,579
49.3	−	48131	47823	309	102	0.50	3.895	11,938
nrdC	−	48391	48128	264	87	0.80	7.183	10,050
nrdC.1	−	48635	48393	243	80	0.97	8.342	9,444
nrdC.2	−	48936	48622	315	104	0.81	6.586	12,159
nrdC.3	−	49859	48933	927	308	0.92	9.01	36,297
nrdC.4	−	50915	49914	1,002	333	0.95	7.63	38,996
Pe (50.0)	−	50937						
nrdC.5	−	51995	50973	1,023	340	0.92	9.327	39,670
nrdC.6	−	52893	52066	828	275	0.96	9.20	31,725
nrdC.7	−	53302	52901	402	133	0.84	6.41	15,309
nrdC.8	−	53885	53358	528	175	0.88	6.11	20,758
Pe (54.0)	−	53907						
nrdC.9	−	54248	53946	303	100	0.75	9.68	11,979
nrdC.10	−	55320	54343	978	325	0.93	4.85	36,691
Pe (54.4)	−	55348						
Term	−	55432						
nrdC.11	−	56445	55435	1,011	336	0.92	6.89	38,899
mobD	−	57208	56429	780	259	0.79	9.957	30,456
mobD.1	−	57828	57283	546	181	0.95	6.01	21,179
mobD.2	−	57932	57828	105	34	−0.05	9.49	4,205
Pe	−	57954						
mobD.2a	−	58165	58049	117	38	0.68	8.85	4,516
mobD.3	−	58349	58155	195	64	0.91	4.95	7,605
mobD.4	−	58534	58352	183	60	0.94	4.41	6,858
mobD.5	−	58722	58534	189	62	0.82	4.061	7,122
Pe (57.9)	−	58744						
Term	−	58813						
rI.-1	−	59205	58819	387	128	0.97	5.61	14,649
rI	−	59495	59202	294	97	0.76	4.83	11,125
rI.1	−	59720	59508	213	70	0.73	10.225	8,273
Pl	−	59740						
tk	−	60344	59763	582	193	0.95	6.49	21,624
tk.1	−	60534	60346	189	62	0.77	3.989	7,238
tk.2	−	60716	60531	186	61	0.67	4.194	7,134
tk.3	−	60925	60713	213	70	0.78	8.628	8,507
Term	−	61369						
tk.4	−	61389	60922	468	155	0.94	6.124	17,491
vs	−	61733	61386	348	115	0.67	8.744	13,057
vs.1	−	62271	61726	546	181	0.95	9.798	20,683
regB	−	62740	62279	462	153	0.85	8.444	17,978
Pe (62.2)	−	62761						
vs.3	−	63078	62800	279	92	0.87	5.378	10,904
vs.4	−	63344	63078	267	88	0.95	4.555	10,211
vs.5	−	63557	63381	177	58	0.17	9.52	6,611
vs.6	−	63919	63557	363	120	0.93	5.902	13,814
vs.7	−	64256	63927	330	109	0.75	9.031	12,836
vs.8	−	64912	64253	660	219	0.87	9.21	25,029
denV	−	65355	64939	417	138	0.94	9.393	16,080
Pe (64.6)	−	65378						
ipII	−	65718	65416	303	100	0.94	9.349	11,086
Pe (65.0)	−	65763						
ipIII	−	66415	65834	582	194	0.89	9.557	21,689
Pe	−	66462						
e	−	66997	66503	495	164	0.97	9.599	18,693
Pl	−	67005						
Pl	−	67018						
Pl	−	67234						
nudE = e.1	−	67490	67035	456	151	0.95	5.141	17,025
e.2	−	67960	67652	309	102	0.96	6.485	12,156
e.3	−	68319	67957	363	120	0.85	8.784	14,156
e.4	−	68693	68301	393	130	0.60	9.647	15,139
e.5	−	69270	68662	609	202	0.97	5.72	23,816
Term	−	69306						
e.6	−	69905	69312	594	197	0.99	6.162	22,045
Pe (69.9)	−	69931						
e.7	−	70303	69968	336	111	0.83	4.214	13,070

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TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
Pe (69.4)	−	70323						
e.8	−	70623	70360	264	87	0.74	4.324	10,199
Pe (69.8)	−	70660						
Term	−	70856						
rnaC	−	71046	70908	139				
rnaD	−	71171	71053	119				
tRNAR	−	71247	71173	75				
segB	−	71918	71253	666	221	0.96	9.320	26,146
tRNAI	−	72033	71960	74				
tRNAT	−	72110	72035	76				
tRNAS	−	72204	72118	87				
tRNAP	−	72280	72203	78				
tRNAG	−	72364	72291	74				
tRNAL	−	72456	72369	88				
tRNAE	−	72530	72456	75				
Pm	−	72593						
Pl	−	72863						
tRNA.2	−	72915	72628	288	95	0.96	5.031	11,285
tRNA.3	−	73328	72918	411	136	0.93	4.736	16,035
tRNA.4	−	73514	73329	186	61	0.69	7.996	6,558
Pe (72.6)	−	73536						
ipI	−	73878	73591	288	95	0.90	8.973	10,177
Pe (73.0)	−	73903						
57B	−	74410	73952	459	152	0.83	5.089	17,246
57A	−	74649	74407	243	80	0.97	4.248	8,731
Pm	−	74877						
Pl	−	74999						
1	−	75374	74649	726	242	1.00	4.947	27,332
Pm	−	75393						
3	−	75954	75424	531	176	0.93	4.267	19,713
2 = 64	−	76885	76061	825	274	0.87	10.144	31,613
4 = 50 = 65	−	77337	76885	453	150	0.77	9.793	17,629
Pl	−	77358						
Pl	+	77362						
Pl	+	77381						
53	+	77385	77975	591	196	0.96	6.005	22,968
Pl	+	77491						
5	+	77959	79686	1,728	575	0.95	5.235	63,121
repEB	−	78118	77981	138	45	0.35	5.19	5,483
repEA	−	79237	79085	153	50	0.24	8.52	6,130
Pe	−	79405						
5.1	+	79721	80215	495	164	0.86	4.593	18,499
Pl	+	79799						
segC	+	80196	80618	423	140	0.90	9.74	15,945
5.3	+	80621	80791	171	56	0.75	9.960	6,089
5.4	+	80779	81072	294	97	0.89	8.462	10,221
6	+	81081	83063	1,983	660	0.97	4.508	74,436
7	+	83060	86158	3,099	1,032	0.96	4.953	119,226
Pl	+	85812						
8	+	86151	87155	1,005	334	0.91	4.453	38,011
Term	+	87161						
Pl	+	87200						
9	+	87219	88085	867	288	0.91	4.929	31,000
Pl	+	87885						
10	+	88085	89893	1,809	602	0.94	4.275	66,238
11	+	89893	90552	660	219	0.91	5.066	23,708
12	+	90549	92132	1,584	527	0.91	6.072	56,220
wac	+	92129	93592	1,464	487	0.95	4.445	51,876
13	+	93624	94553	930	309	0.92	4.917	34,745
14	+	94555	95325	771	256	0.92	4.468	29,575
Pl	+	95337						
15	+	95367	96185	819	272	0.94	4.772	31,558
Pl	+	96153						
16	+	96194	96688	495	164	0.90	4.423	18,388
Term	+	93596						
17	+	96672	98504	1,833	610	0.98	5.638	69,764
Pl	+	96913						

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TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
17′A	+	96933	98504	1,572	523		5.16	59,245
17′B	+	96987	98504	1,518	505		5.02	57,108
17″	+	97254	98504	1,251	416		4.67	46,841
Pl	+	98513						
18	+	98536	100515	1,980	659	0.95	4.795	71,338
Pl	+	100564						
Pl	+	100623						
19	+	100632	101123	492	163	0.99	4.546	18,462
Term	+	101131						
Pl	+	101184						
20	+	101207	102781	1,575	524	0.99	5.341	61,037
Pl	+	102539						
67	+	102781	103023	243	80	0.77	3.662	9,106
68	+	103023	103448	426	141	0.98	10.108	15,874
Pl	+	103146						
21	+	103448	104086	639	212	0.95	4.725	23,253
21′	+	103514	104086	573	190		5.134	20,834
Pl	+	104095						
22	+	104117	104926	810	269	0.92	4.498	29,906
Pl	+	104787						
Pl	+	104816						
23	+	104945	106510	1,566	521	0.97	5.29	56,023
Term	+	106537						
segD	−	107232	106561	672	223	0.99	9.740	25,619
Pl	+	107301						
24	+	107323	108606	1,284	427	0.92	4.618	46,998
Term	+	108613						
Term	+	108668						
rnlB = 24.1	−	109640	108636	1,005	334	0.99	5.666	37,631
24.2	−	109928	109650	279	92	0.87	4.923	11,003
24.3	−	110085	109915	171	56	0.85	10.22	6,550
Term	−	110180						
hoc	−	111317	110187	1,317	376	0.93	4.626	40,388
inh	−	112007	111327	681	226	0.97	4.304	25,570
Pl	−	112029						
Pl	+	112034						
segE	+	112057	112674	618	205	0.92	4.559	22,896
Pl	+	112588						
uvsW	+	112677	114440	1,764	587	0.93	10.304	67,526
Term	−	114472						
uvsY.-2	−	114663	114496	168	55	0.91	4.323	6,062
Pl	−	114681						
uvsY.-1	−	114914	114690	225	74	0.74	4.939	8,963
uvsY	−	115327	114914	414	137	0.88	8.53	15,840
Pm	−	115371						
25	−	115802	115404	399	132	0.95	4.49	15,096
26′	−	116089	115802	288	95		5.27	10,856
Pl	−	116412						
26	−	116428	115802	627	208	0.86	5.748	23,883
Pl	−	116436						
Pl	−	116444						
Pl	+	116467						
51	+	116479	117228	750	249	0.91	6.229	29,340
27	+	117228	118403	1,176	391	0.97	5.24	44,462
28	+	118348	118881	534	177	0.94	5.75	20,122
29	+	118878	120650	1,773	590	0.95	4.931	64,416
48	+	120659	121753	1,095	364	0.76	8.715	39,738
54	+	121753	122715	963	320	0.87	5.383	34,981
Term	+	122720						
alt.-3	−	123032	122742	291	96	0.93	4.58	10,704
Pe	−	123057						
alt.-2	−	123268	123065	204	67	0.70	9.81	7,382
alt.-1	−	123450	123265	186	61	0.95	5.71	6,622
alt	−	125502	123454	2,049	682	0.95	6.158	75,819
Pl	−	125525						
Term	−	125558						
alt.1	−	125748	125560	189	62	0.89	4.371	7,153

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TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
30	−	127208	125745	1,464	487	0.98	6.315	55,299
Pm		127234						
30.1	−	127474	127205	270	89	0.82	8	10,833
30.2	−	128310	127474	837	278	0.94	6.241	32,433
Pm		128355						
30.3′	−	128629	128402	228	75	−0.17	10.4	8,945
30.3	−	128765	128307	459	152	0.85	8.849	17,088
30.4	−	128964	128758	207	68	0.95	4.535	8,064
30.5	−	129158	128961	198	65	0.82	5.091	7,252
30.6	−	129445	129158	288	95	0.88	7.19	10,814
30.7	−	129852	129487	366	121	0.82	7.305	14,131
Pe (128.2)	−	129883						
30.8	−	130253	129921	333	110	0.94	6.612	12,893
Pe (128.6)	−	130274						
Term	−	130358						
Term	−	130402						
30.9	−	130540	130364	177	58	0.92	11.44	6,519
rIII	−	131033	130785	249	82	0.90	8.479	9,325
Pl	−	131167						
31	−	131516	131181	336	111	0.89	5.315	12,079
Pm		131540						
31.1	−	131881	131573	309	102	0.84	9.113	11,520
31.2	−	132118	131882	237	78	0.71	9.806	9,397
cd	−	132699	132118	582	193	0.90	7.833	21,200
cd.1	−	133034	132696	339	112	0.84	8.138	12,814
cd.2	−	133261	133031	231	76	0.69	4.823	10,131
Pe (131.7)	−	133295						
Term	−	133376						
cd.3	−	133609	133334	276	91	0.88	4.82	10,131
cd.4	−	133812	133612	201	66	0.83	4.19	7,918
cd.5	−	134032	133805	228	75	0.81	8.521	8,738
pseT	−	134907	134002	906	301	0.96	8.671	34,622
pseT.1	−	135135	134908	228	75	0.74	8.455	8,833
pseT.2	−	135431	135132	300	99	0.75	8.577	11,645
pseT.3	−	135781	135428	354	117	0.90	8.947	13,136
alc	−	136275	135772	504	167	0.94	7.23	18,962
Pe (134.4)	−	136300						
Pl	+	136889						
rnlA = 63	−	137464	136340	1,125	374	0.96	4.885	43,514
denA	−	137951	137517	435	144	0.94	9.442	16,744
Term	−	137950						
nrdB+	−	138457	137955	503	388	0.92	4.924	45,357
I-TevIII	−	138886	38593	294	97	0.78	9.011	11,331
Pl	−	138933						
Pm	−	138939						
nrdB+	−	139719	139056	664				
Pm	−	139878						
nrdB.1	−	139967	139716	252	83	0.83	9.874	9,409
Term	−	140384						
mobE	−	140416	139991	426	141	0.94	10.102	16,448
nrdA	−	142680	140416	2,265	754	0.98	6.117	85,982
Pm	−	142725						
nrdA.1	−	142997	142671	327	108	0.70	9.035	12,362
nrdA.2	−	143214	142951	264	87	0.96	5.233	10,065
td+	−	143546	143235	312	286	0.89	8.617	33,077
I-TevI	−	144431	143694	738	245	0.83	9.625	28,175
Pl	−	144449						
td+	−	145112	144564	549				
Pm	−	145142						
frd	−	145690	145109	582	193	0.98	6.35	21,714
frd.1	−	146004	145762	243	80	0.75	4.843	9,471
Term	−	146051						
frd.2	−	146529	146143	387	128	0.73	4.281	14,742
frd.3	−	146802	146575	228	75	0.85	3.699	8,820
Pe (144.6)	−	146839	146833					
Term	−	146925						
32	−	147853	146948	906	301	0.96	4.681	33,509
Pl	−	147998						
Pm	−	148057						
segG = 32.1	−	148541	147909	633	210	0.95	7.194	24,564

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TABLE 1—*Continued*

Gene[a]	Strand[b]	Start[c]	Stop[c]	Length (bp)[d]	Length (aa)[d]	Correlation[e] coefficient	pI[f]	M_r[f]
59	−	149196	148543	654	217	0.89	9.387	26,000
33	−	149531	149193	339	112	0.93	4.38	12,831
dsbA	−	149778	149509	270	89	0.96	4.969	10,379
Pm	−	149873						
rnh	−	150704	149787	918	305	0.97	8.535	35,562
Pe (148.6)	−	150727						
Pl	+	150780						
34	+	150809	154678	3870	1289	0.94	5.206	140,416
Pm	−	153011						
35	+	154687	155805	1,119	372	0.84	4.96	40,123
Term	+	155811						
Pl	+	155850						
36	+	155868	156533	666	221	0.92	8.072	23,343
Pl	+	156369						
37	+	156542	159622	3,081	1,026	0.87	8.537	109,226
Term	+	159628						
38	+	159649	160200	552	183	0.88	6.633	22,311
Pl	+	160209						
t	+	160221	160877	657	218	0.94	7.921	25,178
Term	+	160924						
asiA	−	161150	160878	273	90	0.95	5.395	10,590
Pe (158.7)	−	161175						
asiA.1	−	161315	161163	153	50	0.89	4.51	5,935
arn	−	161590	161312	279	92	0.81	4.351	10,903
arn.1	−	161805	161674	132	43	0.54	8.334	5,173
arn.2	−	162172	161876	297	98	0.59	5.243	12,402
arn.3	−	162630	162172	459	152	0.90	5.078	17,837
arn.4	−	162833	162627	207	68	0.99	9.24	12,802
motA	−	163602	162967	636	211	0.96	8.772	23,577
Pe (161.1)	−	163637						
Term	−	163724						
motA.1	−	163879	163730	150	49	0.49	10.036	4,842
52	−	165204	163876	1,329	442	0.99	8.799	50,582
52.1	−	165349	165209	141	46	0.42	8.649	5,098
Term	−	165332						
ac	−	165497	165342	156	51	0.51	3.916	5,472
stp	−	165585	165505	81	26	−0.14	10.28	3,184
ndd	−	166040	165585	456	151	0.85	9.524	16,935
ndd.1	−	166316	166101	216	71	0.86	4.111	8,143
ndd.2	−	166435	166325	111	36	0.09	5.818	4,354
ndd.2a	−	166554	166432	123	40	0.73	7.14	4,303
ndd.3	−	166628	166548	81	26	−0.49	8.25	3,019
ndd.4	−	166764	166636	129	42	0.11	8.622	4,954
Pe (164.2)	−	166771						
ndd.5	−	166913	166815	99	32	0.81	7.082	3,687
ndd.6	−	166996	166910	87	28	−0.05	8.014	3,406
Pe (164.5)	−	167050						
denB	−	167660	167103	558	185	0.91	7.232	21,162
Term	−	167736						
denB.1	−	167937	167743	195	64	0.52	8.134	7,452
rIIB	−	168903	167965	939	312	0.96	6.24	35,544
End			168903					

[a] Genes are listed sequentially as they appear in the GenBank file (accession no. AF158101), clockwise on the circular map (by convention) starting with the first base 5′ of *rII*B. Recently renamed genes, or those with multiple names, are labeled with =. Intron-containing or translational bypass genes ($nrdB^+$, 60^+) are noted with a^+ for each reading frame. Genes marked with a prime (′) are overlapping with, or internal to, the designated gene. Transcription signals listed are Pe, Pm, and Pl for early, middle and late promoters, respectively, and Ter for terminator. Pe entries in parentheses are promoter designations used in earlier literature.

[b] The coding strand is noted as either the GenBank deposited (+) sequence or the complement (−).

[c] Start and stop coordinates denote the first base of the coding region (usually the A of the initiator ATG) and the last base of the stop codon. Promoter coordinates given are either the mapped or predicted transcript start sites (the "+1" position), and terminator coordinates are the first 5′ base of the hairpin.

[d] The length (bp) entry includes the stop codon of each coding sequence. Only the mature protein length (aa) is given for those proteins that arise from spliced or bypassed genes.

[e] The correlation coefficient given for each gene is the probability of an ORF being a T4 gene based on the codon usage in characterized T4 genes. The program was written by Gary Stormo and is available at the web site: http://www.lecb.ncifcrf.gov/~toms/delila/frame.html.

[f] pI and M_r are calculated values.

TABLE 2. Functions and mutant phenotypes of T4 gene products

Gene[a]	Function of gene product[b]	Size (kDa)[b]	Mutant phenotype	Restrictive host or condition[c]	Reference(s)
rIIA	Membrane-associated protein; affect host membrane ATPase	82.9	Rapid lysis; suppress T4 *30* and some *32* mutations	Auxiliary; *rex*$^+$ λ lysogens; P2-like HK239 lysogen; *tabR*	2–4, 56, 59, 95, 96, 106, 121, 159, 181, 184, 191, 198, 216, 224, 263, 292, 293, 365, 375, 441, 430, 431, 451, 504, 582, 768, 769, 774, 793, 810, 811, 834, 851, 874, 940, 1007, 1021, 1059, 1114b, 1159,
60	DNA topoisomerase subunit	18.6	DNA delay; *rc* = acriflavine resistance	Essential; 25°C or below	447, 450, 451, 452, 653, 654, 681, 801, 968, 1037
mobA	Pseudogene of Mob site-specific DNA endonuclease	4.2		Nonessential	E. Thomas, F. Zucker, and E. Kutter, unpublished data
39	DNA topoisomerase subunit; DNA-dependent ATPase; membrane-associated protein	58.0	DNA delay; *rc* = acriflavine resistance	Essential; 25°C or below; synthetic lethal with T4 *49* and *17* mutations, or when host topoisomerase IV is poisoned with novobiocin	264, 297, 295, 296, 432, 447, 448, 449, 451, 452, 454, 571, 589, 653, 654, 708, 789, 768, 769, 801, 834, 853, 1006, 1037, 1047, 1059, 1216, 1236
goF = *comC*-α = *go9H*	Affects mRNA metabolism	16.7	Allows T4 growth in *rho* (*nusD*) hosts	Auxiliary	144, 431, 474, 879, 925, 956, 1028, 1044, 1045, 1062, 1154, 1241
cef = *mb* = *M1* = *motC*	Processing of T4 tRNAs	8.5		Auxiliary; CT439; *roc*$^-$ hosts	431, 869, 870, 878, 937, 956
*pse*F = plaCTr5x?	5′ phosphatase			Auxiliary	956
motB		18.2	Affects middle transcription	Auxiliary	956
dexA	Exonuclease A	26.0		Auxiliary; restricted on *optA* hosts	308, 355, 431, 604, 737, 780, 956, 1152
dda = *sud*	DNA helicase; DNA-dependent ATPase	49.9	Suppress certain T4 *32* mutations	Auxiliary; synthetic lethal with T4 *59* mutations	45, 309, 369, 431, 481, 546, 547, 587, 588, 649, 680, 769, 780, 783, 956, 970; P. Gauss, personal communication
srd = *dda.2*	Postulated decoy of host σ^{70} or σ^S	29.1		Auxiliary	780
modA	Adenylribosylating enzyme	23.4	α subunits of host RNA polymerase are incompletely modified	Auxiliary	324, 431, 435, 780, 1011, 1077
modB	Adenylribosylating enzyme	24.2		Auxiliary	780, 1077
srh = *modA.5*	Postulated decoy of host σ^{32}	8.1	Delays early T4 gene expression at high temperatures	Auxiliary	780
mrh	Affects phosphorylation of host σ^{32}	18.5	Allows T4 growth in a σ^{32} host	Auxiliary	290, 780
soc	Small outer capsid protein	9.1	Unstable T4 capsids	Auxiliary	77, 89, 167, 431, 461, 462, 466, 675, 780, 916, 918
segF = *69*	Intron-like endonuclease. A probable fusion protein, generated from *56* and *69* by hopping of ribosomes across a pseudoknot, is larger	26.2		Nonessential	51, 305, 677, 769, 780, 790, 783
56	dCTPase; dUTPase; dCDPase; dUDPase	20.4	Little DNA synthesis; unstable DNA	Essential	305, 347, 602, 605, 696, 769, 781, 783, 839, 1162
oriA	DNA replication origin; *cis*-acting sequences in *56*, *69*, and *soc*; primer transcript same as transcript for these genes		No DNA synthesis from *oriA*	Auxiliary	160, 674, 678, 691, 791, 1215
dam	DNA adenine methylase	30.4	No DNA adenine methylation	Auxiliary	112, 139, 395, 676, 677, 683, 742, 743, 921, 960, 961, 1072
61 = *58*	Primase; requires interaction with gp41 helicase for priming at unique sequence	39.8	DNA delay	Auxiliary; 25°C or below; synthetic lethal with T4 *49* or *17* mutations	17, 47, 60, 123, 154, 380, 415, 416, 421, 422, 652, 653, 667, 761, 768, 769, 783, 788, 801, 829, 826, 831, 970, 996, 997, 998, 1216
sp = *61.3* = *rIV*	Periplasmic protein	11.0	Rapid lysis; suppresses *e* lysozyme mutations	Auxiliary	2, 261, 492, 585, 851, 971, 1208
dmd = *61.5*	Discriminator of mRNA degradation	7.0	Excessive mRNA degradation	Nonessential; suppressed by *motA* mutations	491, 493, 971, 1102

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TABLE 2—*Continued*

41	Replicative and recombination DNA helicase; GTPase; ATPase; dGTPase; dATPase	53.6	DNA arrest; little DNA displacement synthesis	Essential	17, 54, 60, 154, 155, 184, 197, 227, 228, 264, 309, 424, 415, 416, 421, 451, 478, 479, 554, 593, 653, 652, 651, 761, 768, 769, 826, 831, 838, 930, 931, 950, 970, 1029, 1064, 1122, 1220
40	Membrane-associated protein initiator of head vertex	13.3	Polyheads	Auxiliary; high temperatures	89, 115, 116, 301, 416, 443, 500, 608, 693, 729
uvsX = fdsA	RecA-like recombination protein; DNA-ATPase	44.0	UV- and X-ray sensitive; recombination deficient; suppress *49* mutations	Auxiliary	26, 80, 82, 165, 182, 213, 254, 282, 283, 281, 301, 351, 384, 386, 392, 416, 423, 549, 572, 589, 686, 723, 739, 762, 768, 769, 938, 949, 950, 970, 1047, 1088, 1138, 1222–1225
segA	Site-specific intron-like DNA endonuclease	25.3		Nonessential	986, 988
β-*gt*	β-Glucosyltransferase	40.7	No β-glucosylation of HMC DNA	Auxiliary; *Shigella*	139, 316, 451, 615a, 757, 924, 1075, 1084, 1134
42	dCMP hydroxymethylase	28.5	Little or no DNA synthesis	Essential	60, 68, 124, 184, 264, 320, 348, 383, 451, 476, 475, 477, 598, 611, 612, 695, 698, 834, 1027, 1076, 1114a, 1165, 1192
imm	Inner membrane protein	9.3	No immunity to superinfection	Auxiliary	2, 3, 4, 166, 188, 665, 666, 836, 1113, 1232
43	DNA polymerase; 3′-to-5′ exonuclease	103.6	No DNA synthesis; mutator or antimutator activities of conditional lethals under semipermissive conditions	Essential; nonessential *dsd* mutants do not grow in *optA* hosts	1, 17, 20, 21, 23, 24, 36, 43, 53, 54, 57, 58, 60, 68, 94, 130, 212a, 229, 230, 231, 237, 264, 259, 289, 298, 334, 343, 394, 393, 451, 488, 495, 506, 507, 527, 529, 555, 581, 617, 645, 646, 653, 689, 768, 769, 826, 827, 828, 831, 834, 856, 857, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 970, 978, 983, 1029, 1030, 1033, 1046, 1088, 1128, 1142, 1143, 1147, 1150, 1165, 1207
regA	Translational repressor of several early genes	14.6	Extended synthesis of several early proteins	Auxiliary; restricted in *E. coli rpoB5081* at 42°C	9, 10, 19, 131, 320, 338, 484, 485, 503, 505, 637, 735–738, 835, 860, 951, 952, 953, 975, 1095, 1167, 1182
62	Clamp-loader subunit	21.4	No DNA synthesis	Essential	17, 20, 57, 60, 264, 310, 311, 312, 320, 451, 469, 470, 486, 487, 488, 616, 619, 653, 679, 826, 831, 834, 865, 864, 901, 902, 1089, 1217, 1227
44	Clamp-loader subunit	35.8	No DNA synthesis	Essential	20, 57, 310, 311, 312, 320, 469, 470, 486, 487, 488, 616, 618, 619, 679, 826, 831, 864, 865, 901, 902, 970, 1032, 1089, 1217, 1227
45	Processivity enhancing sliding clamp of DNA polymerase; and mobile enhancer of late promoters	24.9	No DNA synthesis; no late transcription	Essential	17, 20, 22, 264, 299, 310, 311, 312, 320, 334, 404, 405, 451, 469, 552, 552a, 616, 617, 619, 618, 653, 673, 679, 747, 786, 826, 831, 834, 865, 901, 902, 951, 952, 953, 970, 983, 1031, 1079, 1080, 1081, 1082, 1091, 1092, 1186, 1217, 1227
rpbA	RNAP-binding protein	14.7		Auxiliary	444, 552, 786, 1171, 1172, 1174
46	Recombination protein and nuclease subunit	63.6	Recombination deficient; DNA arrest; no host DNA degradation	Essential in B strains; mutants are "leaky" in some K strains	60, 68, 93, 111, 184, 195, 264, 345, 380, 403, 451, 605, 627, 668, 731, 740, 744, 768, 769, 775, 784, 1036, 1047, 1138, 1163, 1164
47	Recombination protein and nuclease subunit	39.2	Recombination deficient; DNA arrest; no host DNA degradation	Essential in B strains; mutants are "leaky" in some K strains	93, 345, 403, 605, 731, 744, 768, 769, 1036, 1164
α-*gt*	α-Glucosyltransferase	46.7	No α-glucosylation of HMC	Auxiliary	140, 316, 345, 437, 924, 1072, 1084, 1191
mobB	Putative site-specific intron-like DNA endonuclease	30.4		Nonessential	48, 1072
55	σ factor recognizing late T4 promoters	21.5	No late transcription	Essential	97, 98, 109, 310, 313, 311, 345, 404, 552, 635, 834, 895, 1038, 1082, 1171, 1173, 1174, 1186

nrdH = 55.7	Anaerobic nucleotide reductase subunit	11.7		Auxiliary	257, 368, 1085
nrdG = 55.9	Anaerobic nucleotide reductase subunit	18.2		Auxiliary	660, 1228
mobC = 55.10	Putative intron-like DNA endonuclease	24.0		Auxiliary	1072
nrdD = sunY	Anaerobic ribonucleotide reductase subunit; RNA contains a self-splicing intron	68.0		Anaerobic growth	39, 342, 882, 1053, 1086, 1203, 1229, 1237; M. Ohman-Heden, personal communication
I-TevII	Endonuclease for *nrdD*-intron homing	30.4		Nonessential	52, 178, 251, 342, 661, 662, 882, 993, 991, 1085
49	Recombination endonuclease VII	18.1	No resolution of recombination junctions; incomplete packaging of DNA; reduced heteroduplex repair, reduced DNA synthesis	Essential	39, 70, 79, 81, 82, 172, 213, 249, 250, 278, 300, 285, 330, 331, 332, 333, 350, 522, 523, 524, 525, 526, 541, 559, 669, 670, 740, 768, 769, 783, 788, 792, 793, 817, 883, 1025, 1030, 1029, 1047, 1083, 1085, 1226; G. Mosig and D. Powell, Abstr. Annu. Meet. ASM, p. 209, 1985
49′	Internal translation initiation product	11.9			39, 784, 788
pin	Inhibitor of host Lon protease	18.8	Degradation of amber peptides	Auxiliary	1005, 1012, 1085
nrdC	Thioredoxin, glutaredoxin	10.1		Auxiliary	64, 257, 341, 460, 632, 815, 816, 1066, 1085
mobD	Putative site-specific DNA endonucleasee	30.5		Nonessential	1072
rI = tk.-2	Membrane protein	11.1	No lysis inhibition	Auxiliary	3, 56, 224, 236, 851
tk	Thymidine kinase	21.6		Auxiliary	156, 157, 348, 604, 696, 733, 1112; Thomas et al., unpublished
vs	Modifier of valyl-tRNA synthetase	13.1		Auxiliary	688, 713, 842, 843, 1112
regB	Site-specific RNase	18.0	Misregulation of early genes; specific mRNAs stabilized	Auxiliary	156, 736, 942, 943, 955, 1106, 1112
denV	Endonuclease V; *N*-glycosidase	16.1	UV sensitive	Auxiliary	35, 219, 222, 223, 232, 304, 339, 575, 604, 620, 621, 622, 623, 656, 657, 685, 714, 715, 716, 718, 758, 806, 812, 813, 832, 862, 884, 885, 899, 969, 1110, 1111, 1112, 1117, 1120, 1151, 1212, 1213
ipII	Internal protein II	11.1* 9.9		Auxiliary	84, 88, 89, 442, 595, 604, 1093, 1112
ipIII	Internal protein III	21.7* 20.4		Auxiliary	84, 88, 89, 442, 434, 451, 595, 604, 802, 803, 804, 1093, 1112, 1114a
e	Soluble lysozyme; endolysin	18.7	No cell lysis	Essential, except when suppressed by *sp* and *5* mutations	2, 3, 4, 50, 261, 268, 346, 500, 594, 604, 704, 720, 787, 850, 871, 872, 948, 1050, 1099, 1158, 1193
nudE = e.1	Nudix hydrolase	17.0		Auxiliary	1204
goF3			Allow T4 growth in *nusD rho* hosts	Auxiliary	720, 1045
rnaC = species 1	Stable RNA			Nonessential	110, 302, 707, 870, 962
rnaD = species 2	Stable RNA			Nonessential	110, 302, 707, 870, 962
$tRNA^{Arg}$			psu_4 opal suppressor	Auxiliary; CT439	5, 110, 284, 302, 328, 361, 366, 367, 501, 707, 710–712, 870, 962, 964, 1178, 1179, 1180
segB	Probable site-specific intron-like DNA endonuclease	26.2		Nonessential	110, 302, 604, 772, 988
$tRNA^{Ile}$				Auxiliary; CT439	302, 707, 962
$tRNA^{Thr}$				Auxiliary; CT439	302, 707, 962
$tRNA^{Ser}$			psu_a; psu_b; psu_t; amber suppressors	Auxiliary; CT439	302, 707, 962
$tRNA^{Pro}$				Auxiliary; CT439	302, 707, 962
$tRNA^{Gly}$				Auxiliary; CT439	302, 707, 962
$tRNA^{Leu}$			psu_3	Auxiliary; CT439	302, 707, 962
$tRNA^{Gln}$			psu_2; SB	Auxiliary; CT439	302, 707, 962
ip1	Internal protein 1	10.2* 8.5		Auxiliary; CT596	6, 84, 87, 88, 89, 110, 442, 543, 595, 1093, 1112
57B		17.3		?	110, 280, 409, 410, 922
57A	Chaperone of long and short tail fiber assembly	8.7	Defective tail fiber assembly	Essential; bypassed by certain host mutations	110, 122, 186, 319, 391, 401, 409, 410, 699, 922
1	dNMP kinase	27.3	No DNA synthesis	Essential	110, 184, 241, 264, 348, 543, 696, 834

Continued on following page

TABLE 2—*Continued*

3	Head-proximal tip of tail tube	19.7	Unstable tails	Essential	7, 186, 264, 535, 536, 543, 648, 1124
2 = 64	Protein protecting DNA ends	31.6	Noninfectious particles with filled heads	Essential, except in *recBCD* hosts	28, 89, 186, 249, 250, 264, 543, 647, 1000, 1001, 1074, 1144
4 = 50 = 65	Head completion protein	17.6	Noninfectious particles with filled heads but tails attached at wrong angles	Essential	89, 249, 250, 264, 543, 787
53	Base plate wedge component	23.0	Defective tails	Essential	186, 249, 250, 530, 531, 532, 787, 1155, 1157
5	Base plate lysozyme; hub component	63.1* 44* 19	Defective tails	Essential	2, 186, 249, 264, 497, 500, 530, 531, 532, 787, 807, 1063, 1119, 1157
oriE	DNA replication origin; *cis*-acting sequences in genes *4*, *53*, *5*; primer transcript in opposite orientation of gene *5* transcripts		No DNA synthesis from *oriE*	Auxiliary	378, 563, 641, 779, 1109, 1215; G. Lin and G. Mosig, unpublished data
repEB	Protein required for initiation from *oriE*	5.48	No DNA replication from *oriE*	Auxiliary; synthetic lethal with *motA* mutation	1109
repEA	Protein auxiliary for initiation from *oriE*	6.13	Anomalous DNA replication from *oriE*	Auxiliary	1109
segC	Site-specific intron-like DNA endonuclease	16.0		Nonessential	490, 641, 988, 989a; Lin and Mosig, unpublished
6	Base plate wedge component	74.4	Defective tails; permit plating of fiberless phage	Essential	186, 193, 249, 253, 264, 537, 1119, 1157; R. Marsh, personal communication
7	Base plate wedge component	119.2	Defective tails; permit plating of fiberless phage	Essential	186, 193, 249, 250, 253, 264, 537, 1119, 1156, 1157; Marsh, personal communication
8	Base plate wedge component	38.0	Defective tails	Essential	186, 250, 249, 253, 264, 537, 1119, 1156, 1157
9	Base plate wedge component, tail fiber socket, trigger for tail sheath contraction	31.0	No attachment of tail fibers	Essential	186, 250, 264, 535, 537, 562, 876, 1114a, 1155, 1157
10	Base plate wedge component, tail pin	66.2	Defective tails	Essential	186, 249, 250, 264, 272, 537, 726, 867, 868, 876, 1119, 1155, 1156, 1157, 1239
11	Base plate wedge component, tail pin, interface with short tail fibers, gp12	23.7	Defective tails	Essential	186, 249, 250, 264, 535, 537, 633, 868, 867, 876, 1119, 1155, 1157, 1239
12	Short tail fibers	56.2	Defective tails	Essential	122, 186, 391, 521, 535, 537, 745, 972, 1114a, 1155, 1157
wac	Whiskers, facilitate long tail fiber attachment	51.9	No whiskers	Auxiliary	186, 214, 745, 877, 1024, 1065, 1114a, 1188
13	Head completion	34.7	Inactive, but filled heads	Essential	89, 249, 250, 264, 973, 1114a
14	Head completion	29.6	Inactive, but filled heads	Essential	89, 250, 249, 264, 973, 1114a
15	Proximal tail sheath stabilizer, connector to gp3 and/or gp19	31.6	Defective tails	Essential	249, 250, 264, 272, 535, 537, 973, 1114a
16	Terminase subunit, binds dsDNA	18.4	Empty heads	Nearly essential	85, 86, 89, 90, 249, 250, 264, 286, 287, 642, 643, 644, 669, 802, 803, 873, 891, 1194
16′	Truncated C-terminal end				
17	Terminase subunit with nuclease and ATPase activity; binds single-stranded DNA, gp16 and gp20	69.8	Empty heads	Essential	75, 85, 86, 89, 90, 249, 250, 264, 286, 287, 288, 433, 586, 631, 642, 643, 669, 746, 769, 784, 785, 873, 891, 892, 893, 1194, 1195, 1196
17′A	Terminase subunits with nuclease and	59.2		?	286, 287, 288, 333, 784
17′B	ATPase activity; internal transcription and translation in frame; does not bind ssDNA	57.1			
17″	Terminase subunit with nuclease and ATPase activity (transcript processing and internal initiation of translation in frame); does not bind ssDNA; several additional proteins most likely initiated from internal ribosome binding sites of the *17* transcripts	46.8		?	286, 287, 288

18	Tail sheath monomer	71.3	Defective tails	Essential	29, 31, 186, 249, 250, 264, 272, 535, 537, 1096, 1119, 1157
19	Tail tube monomer	18.5	Defective tails	Essential	30, 186, 249, 250, 264, 272, 535, 536, 537, 1119, 1157, 1194
20	Portal vertex protein of the head	61.0	Polyheads	Essential	86, 89, 90, 238, 250, 264, 333, 608, 642, 643, 694, 990, 1114a
pip = 67	Prohead core protein; precursor to internal peptides	9.1∗ small peptides	Defective heads	Essential	89, 519, 1130, 1131
68	Prohead core protein	15.9	Isometric heads	Essential	89, 516, 518, 520
21	Prohead core protein and protease	23.3∗ small peptides	No or defective heads	Essential	89, 250, 264, 329, 414, 516, 517, 606, 608, 844, 845, 990, 1116
21′	Prohead core protein and protease (internal initiation of translation)	20.8∗ small peptides	Defective heads		414
22	Prohead core protein; precursor to internal peptides	29.9∗ small peptides	No or faulty heads	Essential	89, 250, 264, 270, 518, 595, 608, 728, 805, 844, 845, 990, 1094, 1093, 1114a
23	Precursor of major head subunit	56.0∗ 48.7∗ 43	No or faulty heads; *gol* mutations in gene *23* allow growth in *lit* hosts (CTR5x)	Essential; Gol peptide together with *E. coli* Lit, cleaves host EF-Tu	27, 65, 86, 89, 90, 158, 218, 225, 226, 250, 256, 260, 264, 270, 315, 396, 461, 466, 606, 608, 684, 719, 754, 825, 841, 854, 936, 1021, 1093, 1094, 1119, 1231
segD	Probable site-specific intron-like DNA endonuclease	25.6		Nonessential	490, 988
24 = os	Precursor of head vertex subunit	47.0∗ 46	No or faulty heads, osmotic shock resistance	Essential; bypassed by certain gene *23* mutations	8, 76, 89, 250, 262, 264, 396, 461, 606, 608, 634, 719, 1114a; G. Yasuda, G. A. Churchill, M. Parker, and D. Moorey, personal communication
mlB = 24.1	Second RNA ligase	37.6		?	426
hoc = eph	Large outer capsid protein	40.4	Unstable capsids	Auxiliary	89, 167, 164, 168, 461, 462, 496, 916, 917, 1205
inh = lip	Minor capsid protein; inhibitor of gp21 protease	25.6		Auxiliary	496
segE	Probable site-specific intron-like DNA endonuclease	22.9		Nonessential	489, 490, 988
uvsW = dar	RNA-DNA- and DNA-helicase; DNA-dependent ATPase	67.5	UV sensitive; fail to unwind R-loops; suppress T4 *59 uvsX*, *uvsY*, and *46* mutations	Auxiliary	132, 195, 196, 207, 208, 212, 244, 722, 737, 768, 769, 1061, 1191, 1197, 1199, 1222, 1240
uvsY = fdsB	ssDNA binding, recombination and repair protein; helper of UvsX, inhibitor of endoVII	15.8	UV sensitive; recombination-deficient; repair-deficient, DNA arrest; suppress T4 *49* mutations	Auxiliary	25, 44, 82, 182, 183, 195, 212, 213, 232, 357, 358, 380, 387, 392, 522, 542, 548, 589, 723, 724, 739, 768, 769, 1013, 1047, 1054, 1055, 1060, 1061, 1138, 1191, 1199, 1210, 1225, 1222, 1223, 1240
oriF = oriuvsY	DNA replication origin; *cis*-acting sequences in genes *uvsY*, *uvsY.-1* and *uvsY.-2*; primer transcript same as *uvsY*, *uvsY.-1* and *uvsY.-2* transcript		No DNA synthes from *oriF*	Auxiliary	46, 133, 357, 378, 563, 574, 573, 576, 577, 678, 724, 779, 830, 1109, 1215
25	Base plate wedge subunit	15.1	Defective tails	Essential	186, 249, 250, 264, 356, 358, 357, 530, 531, 532, 540, 822, 819, 1057, 1155, 1157; B. Szewczyk and J. Nieradko, personal communication; E. Tourkin and B. Poglozov,
26	Base plate hub subunit	23.9	Defective tails	Essential	186, 250, 264, 357, 531, 540, 567, 820, 958, 1108, 1157, 1240
26′	Internal in-frame translation initiation	12		?	357, 823
26″	Internal out-of-frame translation initiation	10.9		?	1108
51	Base plate hub assembly catalyst?	29.3	Defective tails	Essential	186, 249, 250, 264, 357, 540, 567, 821, 958, 1157; Szewczyk and Nieradko, personal communication
27	Base plate hub subunit	44.5	Defective tails; permit plating of fiberless phage	Essential	104, 186, 193, 249, 250, 264, 532, 1157, 1240

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TABLE 2—*Continued*

28	Base plate distal hub subunit	20.1	Defective tails	Essential	186, 249, 250, 264, 532, 565, 566, 568, 1157, 1240
29	Base plate hub; determinant of tail length	64.4	Defective tails	Essential	7, 186, 242, 243, 249, 250, 264, 532, 463, 464, 537, 1114a, 1157, 1240
48	Base plate; tail tube associated	39.7	Defective tails	Essential	61, 186, 242, 243, 249, 250, 264, 463, 464, 535, 536, 1114a, 1157
54	Base plate-tail tube initiator	35.0	Defective tails	Essential	61, 186, 243, 250, 249, 264, 463, 464, 530, 531, 535, 536, 1155, 1157
alt	Adenosylribosyltransferase (packaged and injected with DNA)	75.8	Synthetic defective with *modA* and *modB* deletions	Auxiliary	323, 324, 413, 435, 544, 545, 552, 937a, 1170
30 = lig	DNA ligase	55.3	DNA arrest; hyperrecombination	Essential; can be bypassed by functioning host ligase, when T4 *rII* is defective	32, 68, 184, 269, 439, 504, 580, 734, 776, 769, 821, 826, 1177, 1235; Thomas et al., unpublished
rIII	Unknown	9.3	Rapid lysis	Auxiliary	2, 3, 4, 224, 851, 875, 896, 897, 898, 923, 1235
31	Cochaperonin for GroEL	12.1	Head assembly; gp23 forms lumps; T4 topoisomerase is defective	Essential	27, 89, 226, 250, 264, 318, 319, 528, 607, 613, 693, 818, 824, 875, 896, 897, 898, 926, 927, 928, 1004, 1093, 1094, 1115
cd	dCMP deaminase	21.2		Auxiliary	170, 347, 376, 377, 682, 696, 717, 755, 756
pseT	Deoxyribonucleotide3′ phosphatase, 5′ polynucleotide kinase	34.6		Auxiliary; CTr5x (*lit*)	129, 185, 203, 512, 513, 514, 732, 734, 1008, 1021; Thomas et al., unpublished
alc = unf	RNA polymerase- and DNA-binding protein; transcription terminator on dC-containing DNA	19.0	Allow transcript elongation on C-DNA; no unfolding of host nucleoid	*E. coli* (pR386)	239, 406, 407, 511, 550, 597, 603, 786, 976, 1009, 1019, 1020, 1022
mlA = 63	RNA ligase; catalyst of tail fiber attachment	43.5	Defective tail fiber attachment	Auxiliary	319, 362, 374, 467, 721, 734, 889, 944, 1014, 1114a
denA	Endonuclease II that restricts dC-containing DNA	16.7	Defective in host DNA degradation	Auxiliary; restricted in *E. coli* B *rpoB5081*	137, 139, 134, 136, 135, 431, 569, 734, 737, 1149, 1153
nrdB	Ribonucleotide reductase β subunit (contains intron)	45.4	Reduced DNA synthesis	Auxiliary; *nrd*-defective hosts	63, 169, 173, 247, 341, 342, 348, 349, 382, 398, 696, 734, 1010, 1097, 1191, 1218, 1219
I-TevIII	Defective intron homing endonuclease	11.3		Nonessential	178, 247, 342, 609, 882, 991, 993, 1010
mobE	Putative mobile endonuclease	16.5		Nonessential	Thomas et al., unpublished
nrdA	Ribonucleotide reductase α subunit	86.0	Reduced DNA synthesis	Auxiliary; *nrd*-defective hosts	63, 169, 348, 349, 382, 398, 604, 696, 734, 1098, 1097, 1218, 1219
td	Thymidylate synthetase (contains intron)	33.1	Reduced DNA synthesis	Auxiliary; *td*-defective hosts	114, 162, 173, 179, 255, 274, 341, 342, 348, 349, 373, 377, 397, 431, 604, 695, 698, 717, 881, 882, 991, 1002, 1157
I-TevI	Intron-homing endonuclease	28.2		Nonessential	52, 114, 119, 120, 174, 175, 178, 206, 251, 252, 342, 348, 349, 453, 661, 662, 796, 797, 798, 882, 991, 993
frd	Dihydrofolate reductase	21.7	Reduced DNA synthesis	Auxiliary	162, 173, 347, 349, 377, 381, 431, 604, 734, 763, 880, 881, 882
32	ssDNA-binding protein, scaffold of DNA replication, recombination and DNA precursor-synthesizing protein machines	33.5	DNA arrest, UV sensitive, recombination and excision repair deficient	Essential; Tab32 for *ts* mutants; *32 am* mutations in ochre-suppressor-containing hosts are suppressed by *dda* mutations	18, 60, 107, 108, 142, 145–148, 154, 155, 264, 307, 392, 438, 440, 451, 465, 510, 549, 554, 564, 570, 579, 581, 629, 630, 660, 739, 760, 764, 768, 776, 774, 785, 794, 784, 811, 826, 831, 945, 982, 984, 985, 1034, 1055, 1047, 1054, 1064, 1071, 1087, 1128, 1132, 1161, 1173, 1176, 1198, 458, 473, 508, 509, 562, 663, 980, 1125–1127, 1133, 1136, 1200, 1223
segG = 32.1	Site-specific DNA endonuclease; localized gene conversion, exclusion	24.6		Nonessential	48, 655
59	Loader of gene *41* DNA helicase, ssDNA-binding protein	26.0	DNA arrest; fail to load gp41 helicase onto recombination intermediates, or ssDNA covered with gp32 or UvsX	Almost essential	38, 142, 195, 309, 371, 465, 478, 577, 629, 630, 760, 761, 768, 769, 799, 826, 830, 831, 890, 979, 1030, 1064, 1197, 1199, 1201, 1202, 1221

33	Protein connecting gp45 and gp55, to allow transcription by RNA polymerase from late promoters	12.8	No late RNA synthesis	Essential	97, 98, 109, 142, 264, 371, 404, 405, 436, 552, 786, 895, 1038, 1173, 1175, 1181, 1185, P. Williams, J. D. Mckinney, K. d'Acci, R. H. Drivdahl, C. Spaulding, J. Gleckler, and E. M. Kutter, unpublished data
dsbA	dsDNA binding protein	10.4	Facilitates some late RNA synthesis	Auxiliary	142, 303, 371, 372, 786, 995
rnh = das	RNase H; 5′ to 3′ DNase; yeast FEN homologue	35.6	Defective processing of Okazaki fragments; *das* mutations suppress T4 *46*, *47* and *uvsX* mutations	Auxiliary	41, 71, 72, 73, 142, 371, 372, 389, 402, 427, 429, 584, 731, 800, 826, 1139
34	Proximal tail fiber subunit	140.4	Fiberless particles	Essential	153, 217, 221, 248, 250, 264, 371, 391, 401, 538, 539, 920, 974, 1114a, 1148, 1190, 1187, 1189
oriG = ori34	DNA replication origin; primer transcript in opposite orientation of *34* transcript		No DNA synthesis from *oriG*	Auxiliary	55, 221, 573, 574, 577
35	Tail fiber hinge	40.1	Fiberless particles	Essential	153, 217, 248, 250, 264, 401, 538, 539, 920, 974, 1118, 1187, 1189, 1190
36	Small distal tail fiber subunit	23.3	Fiberless particles	Essential	153, 217, 248, 250, 264, 401, 538, 539, 840, 920, 1114a, 1187, 1189, 1190
37	Large distal tail fiber subunit	109.2	Fiberless particles, host range	Essential	153, 217, 248, 250, 264, 390, 391, 401, 538, 539, 745, 751, 752, 840, 920, 933, 934, 1023, 1067, 1070, 1114a, 1187, 1189, 1190
38	Assembly catalyst of distal tail fiber	22.3	Fiberless particles	Essential	217, 248, 250, 264, 390, 391, 401, 751, 920, 933, 1118, 1187, 1189, 1190
t = rV = stII	Holin, inner membrane pore protein, affects lysis timing and inhibition	25.2	Affect lysis by *e* lysozyme; suppress T4 *rII* and *63* mutations	Essential	2, 3, 4, 235, 374, 483, 583, 749, 851, 932
asiA	Protein that binds to host σ^{70}, inhibits interaction with −35 regions of classical promoters, and facilitates interaction with T4 MotA protein	10.6	Defective middle mode, and (indirectly) late transcription	Almost essential	109, 177, 180, 419, 420, 425, 552, 610, 741, 786, 847, 848, 849, 852, 858, 977, 989, 1038–1040, 1043, 1103, 1104
arn	Inhibitor of MrcBC restriction nuclease	10.9		Auxiliary	140, 215; T. Djavakhishvili, N. Mzavia, A. Poglazov, and E. Kutter, unpublished data
motA = sip	Activator of middle promoters; dsDNA binding protein specific for mot boxes	23.6	Defective middle mode transcription; suppress *rII*-defects in λ lysogens; affects interaction with σ^{70} and AsiA	Almost essential	109, 156, 176, 177, 275, 276, 277, 293, 321, 375, 417, 419, 420, 430, 477, 552, 686, 692, 706, 773, 848, 963, 987, 1043, 1106, 1107, 1109
52	DNA topoisomerase subunit; membrane-associated protein	50.6	DNA delay	Essential; temperatures below 25°C; inhibition of host topoisomerase IV with novobiocin	184, 295, 296, 297, 445, 451, 432, 447, 571, 577, 654, 708, 801, 834, 941, 1037, 1047, 1059, 1216, 1236
ac	Membrane protein	5.5	Acriflavine resistant	Auxiliary	161, 861, 935, 999, 1143
ama = rs		5.4	Acriflavine resistant	Auxiliary	161, 894
stp	Peptide modulating host restriction system	3.18	Suppress *pseT* mutations	Auxiliary	161, 203, 204, 513, 514, 515, 859, 1021
ndd = D2b	Protein that disrupts host nucleoid; binds to host HU	16.9	Nucleoid disruption defective	Auxiliary; CT447	101, 102, 103, 161, 550, 551, 1016, 1017, 1018
pla262	Unknown			CT262	161, 204
denB	Endonuclease IV, single-strand-specific endonuclease	21.2	Allow progeny production of T4 with dC-containing DNA	Auxiliary	138, 140, 204, 1123; H. Krisch, personal communication; M. Saunders and K. Kreuter, personal communication
rIIB	Membrane-associated protein; affects host membrane ATPase	35.5	Rapid lysis; suppresses T4 *30* and some *32* mutations	Auxiliary; rex^+ λ lysogens; P2-like HK239 lysogen; *tabR*	2, 3, 4, 56, 59, 106, 121, 159, 181, 191, 224, 292, 293, 365, 441, 504, 503, 810, 834, 851, 874, 1021, 1059, 1160

[a] Genes are listed by the currently used names, followed by alternative designations in the literature.
[b] Gene products processed into smaller peptides are indicated (∗) with the sizes or size range following the principal product.
[c] Because the distinction between "essential" and "nonessential" is not always obvious, when mutants have not been tested under all possible growth conditions or in all possible hosts, some "nonessential" genes are noted as "auxiliary." Where known, restrictive hosts or plating conditions for mutant genes are noted.

(or ribosome binding sites [RBS]). These include *alc*, *vs.4*, *e.5*, *tRNA.2*, and *57B.* Until further evidence is available, we have listed these genes as simply starting from the first of the two possible sites. It will be interesting to determine if both starts are used in any or all of these cases and if there are special functions for two nearly identical proteins. In bacteriophage lambda, for example, two nested proteins, differing in start sites by only two amino acids, have important complementary functions: one makes the pore to permit access by lysozyme to the peptidoglycan layer, and the other delays formation of the pore (91). The regulation of the balance between these two genes is not understood but is crucial in determining the timing of lysis.

(iii) It is clear that there can be genes within genes in different reading frames. These can be read in the same direction, as seen for gene *30.3′* (1234). They can also be in the opposite orientation, as seen for genes *repEA* and *repEB*, which are associated with initiation from origin E and are located opposite gene *5* (1109).

(iv) Introns that are later spliced out of the transcripts occur in at least three T4 genes: the thymidylate synthase gene (*td*), the gene encoding a subunit of the aerobic ribonucleotide reductase (*nrdB*), and the anaerobic ribonucleotide reductase gene (*nrdD*) (615, 991, 1229).

(v) As first demonstrated in T4 gene *60*, an unusual relationship between nucleic acid and protein sequence can also occur through translational bypassing. A 50-base mRNA segment in the coding region is not translated in gene *60* by a mechanism that depends on *cis*-acting signals in the mRNA, ribosomal protein L9, a pair of GGA codons 47 bases apart, and the structure of the cognate glycyl tRNA (408, 450). This is the only known high-efficiency bypass site; to date, the phenomenon is unique to T4. Bypass with much lower efficiency appears to occur at the junction of genes *56* and *69* (*segF*) (160, G. Mosig, unpublished data).

Programmed frameshifting, which shifts translation by 1 base into the +1 or −1 reading frame, can expand the coding capacity of a genome (13). To date, no instance of programmed frameshifting has been identified in T4, although many other viral DNA and RNA genomes use this approach to "recode" (322).

T4 shows nearly four times the gene density predicted for herpesviruses and yeast and twice that for *E. coli* (92, 556, 557). The high gene density reflects both the small size of many T4 genes and the fact that there are very few noncoding regions (about 9 kb, 5.3% of the genome). Furthermore, regulatory regions are compact, occasionally overlapping coding regions. In many cases, the termination codon of one gene overlaps the start codon of the next gene (see "Translation and posttranscriptional control" below). In addition, T4 has several groups of nested genes as mentioned above. Clearly, computational and bioinformatic tools do not yet identify all the genes and complex coding arrangements in a genome perceived by many to be "simple," like that of T4.

Table 3 summarizes the functional assignments of T4 genes, referring to the color codes used in the functional genome map of Fig. 3. Some T4 proteins have multiple activities and are listed in more than one group. For example, T4 RNA ligase A (*rnlA* or *63*) is also a catalyst for attaching tail fibers. Alternatively, a single activity can be viewed as being involved in multiple processes. For example, the nucleases EndoII and EndoIV (encoded by *den*A and *den*B) are responsible primarily for initiating degradation of cytosine-containing host DNA. They are included in the "nucleotide precursor" category because one important function of these proteins is the timely provision of nucleotide precursors. They are also included among the host alteration/shutoff genes.

TABLE 3. Functional categories of T4 genes[a]

A.	Transcription [red]: *asiA*, *dsbA*, *goF*, *modA*, *motA*, *motB*, *mrh*, *rpbA*, *srd*, *srh*, *33*, *55* (*alc*, *alt*, *45*)
B.	Translation [brown]: *cef*, *dmd*, *modB*, *regA*, *regB*, *vs*, *rnlA*, *rnlB* (*modA*), tRNAR, tRNAI, tRNAT, tRNAS, tRNAP, tRNAG, tRNAL, tRNAE; *rnaC*, *rnaD*
C.	Nucleotide metabolism [orange]: *cd*, *denA*, *denB*, *frd*, *nrdA*,*B*,*C*,*D*,*G*,*H*, *nudE*, *pseT*, *td*, *tk*, *1*, *42*, *56*
D.	DNA replication, recombination, repair, packaging, and processing [yellow]: *dda*, *denV*, *dexA*, *repEA*, *repEB*, *rnh*, *uvsW*, *uvsX*, *uvsY*, *16*, *17*, *30*, *32*, *39*, *41*, *43*, *44*, *45*, *46*, *47*, *49*, *59*, *52*, *60*, *61*/*58*, *62*
E.	Virion proteins [blue]: Head: *soc*, *hoc*, *inh*, *ipI*, *ipII*, *ipIII*, *2*, *4*, *20*, *23*, *24*, *67*, *68*, (*22*, *21*) [dark blue]; Neck: *13*, *14* [medium blue]; Tail: *3*, *5*, *6*, *7*, *8*, *9*, *10*, *11*, *12*, *15*, *18*, *19*, *25*, *26*, *27*, *28*, *29*, *48*, *53*, *54* [light blue]; Tail fiber: *wac*, *34*, *35*, *36*, *37* (*rnlA*) [pale blue]
F.	Chaperonins/assembly catalysts [stippled blue]: *21*, *22*, *31*, *38*, *40*, *51*, *57A*, *rnlA*
G.	Lysis [green]: *e*, *rI*, *rIII*, *sp*, *t* (*rIIA*, *rIIB*)
H.	Host or phage interactions [purple]: *ac*, *arn*, α-*gt*, β-*gt*, *dam*, *imm*, *pin*, *rIIA*, *rIIB*, *stp*, (*gol*, *pseT*, *rnlA*)
I.	Host alteration/shutoff [pink]: *alc*, *alt*, *gol*, *ndd* (*denA*, *denB*, *modA*, *modB*)
J.	Homing endonucleases and homologs [peach]: I-*Tev*I–III, *mobA-mobE*, *segA-segG*
K.	Predicted integral membrane or periplasmic proteins [squiggle]: *denB.-1*, *e.2*, *e.3*, *e.4*, *ndd.3*, *ndd.4*, *ndd.5*, *nrdC.7*, *pseT.3*, *tRNA.4*, *47.1*, *52.1*, *55.8* (*ac*, *imm*, *rI*, *t*, *7*, *29*)
L.	Unknown function [white]

[a] Genes in parentheses appear in another, primary category. Primary functional assignments and the corresponding colors are used in Fig. 3.

Characterized T4 Genes and the Early Genetics

Only 62 of the T4 genes are "essential" under standard laboratory conditions (rich medium, aeration, 30 to 37°C); mutants altered in a few other genes produce very small plaques under standard conditions. Many of these key genes are much larger than the average T4 gene; together, they occupy almost half of the genome. They include genes that encode proteins of the replisome and of the nucleotide-precursor complex, several transcriptional regulatory factors, and most of the structural and assembly proteins of the phage particle. Most of these genes were first identified by the isolation of *amber* or temperature-sensitive conditional-lethal mutations and were assigned numbers (Table 2) before their functions were determined (264).

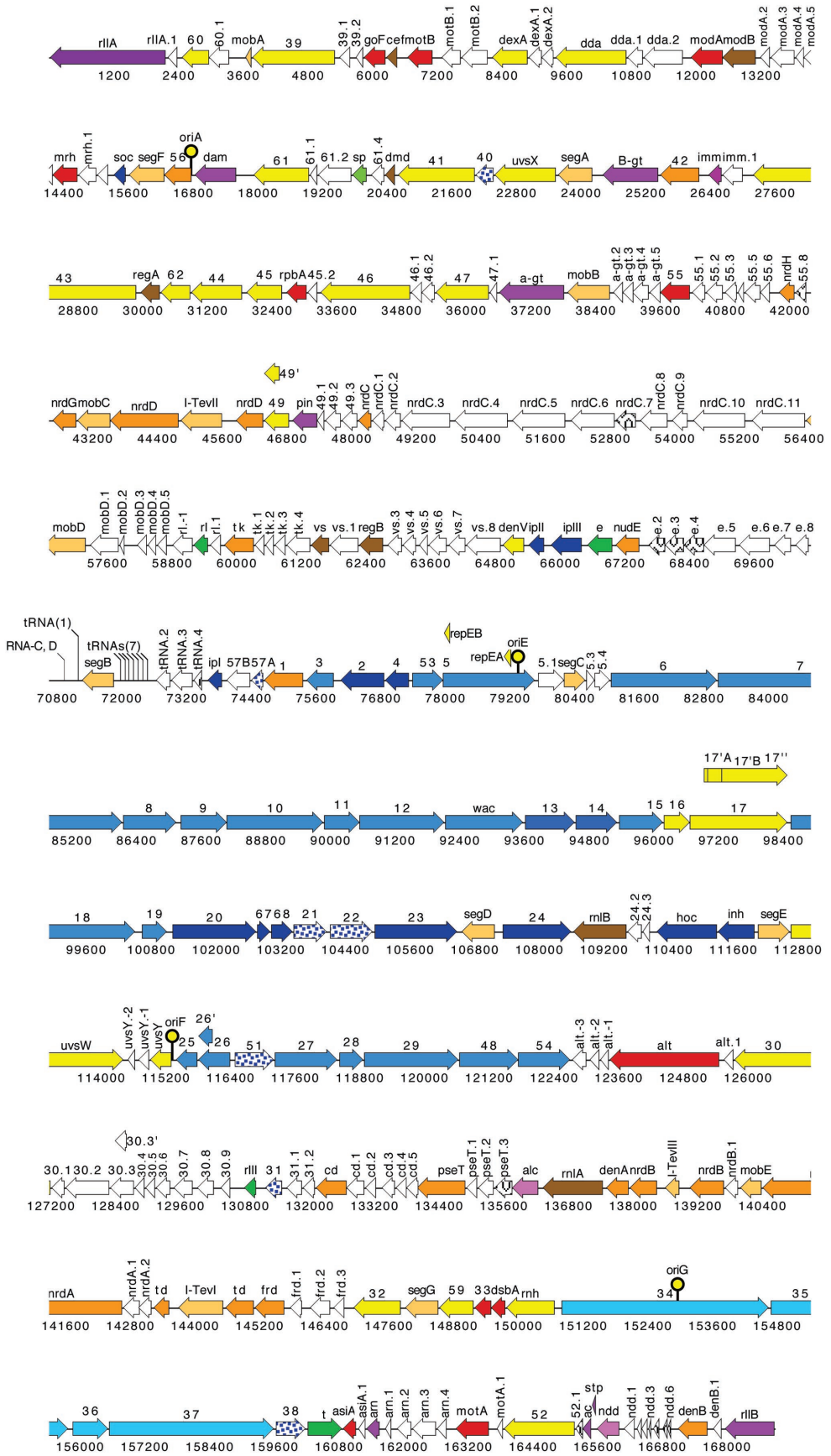

FIG. 3. Functional genome map of bacteriophage T4. The coding capacity of the T4 genome is shown for both characterized and hypothetical ORFs. The color scheme (by gene function) is as defined in Table 3. Origins of DNA replication (*ori*) indicated are those that are best characterized. Locations of the multiple promoters and terminators can be determined from Table 1.

Nonessential genes were typically assigned letter designations, reflecting the phenotype associated with the mutation (Table 2) or the host function that the gene duplicated (*nrd*, *frd*, *td*, etc.). They encode such products as enzymes for nucleotide biosynthesis, recombination, and DNA repair; nucleases to degrade cytosine-containing DNA; proteins responsible for exclusion of superinfecting phage, for lysis inhibition under conditions of high phage/host ratios, and for other membrane changes; and inhibitors of host replication, transcription, and protease activity. Unfortunately, the designation by letters versus numbers does not automatically identify a gene as essential. For example, the products of genes *t*, *motA* and *asiA* are essential under standard conditions, while that of *69* (*segF*) is not. Mutations in genes *46* and *47* still permit the synthesis of a few phage per cell, but too few are produced to reliably produce plaques under most conditions; a burst size of about 10 is generally required for plaque formation. Primase (gene *61*) and topoisomerase (genes *39*, *52*, and *60*) mutants produce plaques at temperatures above 25°C because they can use a recombinational bypass mechanism to prime lagging-strand DNA synthesis (784, 788). In several cases, mutations initially assigned to different genes by spot-test complementation ultimately proved to reside within the same gene; thus, genes *58* and *61* are identical, as are genes *2* and *64* and genes *4*, *50*, and *65.*

Most genes first identified by mutation have now been located in the DNA sequence. However, no genes have yet been identified for any of the reported ribosome-binding proteins or other proteins that might be involved in the shutoff of host translation (reviewed in reference 1166). Mutations *ama*, *stI*, *stIII*, *rs*, *goFB*, and *goFC* have not been assigned to a sequence; the original mutants identifying most of these genes have been lost.

ORFs of Unknown Function and Host Lethality

As noted above, the T4 genome is tightly packed with probable genes. Almost half of these still do not have an assigned function, but most have some or many of the characteristics of true T4 genes that encode known proteins. By convention among T4 researchers, each hypothetical or uncharacterized ORF is named sequentially in the clockwise direction by reference to the preceeding known gene, as in "*xxxY.n*". Therefore, *dexA.1* and *dexA.2* are the two ORFs following *dexA* on the map. This convention immediately locates each such ORF on the T4 map but implies nothing about its function. The only exceptions to this convention are in positions where an ORF follows a gene transcribed in the opposite direction or with very different timing. In those cases, the ORF may be rooted to the following gene on the map, but a minus sign is used (e.g., *uvsY.−1*, *rI.−1*).

Most of the 127 uncharacterized ORFs lie in regions transcribed counterclockwise from strong early promoters. Only 16 of the uncharacterized ORFs would be expressed late in the T4 infection cycle. These are (i) ORFs under control of a late promoter in the clockwise direction, where almost exclusively late genes are found (*5.1*, *5.3*, *5.4*); (ii) ORFs following late promoters (some of which also may still be expressed from upstream early and/or middle promoters) in the counterclockwise direction (*rI.1* and *rI.−1*; *24.2* and *24.3*; *uvsY.−1* and *uvsY.−2*; *alt.−1* to *alt.−3*; and *30.9*); and (iii) ORFs following middle promoters and without late promoters (*denB.1*)

Because they are likely to be expressed immediately after infection, some of the 127 uncharacterized T4 ORFs may be involved in the transition from host to phage metabolism or in resistance to plasmid- or prophage-encoded toxic proteins. Many of these genes (shown in white in Fig. 3) are in regions that can be deleted without seriously affecting phage production under usual laboratory conditions. However, at the same time, they have largely been retained in T4-related phages (534, 596, 919; E. Kutter et al., unpublished data about the *nrdC-tRNA* region). Most of the T4 early promoters are in these widely conserved yet deletable regions, which are densely packed with the predicted ORFs. Many of the hypothetical ORF proteins—at least those over about 9 kDa—have been identified on two-dimensional gels by comparing labeled proteins produced by wild-type and the T4 deletion strains (604). These proteins are often produced in large quantities just after infection. Those that have been tested are generally lethal or very deleterious to the growth of *E. coli*.

Together, these findings suggest that the host-lethal, immediate-early proteins confer selective advantage for the phage but that they are necessary only under certain environmental conditions, for infecting other hosts, or that there is redundancy in their functions. Some of the proteins are quite large, but most are smaller than 15 kDa. In general, work with T-even phages emphasizes that small hypothetical ORF-encoded proteins should not be overlooked. The smallest characterized T4 protein, Stp, consists of only 29 amino acids; 62 predicted T4 proteins have fewer than 100 amino acids.

Most of the unidentified ORFs show very little homology to non-phage genes in the databases. That many of these ORFs are deleterious to *E. coli* when cloned reinforces the notion that their products inhibit or redirect important host proteins and that they may be useful in studying cellular proteins in their active, functional state. One example, the Alc protein, specifically terminates the elongation of transcription on cytosine-containing DNA (599, 601). Alc appears to uniquely recognize the rapidly elongating form of the RNA polymerase (RNAP) complex. It would be a valuable tool for studying the dynamic structural changes that occur in the polymerase during transcription; all other current approaches only examine the polymerase paused at particular sites and infer its behavior from the resultant static state.

Some of the host-lethal proteins may also suggest new targets for antibiotics. They should also aid in studies of evolutionary relationships and protein-protein interactions.

Another interesting set of proteins involved in the transition from host to phage gene expression involves three different ADP-ribosyltransferases. These include Alt, which is packaged in the phage particle and carried into the cell with the DNA, ModA, and ModB. The role of these ADP-ribosylation activities in the T4 transcription cycle is detailed below.

To fully understand the takeover of host metabolism by T4-like phages, it will be necessary to identify the ORFs that indeed encode proteins in vivo and to determine their biological functions and the conditions under which they exert their effects. The sequences of some of the small proteins that have been studied are highly conserved among the T-even phages,

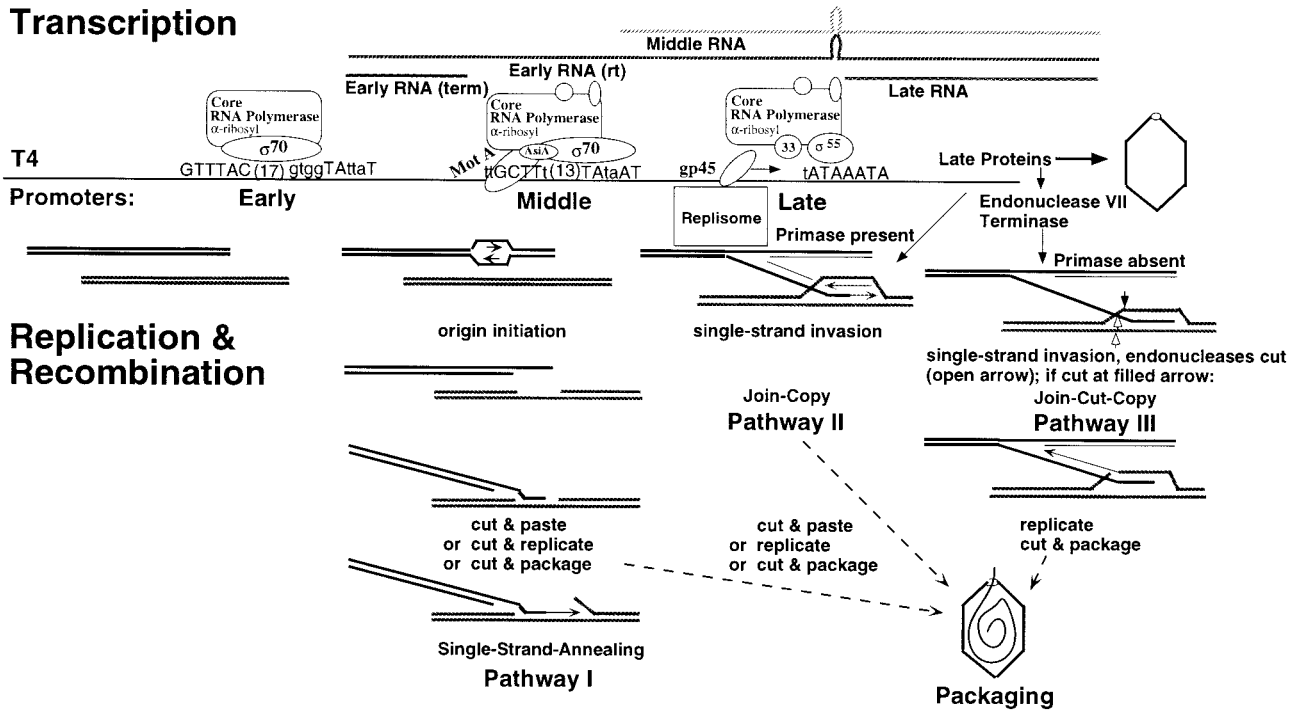

FIG. 4. Diagram of the relationship between the T4 transcriptional pattern and the different mechanisms of DNA replication and recombination. The top panel shows the transcripts initiated from early, middle, and late promoters by sequentially modified host RNA polymerase. Hairpins in several early and middle transcripts inhibit the translation of the late genes present on these mRNAs. The bottom panel depicts the pathways of DNA replication and recombination detailed later in this review. Hatched lines represent strands of homologous regions of DNA, and arrows point to positions of endonuclease cuts. Reprinted from reference 769 with permission from the publisher.

presumably reflecting their complex interactions with multiple cell components.

PROMOTERS AND TRANSCRIPTION FUNCTIONS

T4 transcription uses three major classes of promoters—early (Pe), middle (Pm), and late (Pl)—which broadly define the developmental stages of the T4 infection cycle (Fig. 4). The genomic positions of these promoters and of *rho*-independent terminators are indicated in Table 1. The overall temporal pattern of transcription through the T4 genome is quite complex. Many genes are served by multiple classes of promoters, and so a number of promoters may precede genes and a terminator in a transcription unit. Furthermore, protein-dependent or cotranslation-dependent antitermination contributes to the pattern of active T4 transcripts. Some RNA processing and superimposed translational controls (discussed later) also complicate the interpretation of data.

T-even phages rely entirely on the host core RNAP throughout infection. It is therefore not surprising that T4 promoter specificity and transcription are affected by the multiple interactions of the bacterial RNAP α subunits, β/β′ subunits, and σ^{70} promoter recognition subunit. Most studies with T4 have been done in cells growing exponentially under high aeration, where the host σ^{70} is present throughout infection. Under these conditions, the temporal transition through the different classes of promoters is accompanied by covalent modifications of RNAP and the appearance of new protein transcription factors that act in various ways. All of these functions serve to enhance phage promoter recognition and transcription; no DNA-binding transcriptional repressor protein has been identified in the T4 developmental cycle.

To date, little is known about T4 infection under stationary-phase or anaerobic conditions (such as the phage would encounter in nature [599a]). Preliminary evidence shows that the patterns of infection under these conditions are often very different and that the status of *rpoS* clearly makes a difference in the outcome of aerobic infection in stationary-phase cells (E. Kutter, unpublished data). Corbin et al. (187a) have recently shown that T4 infection affects the morphology of *E. coli* biofilms and that glucose-limited biofilm cells can be a reservoir for phage. Additional study of T4 gene expression under different environmental conditions is warranted.

Early Transcription

At the onset of infection, 39 T4 early promoters (plus a few host-like promoters [see below]) compete with about 650 σ^{70}-dependent bacterial promoters for approximately 2,000 RNAP holoenzymes in the commonly studied, rapidly growing exponential cells; the polymerase number is smaller under more limiting growth conditions. T4 redirects the transcriptional machinery to T4 promoters with high efficiency, as reflected by the appearance of phage-specific proteins soon after infection, the rapid shutoff of host gene expression (reviewed in reference 599), and, ultimately, the virulence of the phage. That T4 early promoters are stronger than *E. coli* promoters presumably plays a major role, since most promoters can be cloned only on

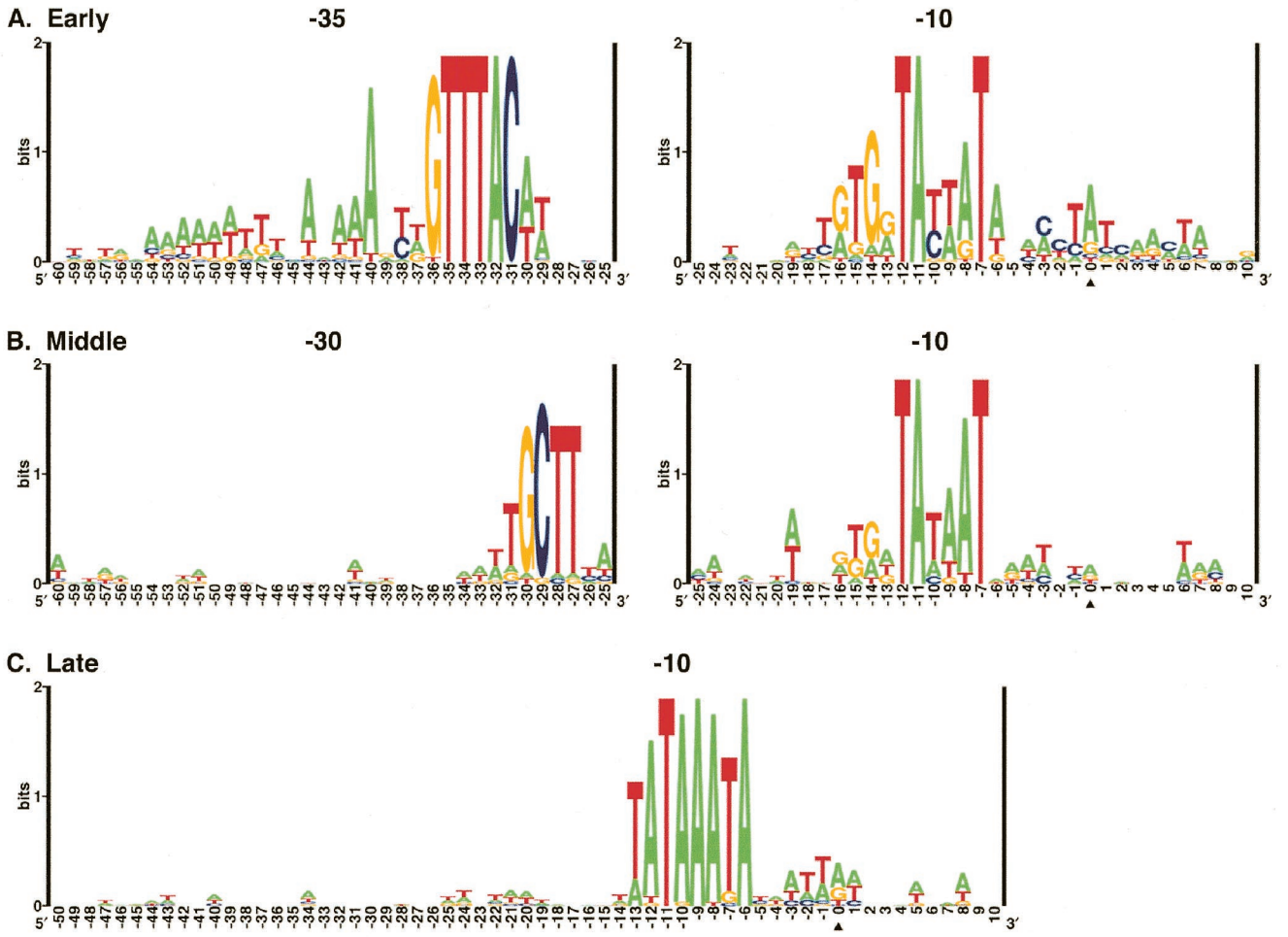

FIG. 5. Logo of T4 promoters. Nearly all the sequences in each alignment have promoter activity, as demonstrated by primer extension, transcription from cloned DNA fragments, or RNA hybridization assays. The promoters included whose start sites have not been mapped all precede a corresponding early, middle, or late gene and show significant similarity to the relevant promoter class. Sequences were independently aligned in the −10, −30, or −35 region. The information content (R_s) is calculated in "bits" and is the sum of the R_s for each region (except for the late logo, which was calculated from the single alignment at −10). Alignments, logos and R_s values were obtained as described previously (966; E. Miller, T. Dean, and T. Schneider, unpublished data). The triangle marks the +1 transcription start site. (A) 39 early promoters, R_s = 38.3 bits; (B) 30 middle promoters, R_s = 21.1 bits; (C) 50 late promoters, R_s = 16.2 bits.

plasmids designed to attenuate their transcriptional activity. Transcription start sites of many of the early promoters have been mapped by primer extension off of mRNA from T4-infected cells and/or from promoter-cloning vectors (reviewed in reference 1169).

The 39 characterized Pe sequences (1168, 1169) are noted in Table 1 and have been analyzed using the information content software developed by Schneider and Stephens (966). The sequence logos, maximizing the alignment at the −10 region and, independently, at the −35 region, are shown in Fig. 5A (E. Miller, T. Dean, and T. Schneider, unpublished data). The analyses show that there is high conservation at the −12, −11, and −7 positions similar to that in the *E. coli* Eσ^{70} promoters. However, T4 Pe sequences have more extended −10 regions, with sequence conservation extending through the G predominating at −14 to −18. In one group of early promoters, significant conservation extends on both sides of the −10 region [5′-GTGG(TAT/CT/AAT)ACAACT-3′] up to the T at position −1 (1169). The start site of the transcript (coordinate 0 in Fig. 5A) is frequently an A. The Pe −35 region has a 6-bp conserved region from position −36 to −31 (GTTTAC) that differs from the *E. coli* -35 consensus sequence (TTGACa). Upstream of the −35 region, T4 early promoters display a bias toward A-rich tracts centered around −42 and −52 (Fig. 5A) (1169). Upstream A-tract sequences (position −42) were first observed with T5 promoters (314) and have since been shown to activate certain *E. coli* promoters, of which the *rrn* operon promoters are the best studied. By affecting DNA curvature, upstream A tracts (UP elements) directly enhance Eσ^{70} promoter activity through interactions with the RNAP α subunit (266, 939). Many of the T4 Pe sequences include the most enhancing type of *E. coli* UP elements, where the two A tracts are separated by a T-rich region (266).

Sequence logo analysis yields a quantitative parameter defined as R_{sequence} (R_s, which is the sequence information content of a collection of aligned sequences) (966). The sum of R_s

for the −10, −35, and A-tract regions displayed for the early promoters in Fig. 5A is 38.3 bits, which is substantially greater than the 17.6 bits (as calculated by Liebig and Rüger [639]) required to select the Pe promoters from a genome of known length and base composition ($R_{\text{frequency}}$ [see reference 966 for a thorough description of logos and information theory as applied to DNA-binding proteins]). The R_s/R_f ratio of >2 for these values suggests that the twofold excess information in the aligned T4 early promoters is due to both unmodified host RNA polymerase and its ADP-ribosylated counterpart (see below) binding and initiating transcription in these regions. The refinement of the analysis of the T4 early promoters by means of information theory is in progress (Miller et al., unpublished). Together, features of T4 early promoters allow them to be distinguished from the host promoters and elevate their transcriptional activity to a level that often exceeds that of the strongest *E. coli* promoters.

In addition to these early T4 promoters, there are some promoters that more closely resemble *E. coli* promoters. P *bac* (639, 1169) has been identified by mapping transcripts from cells carrying plasmid-bome T4 genes. It directs the synthesis of transcripts that are complementary to gene *3* mRNA. P *repE*(coordinate 79405 [Table 1]) has been identified in T4-infected cells (1109). It directs the synthesis of RepEA and RepEB proteins and an RNA primer for *oriE*-initiated replication. This RNA would be complementary to late-gene *5* transcripts but is undetectable by the time when these transcripts are made. Transcripts preceding gene *32* (142) have been detected that also map to σ^{70}-like promoters. While the later are active on supercoiled plasmids, little to no transcription was observed in T4-infected cells. A similar promoter preceding gene 57A was inferred to be active on plasmids (409). These host-like promoters as a group may be of limited significance, when host transcription in general is turned off and RNAP is modified early during T4 infection.

T4 modifies the host RNAP in several ways after infection. However, most of these modifications are not essential to the infection process. A 70-kDa protein, gpAlt, enters the host with the infecting DNA. Alt is a mono-ADP-ribosyltransferase that targets arginine residues. It efficiently ADP-ribosylates one of the α subunits of RNAP in the carboxy-terminal domain at position Arg265 (323, 324, 435, 459, 937a, 1011) and ADP-ribosylates the three other polymerase subunits to a lesser extent, along with a number of other uncharacterized polypeptides. ADP-ribosylation of RNAP by cloned Alt protein leads to enhanced transcription from cloned T4 early promoters (544). Mutation analyses reveal that T4 early promoters interact strongly with unmodified RNAP and even better, in most cases, with RNAP in which only one of the α subunits is ADP-ribosylated. In particular, base position −33 of the T4 promoter and the A-rich UP element at position −42 contribute to the strong interactions with ADP-ribosylated RNAP of T4-infected cells (1026). Therefore, Alt presumably contributes to the preferential transcription from T4 promoters after infection (1168, 1170).

Shortly after infection, two new ADP-ribosyltransferases are expressed, ModA (23 kDa) and ModB (24 kDa) (780, 1077). ModA, first observed by Skorko et al. (1011), ADP-ribosylates the α subunits of host RNAP but shows no activity toward the β, β′, and σ subunits. Like Alt, ModA ADP-ribosylates Arg265 on the α subunit; unlike Alt, it targets both α subunits, not just one. ADP-ribosylation replaces the positive charge of the Arg residue by two negative charges carried by the two phosphate groups and affects DNA-protein as well as protein-protein interactions. This second ADP-ribosylation inhibits transcription from promoters with the UP element; expression of cloned *modA* is highly lethal to the host. (The action of ModB [205] is summarized below.)

Middle Transcription

Thirty T4 middle promoters (Pm) were compiled and are presented in the sequence logo of Fig. 5B. All of the middle promoters used in the logo have been mapped with respect to the 5′ end of the transcript and shown to be dependent on the transcriptional activator protein MotA (reviewed in references 692, 987, and 1043). There appears to be little dependence on an A at the +1 start site of the middle transcripts (coordinate 0 in Fig. 5B). The conserved −10 region resembles that of the Pe sequences (5′-TATAAT-3′ is most common), with −12, −11, −8, and −7 having nearly the same base composition. As seen for T4 early promoters, sequence conservation extends into the traditional spacer region of $E\sigma^{70}$ promoters, up to position −16. Significantly though, T4 Pm sequences have neither the well-characterized $E\sigma^{70}$ −35 region nor the Pe −35 region. Middle promoters are characterized by a specific −30 sequence called the Mot box, which extends between −32 and −27, with GCTT being the most highly conserved. The information content (R_s) calculated for the optimally aligned regions from −60 to +10 of the logo in Fig. 5B is 21.1 bits, with 13.1 bits of the information being associated with the −10 alignment. This is considerably less than the 38-bit R_s value of the Pe promoters, implying that there is less competition with host promoters for RNAP, perhaps because host DNA is already being degraded and ADP-ribosylation of RNAP is completed. Approximately 8 bits of R_s information are required for MotA to recognize the MotA box sequence. T4 middle promoters are all located on the minus strand (Table 1) relative to the GenBank genome entry. Fourteen new middle promoters have been recently described (1095a; R. Nivinskas, personal communication).

T4 gene products AsiA and MotA are required for middle-mode transcription. AsiA is an anti-σ factor protein (see reference 454a for a review of anti-σ proteins) that coactivates RNAP for middle-mode transcription initiation by the formation of AsiA-σ^{70} heterodimers (12, 180, 1104). This interaction interferes with the recognition of −35 promoter sequences and at the same time stimulates T4 middle-mode transcription (180, 425, 1103, 1104). The AsiA-σ^{70} interaction is regarded as the pivotal event in the transition between T4 early and middle transcription: in vitro it both inhibits the recognition of most host promoters and early T4 promoters and stimulates T4 middle-mode transcription (180, 425, 848, 849, 1104). However, in vivo, defective *asiA* mutants do not prolong early transcription (858), suggesting that other proteins (i.e., ModA and ModB) turn off most early T4 promoters. MotA is a DNA-binding transcriptional activator protein that binds to the MotA box sequence (Fig. 5B) through its C-terminal domain, facilitating Pm promoter recognition and transcriptional activation (see the model proposed in reference 987 and in Fig. 4

of that reference). MotA and AsiA together increase the initial recruitment of RNA polymerase to T4 middle promoters and facilitate the clearance of RNAP from the promoter and into the elongation mode (419).

Late Transcription

Late transcription is responsible for the synthesis of T4 head, tail, and fiber proteins, in addition to the several virion assembly factors (1173) and recombination genes required for T4 late recombination/replication (784) (see below). Fifty late promoters (Pl) have been compiled and aligned for the Pl sequence logo shown in Fig. 5C. There is only a slight bias toward purines at the +1 transcription start site, while there is extensive conservation of the −10 sequence TATAAATA from −13 to −6. This sequence alone contributes the major information content for late promoters, which have an R_s value (see the definition above) of 16.2 bits. There is no −35 or MotA-like −30 sequence in T4 late promoters. T4 encodes one of the smallest known sigma factors, gp55 or σ^{55}, for RNAP recognition of late promoters (1173). It specifically recognizes the −10 region sequence. Although σ^{55} is required to selectively initiate transcription at T4 late promoters, it is not sufficient. AsiA does not appear to be a major determinant of middle- versus late-promoter competition (552). Instead, another phage-encoded protein, gp33, acts as a coactivator of late transcription, mediating interactions between σ^{55} and the sliding clamp encoded by T4 gene *45.* The trimeric gp45 protein is a key component in the processivity of the DNA replication complex and is also essential for late transcription (a "mobile enhancer" [405, 1186]). Primer-template junctions and single-stranded DNA (ssDNA) nicks are the most efficient loading sites for gp45, which is loaded by the clamp-loader proteins gp44 and gp62; gp45 slides on the DNA, enhancing the opening of late promoters more than 1,000 bp away from the loading site. Activated late promoters outcompete middle promoters on the same plasmid in vitro, especially at higher ionic strengths. This advantage is enhanced by ADP-ribosylation of RNAP α subunits and by binding of the phage-encoded RpbA protein to the RNAP core (552, 1082, 1173). DsbA protein is thought to also affect transcription from some late promoters (995), although it is not essential (1114).

At least three T4 proteins—Mrh, Srd, and Srh—are implicated in the interactions of different host sigma factors with core RNAP (781). Under heat shock conditions, the host σ^{32} (RpoH) competes with other sigma factors for host core RNAP (354, 482). The products of the two nonessential genes *mrh* and *srh* together modulate the phosphorylation of σ^{32} using ATP (781; Mosig, unpublished). Presumably, this would be most important for T4 late transcription, since T4 σ^{55} is one of the weakest known sigma factors. Consistent with this idea, infection with wild-type T4 of one specific host *rpoH* mutant (but not others) is aborted at the onset of late transcription, unless the T4 *mrh* gene is deleted (290). Srh protein resembles a segment of σ^{32} that interacts with RNAP, suggesting that it acts as a decoy. Similarly, T4 Srd protein resembles an RNAP-interacting segment of σ^{70} and σ^{38} (RpoS; stationary-phase and oxidative stress sigma factor) and would also decoy RNAP from the host promoters. Expression of *srd* from a clone is lethal to *E. coli.*

Microarray Analysis of T4 Transcription

In a recent report (672), the expression profile of the entire T4 genome was evaluated by mRNA hybridization microarray analysis. RNA samples were obtained from 0 to 25 min during a T4 infection cycle at 30°C. Gene expression patterns were then evaluated by cluster analysis. Early-, middle-, and late-gene clusters were clearly identified and were in striking agreement with the extensive literature for individual T4 genes. Exceptions were in regions yielding overlapping transcripts from different promoters, where temporal assignments would be more difficult. Of particular note was the complete absence of late-gene expression prior to 15 min, with the near cessation of all early- and middle-gene transcription following onset of the late period. The analysis, as stated by the authors, not only confirms the extensive literature on T4 but also suggests that microarray-based expression profiling will be a valuable tool in determining the transcription pattern, and ultimately the function, of the hypothetical and uncharacterized T4 genes. Similar strategies will be invaluable for future studies of other phage and viral genomes.

Transcription Termination and Predicted RNA Structures

Intrinsic transcription terminators. Intrinsic, Rho-independent transcription termination sites are characterized by an intramolecular RNA helix (stem-loop or hairpin) in the mRNA, followed by a U-rich sequence (33, 364, 929, 1209). These features were used in the computer programs TransTerm, GCG Terminator, and FindPatterns (211, 265) to predict probable Rho-independent terminators in the T4 genome (E. Miller, unpublished data). About 15 years ago, 4-nucleotide UUCG loop sequences were characterized in T4 as conferring exceptional stability to RNA secondary structures (1100). Following that initial report, other stabilizing RNA tetraloop sequences were described (412, 1183), and their prevalences in *E. coli* Rho-independent terminators were later compiled (201). Identification of T4 transcription terminators was enhanced using pattern searches for the prominent tetraloop sequences (e.g., UUCG and GNRA), which to date are not included in the TransTerm or Terminator search parameters. In some cases, the predicted RNA structures may act to stabilize mRNA against degradation rather than functioning directly in termination (142, 340).

Features of the predicted intrinsic transcription terminators in the T4 genome are summarized in Table 4, and their genome positions are noted in Table 1. Overall, 34 terminators were located between genes or at the 3′ end of an ORF; 24 of these are predicted to be on early transcripts (therefore, their sequence corresponds to the minus strand of the T4 GenBank entry), while 10 are on late transcripts. The predominant tetraloop sequence is UUCG, found in 18 of these terminators, while 3 are GAAA and 3 are GCAA. All are about equally present on early and late transcripts. The remaining 10 transcription terminators have noncanonical 4-nucleotide loop sequences or have 3-, 5- or 6-base loop regions. Their features and locations suggest that they, too, are probably functional.

Many of the probable terminators are located at the ends of long early or middle transcripts, preceding a downstream

TABLE 4. Intrinsic terminators mapped or predicted on the T4 genome

5′ gene	3′ gene	Strand	Start[a]	Stem-loop-stem-poly(U)[a]	Tetraloop	Identifier[b]
Intergenic locations						
39.1	*39*	−	5384	GGCC UUCG GGCC TTTAGCTTTAT	UUCG	TT, Term
soc	*mrh.2*	−	15305	GGACTCC TTCG GGAGTCC TTTTTTCATTT	UUCG	TT, Term
43	*imm.1*	−	27183	GGACC TCCA GGTCC CTTTTT	UCCA	Term
regA	*43*	−	29967	GGGGC TTCG GCCCC TTATTT	UUCG	TT, FP
45	*44*	−	31912	GGGC TTCG GCCC TTTATAATTT	UUCG	TT, FP
a-gt	*47*	−	36622	GGGC TTCG GCCC TTTAGCTTT	UUCG	TT, FP
a-gt.2	*mobB*	−	38731	GGAGC TTCG GCTCC TATATTGCTTTATAAATTTTTT	UUCG	FP
55.3	*55.2*	−	40836	GGGC TTCG GCCT TTTT	UUCG	FP
nrdH	*55.6*	−	41800	GGCCC AGA GGGCC CGTCTTAATCTTCT	None	TT
pin	*49*	−	46884	CCCTTACCT TAAAT AGATAAGGG TATTTATTATTTT	None	TT
nrdC.11	*nrdC.10*	−	55432	GGGAGCC TTCG GGCTCCC TTTTTTATTT	UUCG	TT, Term, FP
rI.-1	*mobD.5*	−	58813	GTCTCC TTCG GGAGAC TTTTTTTCATTTT	UUCG	TT, Term, FP
vs	*tk.4*	−	61369	GGGCG ATATTG CGCCC TTTT	None	TT, Term
e.6	*e.5*	−	69306	GGGGC TTCG GCCCC TATTACTT	UUCG	Term, FP
RNA C	*e.8*	−	70856	GCCCCGACC GAAA GGTTGGGGC TTTTT	GAAA	TT, Term
8	*9*	+	87161	GGGAGCC CATG GGCTCCC TTTTTCTTT	CAUG	TT, Term
wac	*13*	+	93596	GGGGCC GCAA GGCCCC AAAGGATTTT	GCAA	FP
19	*20*	+	101131	GGGGA GAAA TCCCC ATCCTGCTT	GAAA	Term
23	*segD*	+	106537	GGGAACC TTCG GGTTCCC TTTTTTCTATTTT	UUCG	Term, FP
24	*rnlB*	+	108613	GGGACC TTTC GGTCCC TTTTTATTT	UUUC	TT, Term
24	*rnlB*	+	108668	GTACA TCT TGTAC CATTTT	None	TT
hoc	*24.3*	−	110180	GGGGC TTCG GCCCC TTTCTTCATTTT	UUCG	TT, Term
uvsY.-2	*uvsW*end	−	114472	GGCCCTTCC TTTTT GGTTGGGCT TTTTAAT	None	TT, Term
54	*alt.-3*end	+	122720	TGGGGACC GAAA GGTCCATA TTTTTATTT	GAAA	Term
alt.1	*alt*	−	125558	GGCC UUCG GGCC TTTAATTTTAT	UUCG	TT, Term
30.9	*30.8*	−	130358	GGACTCC TTCG GGAGTCC TTTTTTATTTT	UUCG	TT, Term
30.9	*30.8*	−	130402	CGAGATG ATG CTTCTCG TTTT	None	TT
nrdB	*denA*	−	137950	TGGGCC GCAA GGCCCA TTTTATTAT	GCAA	FP
nrdA	*mobE*	−	140384	TTCCCGAGC TCAG GCTCGGGAA CCTTTAT	UCAG	Term
32	*frd.3*	−	146925	GGGACC CTAGA GGTCCC TTTTTTATTTT	None	TT, Term
35	*36*	+	155811	GGGACCC TTCG GGTTCCC TTTTTCTTT	UUCG	TT, Term, FP
37	*38*	+	159628	GGGGC TTCG GCCC TTCT	UUCG	FP
t	*asiAend*	+	160924	CCCTCGTTGAA TTCG TCGATGAGGG TTTTCTTATCTTCTT	UUCG	FP, Term
motA.1	*motA*	−	163724	GGGAGAGC CGAG GCTCTCCC TTTTTTATTTT	CGAG	TT,Term
ac	*52.1*	−	165332	GGGCTA TTCAT TAGCCC TTGCTGCTTTATT	None	Term
denB.1	*denB*	−	167736	GGGC UUCG GCCT TTTGTTTT	UUCG	Term, FP
Peculiar locations or nonpoly(U)3 ′ ends						
56/segF	*segF*	−	16233	GACGCC GAAA GGCGTC TCTTTT	GAAA	FP
uvsX-40	*40*	−	22347	CCCCCTC TTCG GAGGGGG AAGAAGAAAGAAAAGAA	UUCG	FP
in *5.4*	ntr.[c]	−	80949	GCCATGTG TTT CATACGGC TTTTTAATTT	None	Term
5.4/6′	*6*	+	81769	TTGATG GAAA CACTGAA TTCTATTTT	GAAA	FP
34/35′	*35*	+	154701	GGCCGAGTTTGGACA AGGATA TGTCCAAACGCC ATTTTT	None	Term
in *stp*	ntr.	+	165510	GGCGTC CGAA GACGCC TTTAGTTTT	CGAA	Term
rIIB	*denB.1*	−	167967	TAAGGC TTCG GCCCTTA ACTAAGGAAAATTATGTT	UUCG	FP

[a] Numbered 5′ start is the first base of the RNA helix, and underlined characters are nonpaired bases.
[b] Programs that identify the terminator: FP, GCG FindPattern; Term, GCG Terminator; TT = TIGR TransTerm.
[c] ntr., nontranscribed strand.

early or middle promoter. Among these early (or prereplicative) transcription terminators, there are several instances where the 3′ U-rich region of the terminator is a sequence shared with an A-rich UP element for a distal early promoter (see above) (1169). In several instances (such as positions 108613 [between *24* and *24.1*], 122720 [between *54* and *alt.-3*], 114472 [between *uvsW* and *uvsY.-2*], and 160924 [between *asiA* and *t*]), a terminator is located at the 3′ end of one of two adjacent genes transcribed in opposing directions. There is always an intrinsic terminator at the end of a late gene region that otherwise would be transcribed into a prereplicative region on the opposite strand (such as positions 106537, 108613, 122720, and 160924). However, the presence of intrinsic terminators at the ends of early transcripts that enter late regions is not as consistent. At some early-late junctions (e.g., position 114472 [ORF *uvsY-.2* 3′ end]), a terminator is predicted and experimentally identified (356, 357). At other junctions, no prereplicative intrinsic terminator is predicted (see position ca. 160875 [*asiA* 3′ end]) or, if a nearby terminator is indeed the transcript end, there would be ORFs that are not served by an apparent promoter. An example of the latter is position 110180 (*hoc* 3′ end), which orphans *rnlB*, *24.2*, and *24.3* without a promoter, except as available from readthrough transcription.

Seven regions were identified by the programs described in the preceding section as possible transcription termination sites, although they showed unusual attributes with respect to their location and the 3′ U-rich region. Some are located wholly within coding regions (e.g., position 81769).

Overall, the predicted T4 intrinsic terminators generally appear to both define the 3′ ends of multicistronic mRNAs and affect the dynamics of transcription complexes advancing on opposing DNA strands.

Rho-dependent transcription terminators. In enteric bacteria, the RNA-binding protein Rho modulates transcription termination at sites that are distinguished from intrinsic terminators by the absence of both the stable RNA hairpin and the 3′ U-rich region. Rho utilization sequences (*rut*) in RNA generally are C-rich, have small amounts of G, and can be as long as 85 nucleotides (929). In addition, *rut* sites can be 150 to 200 bp 5′ of the actual transcription termination site and therefore appear to function as locations for entry of Rho on transcribed RNA. Some of the better studied Rho-dependent termination sites (i.e., lambda *tR1* and *E. coli tnp*) are regulated by antitermination which also involves host Nus proteins, lambda N protein, and the RNA sequence of the *boxA* and *boxB* regions (344, 553, 929). Together, these complex features have made computational methods for identifying Rho-dependent termination sites problematic relative to the easily defined intrinsic terminators.

Rho-dependent transcription termination sites in T4 have not been extensively characterized; little additional work has been done since the review by Stitt and Hinton (1043). One of the better candidate Rho terminators, or a 3′ end of the RNA that is indirectly influenced by a *rho* mutation, lies between genes *uvsX* and *40* (416). Readthrough transcription from *uvsX* into *40* (and on through the helicase gene *41*) is diminished by the Rho mutant *rho026* (1044). In addition, the low level of readthrough transcripts is elevated in *goF* (*comC*α) mutants, probably by better protection against RNases (416, 1043). The Rop protein of ColE1-derived plasmids has a stabilizing effect similar to that of *goF* mutations (1028). As mentioned above, the *uvsX-40* site (position 22347) is characterized by a stable tetraloop hairpin that is not followed by the typical U-rich sequence (Table 4). However, the *rut*-like C-rich region is part of a hairpin, which is not characteristic of other *rut* sites, and there is not an apparent nearby *boxA* sequence. Nonetheless, the available evidence points to this region as a likely Rho-dependent termination region. Similar properties are predicted for the putative *rIIB-denB.1* terminator at position 167967. These RNA structures may help direct Rho-dependent termination.

Other sites in the T4 genome that have *rut*- and *boxA*-like sequences, and that therefore may be affected by Rho, occur at the end of the *tRNA* cluster (after RNA C at position 70742), in the region between genes *repEB* and *repEA* (position 78810), and between the late promoter at position 77490 and gene *5*. The last two potential sites are near the *oriE* origin of DNA replication (1109; A. Harvey, R. Vaiskunaite, and G. Mosis, unpublished data) (see below). Other *rut*- and *boxA*-like sequences can be identified in the T4 genome, but the significance of these, as well as the entire aspect of Rho-dependent termination in the T4 developmental cycle, requires further study. Mutations in the gene *goF* (*comC*α) have been repeatedly isolated as suppressors of host mutations that affect T4 transcription termination; the GoF protein, which stabilizes residual long transcripts produced in the Rho026 mutant host, does not show overall similarity to other proteins in the genome databases (171, 956, 1043). However, the short acidic region between residues 87 and 111 is similar to amino acids in other RNA-binding proteins and ATP-dependent RNA helicases (Miller, unpublished).

TRANSLATION AND POSTTRANSCRIPTIONAL CONTROL

The transition from host to phage protein synthesis is a rapid and efficient process (601); virtually no host proteins are observed on two-dimensional gels of proteins labeled after 1 min of T4 infection (189). Intrinsic properties of T4 mRNAs, such as the strength of SD sequences, several T4-induced modifications to the translation initiation apparatus, and the translational coupling arrangement seen for many phage genes may play key roles in the shift of host ribosomes to translation of T4 mRNAs.

Ribosome-Binding Sites

In general, T4 RBS have properties that are nearly identical to those of its *E. coli* host (reviewed in reference 736). mRNA sequences 5′ of the initiation codon (the SD sequence) show a variable extent of complementarity to the 3′ end of 16S rRNA, followed by a spacing of 6 to 10 nucleotides and then the initiation codon. Furthermore, there is a modest bias in favor of certain codons for the second amino acid. Many T4 proteins have been purified for biochemical or structural characterization, so that their N-terminal residue and hence their translational start codon are definitively known. Where the N-terminal amino acid has not been experimentally determined, the translation initiation sites were assigned to each gene and ORF (Table 1) using predictions based on the correlation coefficient (described above), the T4 hidden Markov model (671), and the presence of an SD sequence in an appropriate position. Most of the translation start codons of T4 genes are AUG. GUG as initiator occurs at eight T4 ORFs which, at 3%, is similar to the frequency of GUG starts occurring in *E. coli* genes (92). T4 genes and ORFs using GUG initiation codons include *mobB*, *dexA.2*, *46*, *46.1*, *cd.1*, *55.7*, *41*, and *49′*. One occurrence of an AUU initiation codon has been documented; it is an internal start site within gene *26* (823) (see below).

Aligned T4 RBS sequences can be collectively viewed in a sequence logo (966), although the variable spacing between the SD sequence and the AUG initiation codon presents a particular challenge. Figure 6A shows the logo aligned at the AUG. Due to the variable spacing between the SD sequence and initiation codon, only a minor peak for the SD is observed, in the −8 to −9 region. Alignment of the SD sequence alone, independent of the AUG (Fig. 6B), clearly illustrates the importance of the SD sequence. The R_s (defined above) of T4 RBS sequences, using the optimally aligned regions from −15 to +14 (Fig. 6) is 14.3 bits, which is higher than the calculated R_s for *E. coli* RBS sequences (8.9 bits [994]). However, a refined "flexible" model of *E. coli* RBS appears to more accurately account for the variable spacing between the SD se-

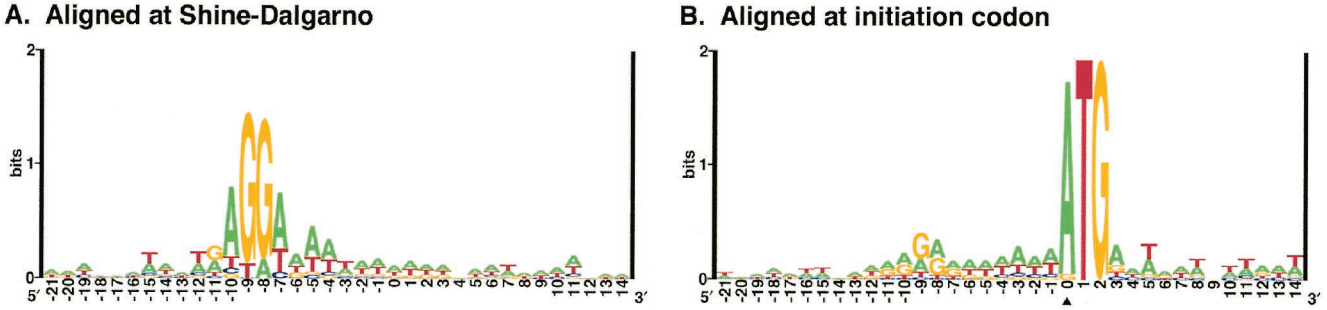

FIG. 6. Logo of T4 RBS. Translation initiation regions of the annotated T4 GenBank file AF158101 were used; genes *25* and *38*, which have extended spacing and RNA hairpins between the AUG and SD region, and gene *26′* were excluded. (A) Genes aligned at the initiator AUG or GUG codon. Information content analysis (R_s, in "bits"), from positions 0 to +14, yields an R_s = 7.5 bits. The variable spacing between the AUG and the SD region yields a reduced contribution of the SD region to the total R_s in the logo. This is seen by the low shoulder of purine-rich nucleotides in the logo from −11 to −6. (B) Genes aligned at the SD region. The region from −20 to −1 (relative to the 0 position in panel A) was independently aligned to achieve the highest R_s value in the SD region. In the region from −15 to −1, R_s = 6.8 bits. Over the entire RBS, spanning −15 to +14, the sum of R_s = 14.3 bits. Shultzaberger et al. (994) describe an alternative approach to modeling RBS R_s values that accounts for the variable spacing between the SD and initiator codon. Logos were created (Miller et al., unpublished) and alignments and R_s values were calculated as described previously (965, 966, 994).

quence and AUG (994). In effect, subtracting the uncertainty of the variable SD-AUG spacing lowers the total R_s; thus, the 14.3-bit R_s value currently calculated for T4 ribosome binding sites is likely to be slightly lower (Miller et al., unpublished). Overall, the strength of the T4 RBS would in part account for the observed redirection of ribosomes from host to phage mRNAs.

A few prokaryotic "leaderless" mRNAs have been identified that lack the SD sequence and have the initiator AUG positioned right at the 5′ end of the transcript; the best-studied phage leaderless mRNA is that for the lambda *c*I repressor protein (833). Some leaderless mRNAs are highly expressed (e.g., *aph* [353, 480]). To date, no leaderless mRNAs have been characterized from T4.

The transition from host to phage protein synthesis may also involve changes that T4 reportedly makes in proteins of the translation apparatus, including IF3 alteration, release of S1 from ribosomes, and synthesis of new ribosome-binding proteins (601, 1166). These modifications to the translation initiation apparatus potentially could have major effects on the initiation efficiency of either phage or host mRNAs. Unfortunately, most of the genes responsible for these changes have not been identified. ModB ADP-ribosylates the S1 protein, elongation factor EF-TU, and the chaperone "trigger factor" (205), and thus these changes may be important for diminished translation of host mRNAs or may have a direct impact on the translation of phage mRNAs.

RNA Structure at Ribosome Binding Sites

Two T4 RBS have unusually long spacing between the SD sequence and the initiation codon, with an additional RNA helix stacked into the RNA structure of the initiating ribosome-mRNA complex. For gene *38* mRNA, an RNA helix (hairpin) in the variable SD-to-AUG spacing region brings the SD sequence from 22 bases away to within 5 bases of the AUG, which is in the range of spacing observed for other T4 genes (326, 388). Gene *25* has an SD-to-AUG spacing of 27 bases, but an intervening RNA structure reduces that to 11 bases (819). These compact intramolecular mRNA and intermolecular rRNA-mRNA helices at the RBS are reminiscent of RNA pseudoknots (428) (the regulatory RNA pseudoknot preceding the RBS of gene *32* mRNA is discussed below). T4 gene *38* and gene *25* mRNAs are good examples of how RNA structure can enhance translation initiation efficiency.

RNA structures can also have the opposite effect. Several T4 mRNAs fold into intramolecular RNA helices that inhibit ribosome binding and translation (736). Usually this is observed with mRNAs that are transcribed from early promoters and extend downstream into a late gene. The longer early transcript forms an RNA helix that sequesters the late-gene RBS (such as in the mRNAs for genes *e*, *soc*, I-*Tev*I, and *49*). Late promoters, located immediately upstream of the late-gene RBS, lack the 5′ region of the helix and present RBS sequences that are accessible for translation initiation. As mentioned below, for gene *49*, the intramolecular helix at the first RBS promotes use of the internal RBS for gp49′.

Internal Initiation Sites

A few overlapping or internal reading frames have been identified in the T4 genome. In each case, the internal translation initiation sites yield proteins shortened from the amino-terminal end. T4 EndoVII (the Holliday junction resolvase), encoded by gene *49*, is 157 amino acids (aa) long. An internal initiation site, utilizing a GUG start codon, yields a protein of 105 aa (39). The shorter protein is synthesized predominantly from a long early transcript in which the first RBS is sequestered in a hairpin. The larger protein is synthesized from a shorter late transcript, in which the RBS is free. The full-length T4 gene *17* product (terminase/DNA-binding protein) is 610 aa. Internal initiation sites on two shorter gene *17* mRNAs (one is initiated from an internal promoter, and the other is cleaved) yield smaller proteins of 523, 505, and 416 residues (286). Because only the largest one contains a single-stranded DNA-binding domain and the second largest one suffices to package DNA of mature size, it has been proposed that the

different-sized proteins recognize different substrate DNA for recombination (288) and for packaging (784) (see below).

The rare AUU initiation codon used by gene *26′* yields a protein, initiated at codon 114, that is only 95 residues long compared to the full-length gp26, which is 208 residues long (823). The function of gp26′ is unknown.

ORF *30.3′* is the one example in T4 of a coding region that is translated in the +1 reading frame entirely within another gene (*30.3*). Translation of the two overlapping ORFs has been confirmed, with the internal RBS of *30.3′* resembling other T4 RBS sequences (1234).

Translational Coupling

In translational coupling, the translation initiation of a distal gene is dependent on the translation of the gene immediately upstream. The process, which has been appreciated for many years (709, 808, 846), facilitates the coordinate expression of proteins that are involved in the same metabolic pathway or that assemble into multimeric complexes. In compact, densely coding phage genomes, translationally coupled gene arrangements are commonplace, although few have been explicitly studied. Translational coupling has been examined in RNA phages (638) and ssDNA Ff phage (1230). The very first intimations of translational coupling in T4 were observed by Stahl et al. (1035). It has been specifically studied in the T4 DNA polymerase clamp loader proteins encoded by genes *44* and *62* (502, 1089, 1095); in this complex, the 44 and 62 proteins occur in a 4:1 ratio. It appears that translational coupling helps determine the relative levels of each subunit, since the frequency of translation initiation of gene *62*, transmitted from the upstream translation of gene *44*, was measured to be about 25% (1089). These and other genes inferred to be translationally coupled have the stop codon of the upstream reading frame close to, or even overlapping, the downstream initiation codon. In the T4 genome, there are 52 clusters of genes arranged in this fashion. Thirty-five involve only two genes. Groups with the largest number of such genes are *wac-9* (five genes), *cd.2-31.1* (five genes), *vs-tk* (six genes), and the *30.6-alt.1* region (eight genes). Many of these include ORFs of unknown function, although the translational configuration would suggest a functional relationship to the adjacent, often characterized, gene. The extent, mechanisms and significance of translational coupling in phage T4 clearly deserve further attention.

Translational Repressor Proteins

Autogenous translational repression by the T4 ssDNA-binding protein gp32 played a significant role in establishing the importance of posttranscriptional gene regulation (reviewed in references 325 and 736). T4 has three well-characterized translational repressors, gp32, gp43, and RegA. The first two proteins have high-affinity binding sites only on their own mRNAs, whereas RegA binds to several other separate mRNAs in addition to its own (736). gp32 binds to an RNA pseudoknot upstream of the RBS, which then promotes cooperative loading in the 3′ direction to block the translation initiation site (240, 428, 984). The protein is a metalloprotein that utilizes a retrovirus-like Zn(II) domain for RNA-binding specificity (363, 985). With the DNA polymerase, gp43, the repression specificity is determined by a smaller helical hairpin upstream of the RBS; binding does extend to the RBS and thereby represses translation initiation (857). T4 gp43 was the first protein used in developing the in vitro selection method (SELEX) for identifying high-affinity RNA-binding sites (1101). RegA binds and translationally represses more than a dozen T4 early mRNAs, but it does so with weaker affinity than that observed for gp32 and gp43, and the binding site is not well defined (reviewed in reference 736). One of the better T4 RegA-binding sites (K_d = 0.2 μM) overlaps the clamp loader gp44 RBS (338). This site is at an upstream RBS, with *regA* positioned as the most distal gene on the transcript. The configuration suggests that repression is transmitted through translational coupling to gene *62* and *regA* itself. SELEX-isolated binding sites did not precisely match any specific T4 site, but the consensus sequence (5′-AAAAUUGUUAUGUAA-3′) resembles many of the RegA-sensitive RBS (113). Interestingly, RegA is conserved in all T-even-related phages examined, although it is nonessential under laboratory growth conditions. Its RNA-binding domain appears to be a unique helix-loop groove structure (338, 484, 975). Structural studies of complexes bound to RNA will have to be done for all three translational repressor proteins before we can fully appreciate the details of the RNA-protein interactions.

Codon Usage

In the 275 T4 protein coding sequences, all the standard codons are used. Kunisawa (590, 591) has compared the synonymous codon usage patterns of T4 with *E. coli* and has found that, as expected, T4 makes greater use of codons with A and U in the third position whereas *E. coli* uses G or C (Table 5). The overall codon usage in T4 genes reflects the 65.5% A+T content of all coding regions and both the general base position preferences and codon biases typically observed in AT-rich genomes. *E. coli* tRNAs can read all T4 codons because of the wobble in third-position recognition of most codons. While T4 encodes eight tRNAs of its own (discussed below), mutants from which they are deleted grow normally in most bacterial strains and under standard laboratory conditions (5, 962, 1179).

Unrestricted use of all codon triplets requires 50% G+C and 50% A+T, whereas an AT-rich genome has an overall reduced codon capacity. This is evident from codon usage patterns. From the T4 codon usage table (Table 5), it can be calculated that T4 uses 64.7% A+T in its codons and only 35.3% G+C. These values are close to the approximate theoretical edge of 66.6% A+T to allow, by probability, for amino acids encoded predominantly by GC-rich triplets (e.g., Arg, Ala, Gly, and Pro) to be encoded only rarely. An analysis of the intrastrand bias of bases in the first, second, and third positions of codons in T4 genes has been presented by Kano-Sueoka et al. (499) and is summarized above (see "Nucleotide skew in the T4 genome"). The correlation coefficient for T4 genes (Table 1) in part utilizes the skew to predict probable coding regions for most genes—for example, over half of the G's in coding regions are found in the first position of the codon.

TABLE 5. T4 and *E. coli* codon usage and tRNA availability

Amino acid	Codon usage[a]				tRNA availability, gene copy no. [relative content][b]	
	Codon	Cumulative frequency (per 10^3)		Anticodon		
		E. coli	T4		*E. coli*	T4
Arg	CGU	20.9	19.1	ACG	4 [0.9]	
	CGC	22.0	5.7			
	CGA	3.6	5.6			
	CGG	5.4	1.1	CCG	1 [minor]	
	AGA	2.1	9.9	UCU	1 [minor]	1
	AGG	1.2	1.8	CCU	1 [minor]	
Leu	UUA	13.9	27.8	UAA	1 [0.25]	1
	UUG	13.7	10.7	CAA	1 [0.2]	
	CUU	11.0	18.3			
	CUC	11.1	4.1	GAG	1 [0.3]	
	CUA	3.9	7.0	UAG	1 [minor]	
	CUG	52.6	5.6	CAG	4 [1.0]	
Ser	UCU	8.5	24.7			
	UCC	8.6	3.6	GGA	2 [0.25]	
	UCA	7.2	18.4	UGA	1 [0.25]	1
	UCG	8.9	3.8	CGA	1 [0.05]	
	AGU	8.8	10.5			
	AGC	16.1	5.6	GCU	1 [0.25]	
Ala	GCU	15.3	31.1			
	GCC	25.5	5.2	GGC	2 [0.3]	
	GCA	20.1	19.6	UGC	3 [1.0]	
	GCG	33.6	6.5			
Gly	GGU	24.7	27.7			
	GGC	29.6	8.1	GCC	4 [1.1]	
	GGA	8.0	19.5	UCC	1 [0.15]	1
	GGG	11.1	3.9	CCC	1 [0.1]	
Pro	CCU	7.0	14.3			
	CCC	5.5	1.1	GGG	1 [minor]	
	CCA	8.4	13.9	UGG	1 [0.3]	1
	CCG	23.2	4.8	CGG	1 [0.3]	
Thr	ACU	9.0	27.9			
	ACC	23.4	6.3	GGU	2 [0.8]	
	ACA	7.1	16.8	UGU	1 [0.1]	1
	ACG	14.4	5.4	CGU	2 [0.1]	
Val	GUU	18.3	31.6			
	GUC	15.3	5.4	GAC	2 [0.4]	
	GUA	10.9	20.1	UAC	5 [1.05]	
	GUG	26.4	6.2			
Ile	AUU	30.3	51.3			
	AUC	25.1	11.2	GAU	3 [1.0]	
	AUA	4.4	12.0	CAU	2 [0.05]	1
Asn	AAU	17.7	42.3			
	AAC	21.7	14.8	GUU	4 [0.6]	
Asp	GAU	32.1	47.4			
	GAC	19.1	14.8	GUC	3 [0.8]	
Cys	UGU	5.2	7.3			
	UGC	6.5	3.8	GCA	1 [minor]	
Gln	CAA	15.3	21.9	UUG	2 [0.3]	1
	CAG	28.8	11.1	CUG	2 [0.4]	
Glu	GAA	39.4	60.0	UUC	4 [0.9]	
	GAG	17.8	10.8			
His	CAU	12.9	13.7			
	CAC	9.7	4.0	GUG	1 [0.4]	
Lys	AAA	33.6	63.5	UUU	6 [1.0]	
	AAG	10.3	17.3			
Phe	UUU	22.3	33.4			
	UUC	16.6	11.1	GAA	2 [0.35]	
Tyr	UAU	16.2	33.7			
	UAC	12.2	9.7	GUA	3 [0.5]	
Met	AUG	27.9	26.8	CAU	6 [0.8]	
Trp	UGG	15.2	14.3	CCA	1 [0.3]	

[a] The total number of codons is 1,363,498 for *E. coli* (4,290 protein-coding genes) and 54,574 for T4 (274 genes). Optimal codons of *E. coli* are underlined.

[b] The cellular tRNA contents relative to Leu-tRNA with anticodon CAG are shown in brackets. Low-abundance tRNAs that are difficult to quantify by the two-dimensional gel analysis are shown as [minor].

tRNAs

As indicated (Tables 1, 2, and 5), T4 encodes eight tRNAs, with the following specificities: Ile (AUA), Thr (ACA), Ser (UCA), Pro (CCA), Gly (GGA), Leu (UUA), Gln (CAA), and Arg (AGA). A prominent late transcript contains all eight tRNAs, although early and middle promoters direct transcription into the tRNA cluster as well (772). Maturation from the primary transcript occurs through the activity of host-encoded processing enzymes (962) and autocatalysis (reviewed in reference 772). In each case, the T4 tRNA recognizes a codon that is relatively minor in *E. coli* but more frequent in T4 genes. There is no positive correlation between the most abundant amino acids in the T4 proteome and the tRNAs encoded by the phage (591). *E. coli*-optimal codons are in fact used more frequently for T4 proteins present in large numbers per phage particle (such as in gp23, the major capsid protein), while T4-optimal codons, defined as those recognized by the phage tRNAs, are used more frequently for T4 proteins present in small numbers per phage particle (and probably in weakly expressed genes). This may serve to enhance the expression of low-abundance T4 late proteins, whose products are required in larger amounts than the typical low-abundance *E. coli* protein (590–592).

The T4 tRNAs may have been acquired more recently in the evolutionary history of the phage, possibly through the activity of the *segB*-encoded endonuclease located in the T4 tRNA gene cluster. Schmidt and Apirion (962) and Mosig (772) discuss how the T4 tRNAs are required in certain hosts and may help increase fitness in some environments. Phages related to T4 that have been examined also encode some tRNA genes, yet there is a surprising variation in the specific tRNAs represented (919). Additional work on the importance of the T4 tRNAs under different growth conditions, and in different hosts, would be of interest.

The program tRNAscan-SE (664) combines up to three algorithms to examine genomic sequence for putative tRNAs and pseudo-tRNAs, identifying the specific anticodon of each tRNA (http://www.genetics.wustl.edu/eddy/tRNAscan-SE/). tRNAscan-SE was used to analyze the complete T4 genome for previously undetected tRNAs, and none were found. T4 also encodes two small RNAs (RNAD and RNAC) that immediately follow the tRNA genes and are cotranscribed with them. The functions of these RNAs remain unknown.

Introns

The first intron identified in the prokaryotic world was found in the thymidylate synthase gene (*td*) of T4 (174). T4 has three self-splicing group I introns, one each in *td*, *nrdB*, and *nrdD* (*sunY*) (reviewed in reference 992); the last two genes encode subunits of the aerobic and anaerobic ribonucleotide reductases, respectively. All three introns are structurally similar, and all use guanosine nucleotide (GTP) in transesterification reactions that lead to ligation of the flanking mRNA exons. T4 introns are clear structural members of group IA2, which are prevalent in *Eucarya* (993). Each intron contains an ORF that is located on the periphery of the intron structure and does not interfere with the catalytic activity of the RNA. The ORF products, designated I-TevI, I-TevII, and I-TevIII, are DNA endonucleases involved in the "homing" or dissemination of

the intron DNA into intronless sites of homologous sequence. Homing enzymes are also commonly encoded by group IA introns of *Eucarya.* The T4 I-Tev enzymes are related to the non-intron-encoded Seg and Mob endonucleases distributed throughout the T4 genome (see below) (988).

T4 introns are similar to other group I introns in that they fold into a "core" secondary structure involving the paired regions designated P3, P4, P6, and P7 (151). The catalytic RNA center has binding sites for GTP and for Mg^{2+}, which is important for proper folding of the RNA. An internal RNA guide sequence (usually located in P1) is important for properly positioning the 5′ exon with the 3′ exon splice site. Folding of the T4 *td* intron into the catalytically active RNA is affected by host RNA chaperones, such as the *E. coli* RNA-binding proteins StpA, ribosomal protein S12, and Cyt-18 (179, 1140, 1238). Splicing in vitro can occur without these chaperones. Most of what is known about RNA catalysis by group I introns, including those of T4, derives from experiments conducted on the *Tetrahymena* introns (150, 152). The similarity between T4 introns and group I introns of *Eucarya* is thought to reflect a common ancestry (993).

Although the *td* intron was identified by the sequence disparity between the DNA, RNA, and protein, the *nrdB* and *nrdD* introns were detected by in vitro labeling of the excised intron with [α-^{32}P]GTP (341). This approach has emerged as a general method of identifying group I introns in mRNAs (915), showing that they are variably distributed among different groups of phage and bacteria. Other T-even phages (including the recently sequenced RB69 genome [J. Karam et al., personal communication) lack one or more of the introns (247, 882). In phage RB3, for example, the *nrdB* intron and its homing endonuclease, I-TevII, are intact and functional whereas the T4 I-TevII is partially deleted and inactive (247).

More recent work on phage group I introns has focused on phage of gram-positive bacteria. Such introns are present in lysin genes of lambdoid phages infecting *Streptococcus thermophilis* (279), thymidylate synthase (*thy*) of *Bacillus subtilis* phage B22 (42), and the DNA polymerase genes of *B. subtilis* phages SPO1, SP82, 2C, and phi e (336). Three introns disrupt orf142, and two introns disrupt the large subunit of ribonucleotide reductase2 (*nrdE*) of *Staphylococcus aureus* phage Twort (614, 615); this phage, the first ever identified and described, therefore has at least five functional group I introns. As in T4, phage and bacterial group I introns are usually located in important genes for enzymes of DNA metabolism and usually are inserted in or adjacent to codons for conserved amino acids (614). The distribution and ancestry of group I introns in phage populations have been discussed (251); expression of the homing endonuclease, the cleavage specificity of these enzymes, and the likelihood of a phage infecting a cell where introns are present can all impact their distribution.

Although inteins (intervening sequences excised at the protein level) have been identified in other bacteriophages (863), none have yet been observed in T4 proteins or proteins of T4-like phages.

mRNA and tRNA Turnover

The early T4 literature on RNA processing and mRNA decay has been reviewed (962, 1166; also see reference 359). An RNA helix at the 5′ end of a transcript stabilizes the mRNA against degradation; the T4 gene *32* 5′ hairpin is well documented to confer stability on its mRNA (340, 658). Host-encoded enzymes (such as RNase E), comprising an RNA "degradosome," directly participate in the decay of T4 mRNAs (142, 795; reviewed in reference 359). However, the phage does not appear to modify the RNA degradosome or to encode any accessory proteins.

T4 does encode a riboendonuclease, RegB, that inactivates numerous early mRNAs by cleaving them at the SD sequence, GGAG (942, 943, 954). RegB also decreases the chemical half-life of early mRNAs, whereas middle and late mRNAs are neither cleaved nor destabilized. It appears that RegB recognizes a structured conformation of the GGAG sequence that is presented or stabilized by the 30S ribosomal protein S1 (628). It is not clear how RegB-mediated cleavage at these sites is affected (or not) by the covalent modification of S1 directed by the T4 ModB ADP-ribosylation enzyme. Kai and Yonesaki (494) described effects of mutations in *dmd* that lead to the accumulation of discretely cleaved mRNAs of middle and late mRNAs. The presence of the wild-type *dmd* gene, directly or indirectly, stabilizes these T4 mRNAs; RNase I (also called RNase M [1052]), among others, was implicated in the mRNA cleavage. As mentioned in the discussion of transcription termination, the goF product is also implicated in mRNA degradation.

On infection of certain *E. coli* strains, the 26-aa polypeptide encoded by the T4 *stp* gene activates the latent DNA and RNA restriction system of the host *prr* locus. The *prrC* anti-codon nuclease cleaves Lys tRNA, the most frequently used tRNA for T4 protein synthesis. While *stp* would serve to self-destruct the mRNA translation of the infecting phage, the T4 genes *pnk* and *nlA* encode the requisite 3′-phosphatase-polynucleotide kinase and RNA ligase, respectively, to restore the functional tRNA Lys (859). Quite possibly *stp* and *prrC* represent components of an evolutionarily important RNA restriction system, and the T-even phages, in their various hosts, employ tRNA cleavage reactions to exclude the propagation of related viruses (see below) (859).

Proteolysis

Another interesting degradative "restriction system" operating on the translational apparatus during T4 infection is the Gol-Lit interaction (1021). The defective prophage e14 present in certain *E. coli* strains encodes a latent metalloprotease (Lit, for "late inhibition of T4"). During the late stages of the T4 infection cycle, Lit is active in cleaving host translation elongation factor EF-Tu between amino acids Gly59 and Ile60. These residues are central to the RGITI motif of the Mg-GTP-binding domain (1231). Consequently, all translation is inhibited, albeit at a time shortly before lysis of the T4-infected cells. Activation or binding of the Lit protease is promoted by T4 Gol (for "grows on Lit-producing bacteria"), a 29-residue peptide (AVMGMVRRAIPNLIAFDICGVQPMNSPTG) corresponding to residues 93 to 122 of the gp23 protein (78). Lit associates with the EF-Tu–GDP open complex, which appears to be stabilized by the Gol peptide, resulting in EF-Tu cleavage. Because the Gol peptide is a segment of the N-terminal proximal region of the phage gp23 head protein, it has been

proposed that binding of EF-Tu to the Gol domain may also assist in the assembly of phage capsids during synthesis of gp23 (78). The Gol (gp23)–EF-Tu interaction is just one of several associations between viral proteins and cellular translation factors that suggest ubiquitous strategies for viral development and maturation (78).

The T4 Pin protein (1012) inhibits the host Lon protease. As one consequence, truncated peptides of T4 nonsense mutants are more stable than those of *E. coli.*

DNA METABOLISM, REPLICATION, RECOMBINATION, AND REPAIR

A large fraction of the T4-encoded enzymes with known metabolic functions are devoted to DNA metabolism. T4 not only encodes all of the components of its own replisome and recombination systems but also makes most of the enzymes involved in preparing nucleotides for incorporation into DNA. A number of these duplicate host enzymes (aerobic and anaerobic ribonucleotide reductases, thymidylate synthase, and thymidine kinase). Others are uniquely related to the utilization of hydroxymethylcytosine rather than cytosine in T4 DNA (dCTPase, dCMP hydroxymethylase, dHMP/dTMP/dCMP kinase, and DNA glucosyl transferases that sugar coat the HMC-containing DNA to protect it from attack by certain host nucleases).

Many known T4 proteins function only as parts of macromolecular complexes (14). This is true not only for the assembly of the complex phage particle (see below) but also for most of the T4 enzymes of nucleotide biosynthesis, DNA replication, recombination, and transcription. Understanding these complex protein machines requires not only work with purified proteins but also analysis of the effects of mutations in these proteins in vivo and examination of the conformational changes that occur in the proteins while they interact with different components of the complexes.

Enzymes of Nucleotide Metabolism

Among the best understood of these machines is the T4 nucleotide precursor complex (reviewed in references 348 and 695). It takes both cellular nucleoside diphosphates (NDPs) and the deoxynucleoside monophosphates (dNMPs) from host-DNA breakdown and converts them into deoxynucleoside triphosphates (dNTPs), in the proper ratios for T4 DNA (two-thirds A+T, in contrast to the 50% A+T found in the host). The precursor synthesis occurs at the appropriate rate for normal T4 DNA replication even when DNA synthesis is otherwise blocked, implying that the regulation is not via feedback inhibition. Proteins of the nucleotide-precursor complex, which includes two host proteins, are thought to interact with the replisome as they funnel nucleotides directly into the DNA replication complex. T4 ssb (gp32) is thought to be an essential coupler of the precursor and replication complex (1161). The interactions at all these levels have been documented by such methods as in vivo substrate channeling, intergenic complementation, cross-linking, immunoprecipitation, and affinity chromatography, as well as by kinetic studies of substrates moving through the purified precursor complex (1161). One consequence of the tight coupling is that dNTPs entering permeabilized cells must be partly dephosphorylated to enter the complex and must then be rephosphorylated to enter the DNA, so that exogenous dNTPs are used severalfold less efficiently than are dNMPs or dNDPs. A similar complex has also been documented during anaerobic growth (696, 900), but the exact relationship of the T4 two-subunit anaerobic NTP reductase to the other enzymes of the complex is not yet clear. Since the T4 dCDPase/dUDPase is also a dCTPase/dUTPase, the pathways for dTMP/dTTP and HMdCMP/HMdCTP synthesis would not be disrupted by reducing the nucleotides at the triphosphate rather than the diphosphate level. The process of host DNA breakdown clearly also channels nucleotides into this complex in a way that is not subject to competition by exogenous thymidine (605), but the nucleases involved have not been identified as members of the nucleotide precursor complex.

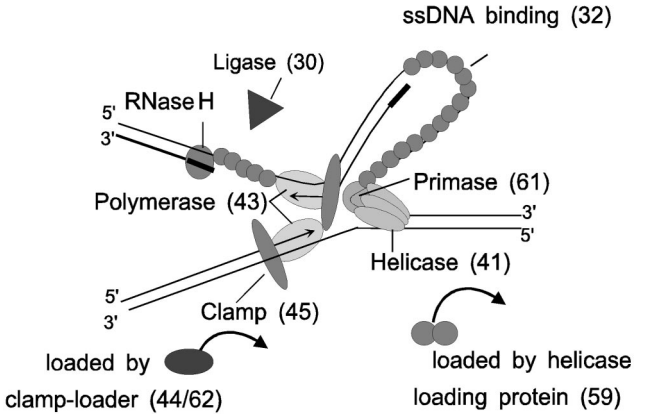

FIG. 7. The T4 replisome. A model of a T4 DNA replication fork and the central proteins is shown. Numbers indicate the gene encoding each protein. See the text for a description of the functions of each protein. Reprinted from reference 478 with permission from the publisher.

DNA Replication Proteins

From a combination of genetic experimentation and virtuoso biochemical and biophysical characterizations has emerged a detailed understanding of the functions and interactions within the T4 replisome (53, 826, 830). The seven T4 proteins encoded by genes *43* (DNA polymerase), *44* and *62* (sliding clamp loader), *45* (sliding clamp), *41* (DNA helicase), *61* (primase for lagging-strand synthesis) and *32* (ssDNA binding protein) make up the basic replisome, a biological machine (14, 15) that can move the replication fork through model templates at in vivo speeds (Fig. 7). Additionally, RNase H (*rnh*) and DNA ligase (*30* = *lig*) are required to seal Okazaki fragments and other interruptions in DNA, and T4 gp59 accelerates the loading of the gp41 helicase in vitro (38, 478). The DNA arrest phenotype of gene *59* mutants had suggested that gp59 is not required during origin initiation but is required for recombination-dependent DNA replication (see below). The 5′-to-3′ exonuclease function of host DNA polymerase I can substitute for defective T4 RNase H (427) and *E. coli* ligase can substitute for T4 ligase, if the T4 *rII* genes are mutated (59, 159, 504, 580, 776). Amino acid alignments and three-dimensional structures of several of these proteins (or segments of

them) (799, 800, 982–983) show homologies to replication proteins of many other prokaryotic and eukaryotic organisms. The two most striking examples are the DNA polymerase, gp43, and the sliding clamp of T4, gp45. Like the eukaryotic sliding clamp, T4 gp45 forms a pseudo-hexameric protein which is trimer of a protein with two similarly folded domains. In contrast, the *E. coli* sliding clamp is a dimer of trimers. Moreover, the clamp loader of T4 can partially substitute for a eukaryotic clamp loader in an *in vitro* replication system (1135).

Mutations in many other genes affect DNA replication in vivo (Table 2), because these genes are important for recombination-dependent DNA replication and repair of broken forks (see below). Since DNA is constantly assaulted by intrinsic and extrinsic damaging agents, DNA replication and recombination are tightly correlated and should not be considered in isolation. Studies of T4 have paved the way to understanding these relationships (200, 572, 575, 577, 668, 771).

DNA replication genes are scattered throughout the genome, with a major cluster that includes the DNA polymerase (gene *43*); most of these genes are transcribed from both early and middle promoters. Coordination of the T4 DNA replication functions is achieved by the assembly and disassembly of protein complexes that appear to use stretches of DNA covered with ssDNA-binding protein, gp32, as scaffolds (283, 765, 766, 774, 793, 1161). In wild-type T4, the syntheses of the leading and lagging strands are coupled, but both in vitro and in vivo leading-strand synthesis can be uncoupled to proceed on single-stranded templates, or by displacement of one parental DNA strand on double-stranded templates (488, 788).

In contrast to the *E. coli* replisome, the T4 replisome has not been isolated as a functional complex. Possibly, the weak interactions of the core replisome components facilitate interactions of DNA polymerase with different accessory replication and recombination proteins, as discussed below. These various interactions can be correlated with the three-dimensional structures of the DNA polymerase, the sliding clamp and the core of the ssb, gp32, from T4 and the related phage RB69 (983, 1141, 1146). Extensive analysis of mutator and antimutator strains has also facilitated our understanding of these interactions (827, 904, 906, 909).

Replication and initiation of late transcription are strongly coupled by the requirement for the sliding clamp of DNA polymerase, gp45, to transform closed to open RNA polymerase-promoter complexes, and the requirement for ssDNA interuptions to load the clamp (552a, 951, 1082, 1173). The replication complex moves along the DNA at 10 times the speed of the transcription complex. Because both processes proceed in both directions, frequent collisions must occur. In vitro evidence shows that T4 transcription and replication complexes can pass each other when they meet head-on, with the RNA polymerase changing templates without interfering with the total processivity of transcription (650). It now appears that this surprising and very useful ability is not universal. For *E. coli* (294), evidence indicates that head-on collisions between DNA and RNA polymerases retard the movement of both.

Initiation of DNA Replication

The first round of T4 DNA replication is initiated from one of several different origins (Table 1; Fig. 3). Replication is mediated by T4-encoded enzymes, with the exception that the host RNA polymerase synthesizes the primers for leading-strand initiation at origins (577, 668) and that host DNA polymerase I can remove RNA primers of Okazaki fragments (427). T4 primase then synthesizes primers for Okazaki fragments. In its absence, unidirectional displacement synthesis occurs (46, 47, 778, 779, 788). The displaced strand is later copied by a recombination-dependent "join-cut-copy" mechanism (discussed below). Combinations of density shift with electron microscopy analyses (199, 200) have shown that in most cases only one origin is used and is used only once, probably because at the time of origin initiation there are limited supplies of DNA polymerase and other replisome components. When the timing of early-gene expression is distorted by mutation, origins can be used repeatedly (for a review, see reference 563). As soon as the first replication forks have reached an end, recombination intermediates compete effectively for assembly of replisomes, and because T4 chromosome ends are circularly permuted, less dependence on specific origins is observed (200).

Four major DNA replication origins have been mapped to specific sequences, which are different in each case. The transition from RNA primers to leading-strand DNA synthesis in vivo occurs at several sites located over 1 kb downstream of the promoter that initiates primer transcripts (778, 779, 1109). At *oriA*, *oriF*, and *oriG*, the priming transcripts are initiated from MotA-dependent middle promoters (577). Priming of DNA synthesis by a transcript requires that the transcript reinvade the DNA, forming an R-loop. This reinvasion can be facilitated by global torsional stress in the DNA. Indeed, in vitro initiation from *oriF* has been achieved with an RNA primer that had been taken up by a supercoiled plasmid (830). The end of the R-loop used in these experiments was designed to be the same as in R-loops isolated from replicated DNA in vivo and probed for single strandedness of the displaced DNA strand. By analogy to *E. coli* (551a), this RNA end was postulated to be processed from a longer transcript by RNase H (133). However, this site is different from the major in vivo priming sites detected by primer extensions on nascent DNA (779). These occur in the terminator region between genes *uvsY.-2* and *uvsW* and require little or no processing. Possibly, both priming mechanisms are used in the *oriF* region.

In contrast, *oriE* can still function when torsional stress is reduced (for instance, by mutation in the host gyrase [789]). At *oriE*, the priming transcript is initiated from an early promoter. *oriE* function depends, in addition, on a small protein, RepEB, and the auxiliary protein RepEA, both encoded by transcripts related to the primer. In contrast to the other origins, *oriE* contains repeat sequences, the so-called iterons (779, 1109). The binding of RepEB to one or more of these iterons is required for *oriE* to function (Harvey et al., unpublished). It is postulated that binding of RepEB to the iterons facilitates the loading of a DNA helicase and that unwinding by the helicase can compensate for the lack of global torsional stress in *oriE.*

The different structures and functional requirements of different T4 origins may be considered as models for poorly

understood complexities of other multiorigin chromosomes. For example, in the major origin of *E. coli*, *oriC*, leading-strand synthesis can be primed by primase-dependent or RNA polymerase-dependent RNAs (558); *E. coli* can use other origins, *oriK*, which, like T4 origins, depend entirely on transcripts for priming (34). Similarly, different yeast origins are detected in different labs using different methods (1042).

Recombination and Recombination-Dependent DNA Replication

The discovery of recombination provided a powerful argument that phages can be used as model systems (411), and a strong connection between replication and recombination was suspected early on (1129). Our current view of these tight interconnections and the interactions with the transcriptional and posttranscriptional developmental program of T4 are summarized in Fig. 4.

Although the onset of DNA replication is largely dependent on replication origins, most T4 replication forks are initiated by using intermediates of recombination as DNA primers at more or less random positions throughout the genome. Because origin-dependent DNA replication is inactivated during the developmental program, recombination-deficient T4 mutants arrest DNA replication prematurely.

There are several different recombination-dependent replication modes, which require different recombination proteins; these have been thoroughly reviewed (768, 769, 784). In undamaged chromosomes, early T4 join-copy recombination depends on origin-dependent replication; it is initiated from the ssDNA at the unreplicated end of the template for lagging-strand synthesis. In damaged T4 chromosomes, similar mechanisms can be used to repair broken replication forks (575) (see below). When origin-initiated DNA replication is inhibited, recombination can occur, but it begins later and requires additional nuclease activities (111). Electron micrographs of such T4 DNA intermediates provided the first compelling evidence for annealing of single strands as one way to initiate recombination (pathway I in Fig. 4) and for the importance of branch migration in homologous recombination (111). Under replication-deficient conditions, no viable progeny particles are produced. There is no late join-cut-copy recombination, no packageable DNA concatemers are formed, there is little late transcription (since that is dependent on DNA replication), and no heads are formed that can be filled.

The main genes required for join-copy recombination-replication (Fig. 4) (in addition to the SSB gene *32* that is required for most aspects of DNA repication, recombination and repair) are *uvsX*, *uvsY*, *46*, and *47* (Table 2). The 46 and 47 proteins, acting in a complex, have similarity to the *E. coli* SbcBC and RecBC proteins and the eukaryotic Rad50/Mre11 complex. The strand invasion UvsX protein is a structural and functional homologue of the *E. coli* RecA protein and the eukaryotic Rad51, Dmc1, and Rad54 proteins (69, 192, 739). As expected, if this is the major pathway to initiate T4 replication forks, defective mutants arrest DNA replication after limited origin replication has occurred. The corresponding genes are expressed from early and middle promoters, concomitantly with the replication proteins acting at the fork. Thus, this pathway can operate early.

In contrast, the endoVII (*49*) and terminase (*17*) genes required for join-cut-copy recombination-replication are predominantly expressed late and therefore are exclusively part of a late recombination pathway that has been called the "join-cut-copy" pathway (768, 769). The late *uvsW* gene, encoding an RNA-DNA helicase and a functional homologue of the *E. coli* RecG protein (132), is probably also specifically important in this late recombination pathway (722). This pathway is also implicated in horizontal transfer between different phages of DNA segments with limited homology (777, 784).

Together, these mechanisms generate the branched, concatemeric intracellular T4 DNA. This DNA is debranched in vivo by T4 endonuclease VII (gp49), which can cut Holliday junctions, Y-junctions, and mismatched base pairs in heteroduplex DNA (reviewed in reference 522), and by the largest (70-kDa) subunit of the heteromeric terminase (288). As mentioned above, genes *49* and *17* both code for several nested proteins by initiation from internal ribosome binding sites, and the function of EndoVII (gp49) in vivo depends on the regulated timed synthesis of the two nested proteins (reviewed in reference 784). This can now be correlated with the three-dimensional structure of EndoVII (883).

DNA Repair

As in other organisms, damage and mismatches in T4 DNA can be repaired in several different ways, and repair defects result in increased sensitivities to such damage or increased mutation rates. The consequences of such mutations have been summarized by Bernstein and Wallace (67).

The first mechanism shown to repair UV-damaged T-even DNA was photoreactivation (245). It is now known that the host enzyme responsible for this repair causes the reversion exclusively of pyrimidine dimers to the monomeric state (reviewed in references 233 and 234).

Harm (384) first isolated DNA repair mutants with mutations in T4 genes that are now called *denV* and *uvsX.* EndoV, the product of *denV*, is the prototype of a base excision repair protein. It has both *N*-glycosylase and abasic lyase activities (222, 656), which incise the DNA (forming a covalently linked protein-DNA intermediate). Together, these activities remove the pyrimidine dimers to allow resynthesis by DNA polymerases, notably including *E. coli* PolI (1056) and the T4 ssDNA-binding protein, gp32 (764). The profound difference in UV sensitivities of T4 and T2 is due to the presence of *denV* in T4 but not in T2 (222, 384).

The T4 *uvsX* gene encodes a RecA homologue, the major protein required for invasion of ssDNA into homologous double-stranded DNA (dsDNA) to form D-loops, which can be extended to form two heteroduplexes joined by Holliday junctions. The radiation sensitivity of *uvsX* mutants is now understood to be a consequence of defective recombination-dependent DNA replication that can repair or bypass DNA lesions. Therefore, all recombination-deficient mutants (Table 2) are also defective in DNA repair (60, 68, 1056; reviewed in references 67, 572, and 575).

Heteroduplex (or mismatch) repair of T4 DNA in vivo and in vitro is mediated by EndoVII, the enzyme that cuts Holliday junctions (522, 526, 793), not by MutHLS-like enzymes. The specificity of this activity is thought to contribute to the exclu-

sion of viable recombinants between different T-even phages whose sequences have diverged (305, 784).

MOBILE ENDONUCLEASES, GENE TRANSFER, AND GENE EXCLUSION

Following discovery of group I introns in T4 (see above) (991), site-specific endonucleolytic DNA cleavage by the protein of the intron ORF was demonstrated (882); reviewed in reference (178). The three intron ORFs of T-even-like phages are I-*Tev*I (*td* intron), I-*Tev*II (*nrdD* intron), and I-*Tev*III (*nrdB* intron). In T4, I-*Tev*III is partially deleted so that the endonuclease activity is absent; the T4-related phage RB3 has an intact ORF, and endonucleolytic activity of the I-TevIII enzyme is detected (247). Each endonuclease recognizes a so-called "homing" site that is cleaved by the enzyme, with the double-strand break (DSB) serving as a recombination site for insertion, or conversion, of the intron. Thus, intronless sites, when present in mixed infections with intron-containing phage or other DNAs containing the intron and its ORF, are efficiently converted to contain the intron. The apparent DSB recombination process involves the I-Tev nuclease only for the generation of the DSB. The specificity of these nucleases involves a site on the DNA for binding and a separate cleavage site, which for I-TevI is 23 to 25 bp upstream of the insertion site (202). Subdomains for DNA binding by the I-TevI nucleases include a zinc finger, an α-helix, and a helix-turn-helix. Homing endonucleases of introns can be viewed as systems that target localized gene conversion events, mobilize specific DNAs from one chromosome to another, or, as for SegF (see below), effectively exclude genes or larger regions from "invading" a related chromosome.

At least 15 T4 genes (including the I-*Tev* genes) belong to two of the four structural families of homing endonucleases (163, 992) defined by the conserved sequences GIY-YIG, LAG LIDADG, H-N-H, and His-Cys (49). Sharma et al. (988) recognized and described the *segA-segE* set of T4 proteins, which are not associated with an intron, and provided convincing evidence for the endonuclease activity of SegA. Kadyrov et al. (489, 490) later demonstrated that *segE* promotes its own transfer to the related phage RB30, which does not carry this gene. They reported that efficient transfer requires bases upstream and downstream of the *segE* cleavage site, and they cited unpublished data that SegB and SegD can initiate similar nonreciprocal genetic exchange. The location of SegB in the tRNA gene cluster suggests that its cleavage site is in or near these genes and that it could be responsible for maintaining (recombinational exclusion) or transferring the tRNAs. Errors near the putative start codons in the initially published sequences of the three *seg* genes (which were sequenced from clones) have been corrected (489, 490). This is consistent with the suggestion that they are expressed and lethal to the host and that mutated versions were selected during cloning. Indeed, the recombination-dependent gene exclusion in the T4 *56-69* region (305) is due to a DSB generated by the product of the gene *69* ORF, prompting the renaming of the gene as *segF* (51). A similar localized gene conversion activity in the gene *32* (encoding the essential T4 SSB protein) region has been recently demonstrated for the product of ORF *32.1*, which has been renamed *segG* (48; Q. Liu, A. Belle, D. A. Shub, M. Belfort, and D. R. Edgell, submitted for publication).

I-TevI, I-TevII, and SegA through SegG all appear to have the GIY-YIG family signature (cited in references 51 and 202; also see the pfam alignment at http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF01541). SegF aligns in the N-terminal half with the GIY-YIG domain, but in the C-terminal half it aligns with MobD, a member of the H-N-H family (51, 305).

I-TevIII and T4 Mob proteins (MobA through MobE) group with the H-N-H family of DNA endonucleases, which are rooted by the sequence and structure of the DNase colicin e7 (microcin e7). The H-N-H signature sequence also includes the mobility endonucleases of group II introns and the *E. coli* restriction endonuclease McrA (337, 992). Reiterative PSI-BLAST analyses of the uncharacterized T4 ORFs may yet yield more members of these DNA endonuclease, which appear to be surprisingly abundant in the T4 genome.

It is not yet clear how many of the *mob* genes are actually expressed during T4 infection. Two of them—*mobA*, between genes *39* and *60*, and the nuclease gene in the T4 *nrdB* intron—seem clearly to be pseudogenes and are nonfunctional (247). *segD* is situated in reverse orientation with respect to adjacent genes, with antisense RNA from gene *24* occurring between *segD* and the nearest promoter from which it could be expressed. No functional or homing studies have yet been carried out for any of the *mob* genes, although *mobD* has been successfully cloned and overexpressed (Kutter, unpublished). The role that these enzymes play in gene mobility and transfer and/or in gene exclusion and recombination processes merits further analysis.

T4 PARTICLE, INFECTION, AND LYSIS

T-even phages build some of the most complex virus particles known (Fig. 1 and 8). They devote more than 40% of their genetic information to the synthesis and assembly of the prolate icosahedral heads, tails with contractile sheaths, and six tail fibers that contribute to their very high efficiency of infection. Most of the genes for the structural proteins are transcribed in the clockwise direction on the standard genomic map. The genes responsible for each substructure are largely clustered, with these clusters distributed over more than half of the genome (Table 1; Fig. 3). There are some interesting exceptions to the clustering. For example, the tail is built on a baseplate made of a hub and six wedge components, and each of the substructures is encoded by a gene cluster. However, gene *5*, one of the five genes involved in assembling the hub, is actually located with the genes for the wedge, while a wedge gene, gene *25*, is located with hub genes; these two clusters are separated by the head and other tail proteins. Interestingly, each cluster also contains a replication origin and the direction of transcription switches within each cluster.

Exquisite genetic and biochemical analyses revealed the complex assembly pathways of the T4 particle (89, 186, 272). Twenty-four proteins are involved in head morphogenesis, and there are 22 for tail morphogenesis and 7 for tail fibers, including one for tail fiber attachment (Tables 2 and 3). As described below, 5 of the 54 proteins are catalysts for assembly rather than components of the final virion. In the assembly pathway, the head, tail and tail fibers are assembled indepen-

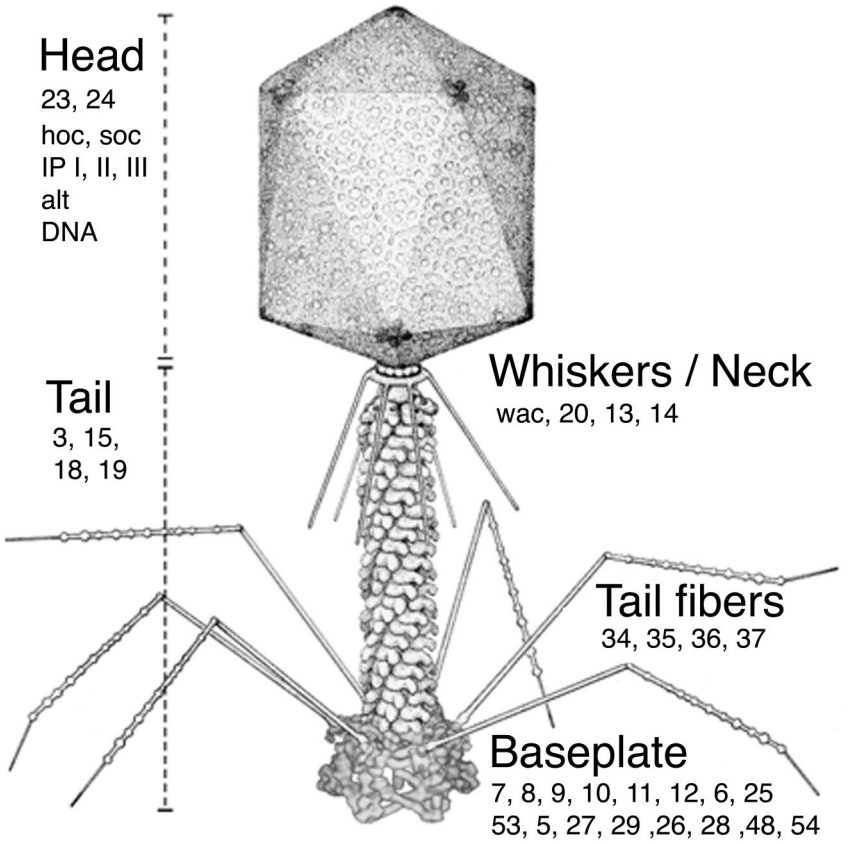

FIG. 8. Structural components of the T4 particle. Features of the particle have been resolved to about 3 nm. The positions of several head, tail, baseplate, and tail fiber proteins are indicated (see the text for details and references). Adapted and reprinted from reference 506 with permission from the American Society for Microbiology, with baseplate modifications introduced by Petr Leiman (M. Rossmann laboratory, Purdue University).

dently. A head and tail are associated, and then the six tail fibers attach to the baseplate (250).

Heads

Of the 24 proteins assigned to head morphogenesis, 16 are involved in prohead formation and maturation, 5 are responsible for DNA packaging, and 3 complete and stabilize the head. Only 10 of the 16 genes for prohead formation are essential; these include GroEL, the one host-encoded protein involved in head assembly. This contrasts with phage lambda, where GroES, DnaK, DnaJ, GrpE, and GroEL are all essential (187, 317, 318, 1078). van der Vies et al. (1115) showed that T4 gp31 can substitute for the function of GroES. Since then, crystallographic analysis revealed that gp31 forms a heptameric ring that is quite similar to the GroES structure. However, T4 gp31 has an extra loop that makes the inner cavity of the GroEL-gp31 complex larger so that it can accommodate the folding intermediate of gp23, the major capsid protein (455). The head is assembled on the initiator complex, which is a 12-mer of gp20 arranged in a ring. The scaffold, made of gp22-gp21 (stoichiometry = 576:72) and the capsid protein, gp23, are assembled onto the initiator, which eventually becomes the portal vertex. Pentamers of gp24, which is 28% identical in amino acids residues to gp23, are placed at the other 11 vertices. After the scaffold is completely surrounded by gp23 and gp24, the T4 prohead protease, gp21, degrades the scaffold and cleaves most of the other head proteins, including gp23 and gp24. This creates space in the cavity of the prohead. The prohead thus formed is then detached from the membrane (ESP = empty small particle). Jardine and Coombs (471, 472) demonstrated by pulse-chase experiment that ESP then initiates DNA packaging and forms the ISP (initiated small particle), which contains about 10 kb of DNA. The ISP is expanded about 15%, resulting in a twofold ($1.15^3 = 1.98$) increase of the inner volume (ILP = initiated large particle). The resulting mature head is much more resistant to any kind of perturbation.

DNA Packaging

Packaging of DNA is initiated from double-stranded ends. For intracellular concatemers, the terminase complex initiates packaging by first generating ends. This complex contains a small subunit, gp16, and large subunits, gp17, gp17′ and gp17″ (286, 288). The nuclease activity of terminase resides in the products of gene *17* (74, 75, 288). The terminase-DNA complex is translocated from the cytosol to the portal protein gp20 at the vertex of the head to form the "packasome" (893), which uses the energy of ATP hydrolysis to translocate DNA into the

head. Expansion of the head is coupled to entry of DNA (471, 472). There is a symmetry mismatch between the neck initiator complex, which has 12-fold symmetry, and the head, which has 5-fold symmetry. It has been suggested (399) that the neck rotates during DNA packaging. The packaging mechanism cuts the DNA when the head is filled, and it appears that EndoVII trims branches of DNA even after packaging has been initiated (523). The head full of DNA is about 3% longer than the genome size, accounting for the circular permutation of T4 genomes, with terminal redundancy of each genome; this circular permutation is the basis for the circular T4 genetic map (1048, 1049, 1073). Shorter or longer phage heads are occasionally formed, due to assembly errors that are increased by specific mutations in some head genes (256) or by incorporation of arginine analogues (194). The amount of DNA packaged into the head is altered accordingly. While short-headed phages cannot infect singly, they can complement each other to give a normal infection (767, 770, 782). After packaging, gp13, gp14, and six trimers of gp wac (whisker or fibritin) bind to the portal vertex to complete the head, which then binds to the tail.

Although the complex head assembly pathway has resisted full in vitro reconstitution, either T4 or foreign DNA can be packaged in vitro into empty heads. These can then be assembled in vitro with tails and tail fibers to form infectious or transducing particles (434, 802, 893).

Nearly all the genes for virion structural proteins, the assembly catalysts, and the scaffold appear to be present in the genomes of T4-like phages examined to date (701, 1069), although some exceptions have been noted for the *Vibrio* phage KVP40 (E. S. Miller, J. F. Heidelberg, J. A. Eisen, W. C. Nelson, A. S. Durkin, A. Ciecko, T. V. Feldblyum, J. Lee, B. Szczypinski, O. White, I. T. Paulsen, W. C. Nierman, and C. M. Fraser, submitted for publication). Two T4 head proteins—encoded by *soc* and *hoc*—are nonessential. The unusual locations of their genes, their absence in some T4-related phages, and the fact that they are added only after head expansion during assembly are consistent with their being a later acquisition. They are possibly retained because they enhance particle stabilization. The dispensable nature of Soc and Hoc has provided a rationale for a T4 phage display system capable of presenting large polypeptides on the capsid surface (916, 918).

Baseplate and Tails

The tail and tail fibers are responsible for the high efficiency of T4 infection. The tail is made of a baseplate and two slender cocylinders. The inner cylinder, called the tail tube or simply tube, consists of 144 subunits of gp19 arranged in 24 stacked hexameric rings. The inner space of the tail tube allows for the passage of phage DNA. The same number of gp18 molecules form the outer tail sheath, with the subunits arranged in the same manner as gp19. Each stacked sheath ring is offset 17 degrees to the right of the one below it, which gives an apparent right-handed helix (753). While the noncontracted tail sheath is 98.4 nm long, the contracted tail sheath is only 36 nm long and the offset (or twist angle) of sheath proteins is increased to 32°. The assembly and three-dimensional reconstruction of the tail and tail sheath have been reviewed (186).

The baseplate consists of a hub surrounded by six wedges, which are assembled independently. Hub assembly is fairly complex. The six products of genes *5*, *27*, *29*, *26*, *28*, and *51* have been reported to be involved in the assembly. gp51 is a catalytic protein, while gp26 and gp28 have not been rigorously proven to be components of the hub or baseplate. gp5 and gp27 associate first. The hub is completed by binding of gp29 to the gp5–gp27 complex. It appears that some structural modification of gp29 is necessary before associating with the gp5–gp27 complex. Wedge assembly is initiated by association of gp10 and gp11, followed by addition of gp7, gp8, gp6, gp53 and gp25, in that order (except that gp11 can be added later, along with gp12). In the absence of any of the other components, the assembly stops at that point and the remaining components are left free in "assembly-naive states" (532). After six wedge segments bind to the hub, gp9, gp12, gp48, and gp54 are added.

The reported stoichiometry of the subunits has been summarized (186), but some corrections have since been made. There are 18 molecules of gp9 instead of 24 (560), 18 each of gp10 and gp11 instead of 12 (1239), 3 each of gp5 and gp27 instead of 6 (498), and 12 of gp8 (P. G. Leiman, unpublished data). The stoichiometry of gp3 was not known but has now been determined to be 6 (L. Zhao, unpublished data). Three-dimensional structures of gp11 (633), gp9 (560), and the gp5–gp27 complex (498) have been determined by X-ray crystallography. Interestingly, all these structures (except gp8) involve trimers of each component.

Baseplate morphogenesis appears to occur in association with the cell membrane. The baseplates remain attached to the membrane by 300-Å fibers from the six corners of the baseplate during the remainder of phage assembly until the time of cell lysis, as shown by electron microscopy (1003). This is seen even in mutants lacking gp12, which encodes the short tail fiber involved in irreversible phage binding during infection (see below). The finding that gp7 has a predicted membrane-spanning domain near its C-terminus (see below) suggests a possible mechanism for this attachment.

The presumed localization of the tail lysozyme gp5–gp27 complex in the baseplate is shown in Fig. 9. The baseplate protein gp5 is a natural chimera. A lysozyme domain, a paralog of the soluble lysozyme of T4 (787), is inserted into the center of a structural baseplate component. The overall shape of the trimeric gp5 resembles a torch, where the N-terminal domains, together with the trimeric gp27, form a cup, the lysozyme domains form the rim, and the C termini of gp5 form the handle. This "handle" is the most conspicuous structure—a three-stranded beta-helix 110 Å long and 28 Å wide. The primary structure of the β-helix region has a peculiar motif of VXGXXXXX (8 residues) repeated 12 times. The cross-section of the cylinder is not a circle but, rather, a triangle, with the glycine at position 3 located at the edges to form a kink. Among some T4-related phages (e.g., RB69, RB49, KVP40, and S-PM2) the beta-helix is well preserved, but there is some indication that its length can vary (F. Arisaka, unpublished data).

The gp5–gp27 heterohexameric complex is attached at the tip of the tube. When the tail sheath contracts and the tail tube protrudes from the bottom of the baseplate, the triple-stranded β-helix is considered to play a role like that of a needle to puncture the cell. gp5 is the only protein in the tail that experiences processing; the peptide bond between Ser351 and Ala352 is cleaved during assembly, but the C-terminal

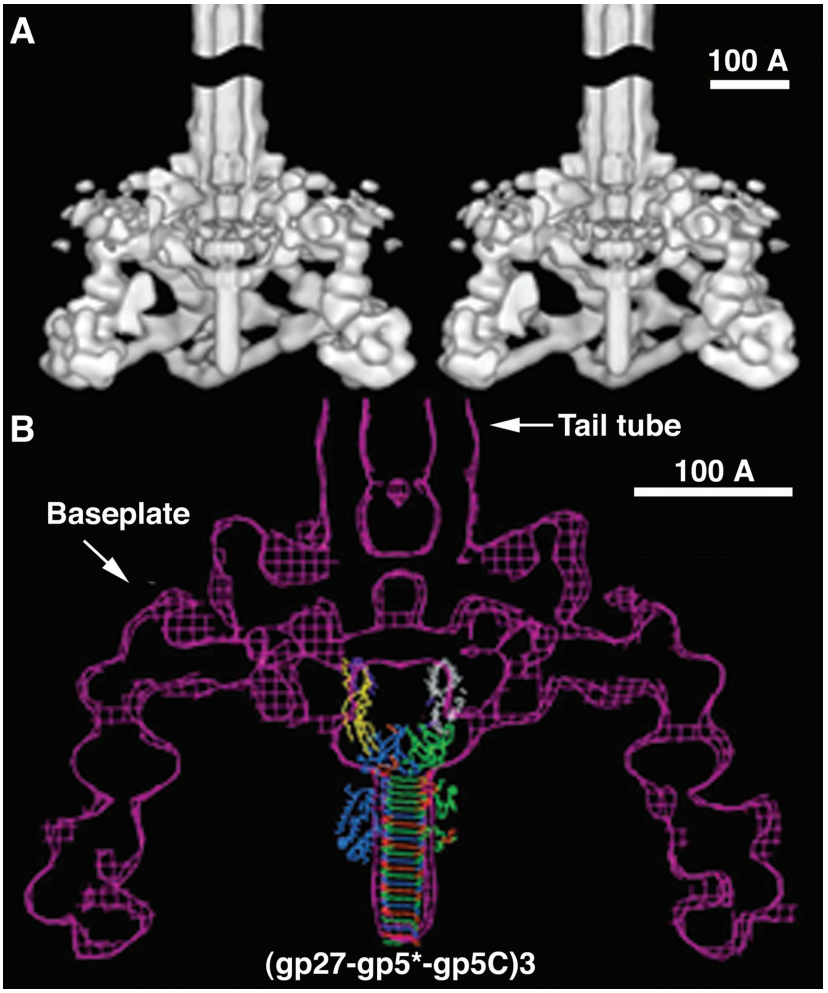

FIG. 9. Three-dimensional image reconstruction of the T4 tube-baseplate from cryoelectron microscopy. (A) Stereo image view of the baseplate and part of the tube at 17 Å resolution. The top quarter of the baseplate has been removed to show the internal features. Note the presence of the needle-like stick at the center of the baseplate beneath the tube. The arrangement of the six short tail fibers is also clearly visible. (B) Cross-section of the reconstituted baseplate into which the atomic structure of the $(gp27\text{-}gp5*\text{-}gp5C)_3$ complex solved by X-ray crystallography at 2.9 Å resolution is fitted. The conspicuous three-stranded β-helix, the C-terminal domain of gp5 or gp5C, with a length of 110 Å, precisely fits into the needle-like stick. gp27 constitutes the "cup" on top of the needle. The three gp5 monomers are colored red, green, and blue. The contour map of the baseplate is in purple. Reprinted from reference 498 with permission from the publisher.

domain stays associated with the other part of the molecule in the mature virion. The lysozyme activity is activated only when the C-terminal domain is detached from the other part of gp5. It has been proposed (498) that the C-terminal domain of gp5 is detached from the lysozyme when the needle penetrates into the outer membrane upon infection (see "Infection and superinfection exclusion" below). The activated gp5 lysozyme in vitro is monomeric (497).

The complete assembly of the tail requires two chaperones, namely, gp51 and gp57A (1015). In the established model (531), gp51 is involved in the hub assembly while gp57A is involved in assembly of both the short and long tail fibers. gp57A consists of 79 aa, and more than 90% is α-helix (391, 699). Although the molecular nature of the protein has been worked out, the interactions with the short and long tail fibers are unknown.

The short tail fiber is a trimer of gp12; its partial three-dimensional structure has been reported (1118). It consists of three domains called the pin (N terminus), shaft, and head (C terminus). The shaft is mainly β-helix and β-spiral. gp11 is located at the tip of the tail pin and bound to the middle part of the P12 trimer, at a site where the P12 shaft is bent about 94°.

gp9 forms the socket of a long tail fiber (1105) consisting of four gene products, gp34, gp35, gp36, and gp37, where gp34 and gp37 are the proximal and distal long tail fibers, respectively. gp35 and gp36 attach to the distal fiber, forming the junction between the half-fibers. Presumably one or both interact(s) with the tip of the whiskers (fibritin; wac). Structural analysis of the C-terminal portion of the whisker (1051) revealed a three-stranded coiled-coil structure with a beta structure "propeller" at the C terminus. This beta structure is thought to bind the bend or "knee" in long tail fibers to facilitate tail attachment to the baseplate. The assembly of the tail fibers requires two molecular chaperone-like proteins, gp57A and gp38. In a major difference from the T4 system, T2 gp38

(which is unrelated to T4 gp38) is a structural component of the tail fibers; it, rather than the C terminus of gp37, recognizes the host bacterium (750, 751).

Infection and Superinfection Exclusion

The initial energy for infection is provided by the baseplate, which is built like an exquisite, "cocked" mechanical device. gp9 is the stabilizer between the long tail fibers and the baseplate. After at least three of the six long tail fibers bind to a glucose residue of the outer core of the lipopolysaccharide on the bacterial surface, a structural rearrangement of the baseplate from "hexagon" to "star" is triggered (190). This deploys the six short tail pins, after which the short tail fibers (gp12) previously in the baseplate firmly bind to the bacterial outer membrane at the heptose residue of the lipopolysaccharide inner core (751, 933). This is referred to as the second receptor of the phage. The conformational change of the baseplate simultaneously triggers contraction of the tail sheath, pushing the inner tube through the outer membrane. Contraction of the tail sheath appears to advance as a wave of compression transmitted through the helix-like arrangement of tail sheath annuli. The tail lysozyme (gp5), after detachment of the C-terminal "needle," helps to digest the peptidoglycan layer and reach the inner membrane. The beautiful baseplate/needle structure (498) is reprinted in Fig. 9. Phosphatidylglycerol in the inner membrane appears to play a role in release of the DNA through the tip of the tail tube, but the electrochemical potential across the inner membrane is necessary for the DNA to be pulled into the cytoplasm (reviewed in reference 327). In the absence of the electrochemical potential, DNA remains in the periplasm and is eventually degraded.

Host range is determined primarily by distal sites on the long tail fibers. A C-terminal region of gp37 is hypervariable in different T-even phages (390, 750), allowing for adaptation to different host receptors. The system has been referred to as a primitive prokaryotic immunity system. As shown by Wais and Goldberg (1137), T4 can grow well in a number of other gram-negative bacteria if it can gain entry, such as when the bacteria are converted to spheroplasts and the phage are treated with urea. The urea leads to contraction of the tail sheath and formation of activated phage particles that, on contact with bacterial inner membranes, can release their DNA into a spheroplast.

The initial infection leads to poorly understood membrane alterations involving the product of the T4 *imm* (immunity) gene. One consequence of these changes is that by about 4 min after infection, the DNA from T4 or related phages attempting to penetrate the cell envelope is released into the periplasm, where it is degraded by nucleases, resulting in a phenomenon called superinfection exclusion (665, 666). Other genes that appear to be involved in this process include *sp*, *rIIA*, *rIIB*, and *rI*, but their precise functions are not well understood.

Lysis and Lysis Inhibition

Normally, 100 to 150 phage particles have accumulated in the cell by the time lysis occurs. As in many other tailed phages, two proteins are involved in the lysis process: gpe and gpt. gpe is the so-called T4 lysozyme (1050), whose structure has been extensively studied by Mathews and colleagues (1193, 1206). Under special conditions, the gp5 lysozyme discussed above can substitute for gpe (500). gpt is the T4 holin, which, by analogy to other well-studied phagelysis systems, creates a hole in the inner membrane so that lysozyme can reach the peptidoglycan layer from the cytosol; the timing of holin assembly thus determines the timing of lysis (360, 887). In the absence of either lysozyme or the holin, lysis does not occur.

The T-even phages display a unique phenomenon, lysis inhibition, which allows them to sense when there are numerous phage around and respond appropriately to delay lysis, maximize the use of their current host, and potentially await the accumulation of additional bacterial hosts (41a, 851). Lysis is extensively delayed if more phage attack the infected cell at any time after 5 min into infection. This signal is somehow mediated by the rI protein, which regulates assembly of the t holin (851). Recently, Ramanculov and Young substituted the T4 *t* gene for the holin of bacteriophage lambda and showed that these lambda phage could now produce lysis inhibition if they infected *E. coli* that carried a cloned T4 *rI* gene (886, 887). T4 gprIII further extended lysis inhibition, but no other or additional T4 proteins were required. We still do not know the specific signal that gprI senses to establish lysis inhibition; possibilities include the phage DNA or the internal proteins that have been injected into the periplasm rather than the cytoplasm under these circumstances.

The classic *rII* genes were involved in defining the phenomenon of lysis inhibition when T4 was propagated on *E. coli* B strains (224). The T4 *rII* mutants provided an example of phage exclusion by genes of resident prophages. They are completely excluded by the lambda *rexA* and *rexB* genes expressed in lysogens. This phenomenon was elegantly used in Benzer's fine-structure analysis of the gene (56). Exclusion occurs at the time of transition from join-copy to join-cut-copy recombination and involves several enzymes important in the latter process (769, 793). The molecular mechanism of this exclusion is still poorly characterized. It has been proposed that RexB forms an ion channel that is opened after infection with T4 *rII* mutants or various other phages, leading to loss of ions and cellular energy (855). However, the way in which the rII proteins bypass this process is still unclear (reviewed in reference 1021). More recently (851), it was demonstrated that gprIIA and gprIIB are also primarily responsible for protecting T4-infected *E. coli* B cells against the attack of a P2-related resident prophage, with less severe consequences than when T4 *rII* mutants infect K-12 strains lysogenic for lambda. A similar phenomenon appears to be responsible for the large size of *rII* plaques on the lysogenic *E. coli* B strains (851). In that case, DNA replication is not affected and lysis does not occur until about 25 min after infection, so that a reasonable burst is produced. If the host B cell has been cured of the P2-related prophage, *rII* mutants show normal lysis inhibition. As first shown by Rutberg and Rutberg (947), many *E. coli* B strains carry a defective prophage related to P2. The primary role of the *rII* genes seems to be related to cellular energetics. The apparent "lysis inhibition" phenomenon seen on lysogenic B strains, rather than the phage death seen on K-12 lambda lysogens, appears to be due to the breakdown of cell energetics occuring near the normal lysis time on B cells, rather than at 12 min after infection of K-12 (lambda) cells.

RESTRICTION-MODIFICATION SYSTEMS AND PHAGE EXCLUSION

As mentioned above, the T4 nucleotide metabolism enzymes result in HMC-containing DNA that is protected from T4-encoded nucleases that degrade host DNA. These enzymes (encoded by *denA*, *denB*, *dexA*, and others genes) can be viewed as DNA restriction systems and also as mechanisms for generating nucleotide precursors for T4 DNA replication (139). Indeed, the DenA (EndoII) recognition sequence is the C-rich sequence 5′-CCGC-3′, which more frequently nicks the complementary strand of the sequence shown but does generate double-strand breaks (135). The modified T4 HMC DNA is resistant to cleavage, so that EndoII serves to restrict "foreign" phage or host DNA. Properties of EndoII have prompted the suggestion that the free DNA ends it generates would be recombinogenic for acquisition of DNA into the T4 genome (134). DenB (EndoIV) also cleaves cytosine-containing DNA and not the phage HMC DNA, but there is still only limited information available on its specificity (140).

In addition to the protection afforded by the HMC in T4 DNA, the phage encodes other nucleotide modification enzymes that act postreplicatively and protect the DNA. The *dam*-encoded DNA-(N^6-adenine)methyltransferase of T4 belongs to the α group of GATC family of DNA methyltransferases. Using *S*-adenosylmethionine as the methyl donor, it modifies adenine in GATC and in the T4 sequence GAT HMC (140, 267). This modification protects otherwise unmodified T4 DNA from a restriction system of P1 phages.

The α-*gt*- and β-*gt*-encoded enzymes (α- and β-glucosyltransferases, respectively) modify the T4 HMC residues to the extent that there is ca. 70% in α-glucose linkage and 30% in β-glucose (reviewed in reference 139). Restriction of nonglucosylated T4 DNA (strains defective in gt activity) led to the discovery of the host restriction enzymes RglA and RglB, which were then recognized as broader systems for modified cytosine restriction and hence were renamed McrA and McrBC, respectively (139). The enzymes do not distinguish between mC and hmC modified DNA. *mcrA* of *E. coli* K-12 resides in a cryptic prophage-like element, e14, that is not present in all *E. coli* strains (37), whereas *mcrBC* resides at an unlinked location adjacent to the *mrr* and *hsd* restriction systems. T4 provided an important entry into unraveling the genetic organization and specificities of these enzymes. The presence of Mcr enzymes in *E. coli* or other bacterial hosts may have provided selective pressure to maintain the different DNA-glycosylating enzymes of T-even phages. In addition, the T4 *arn* gene encodes an antirestriction endonuclease that inhibits the host McrBC (RglB) enzyme (533).

Exclusion of T4 *r*II mutants by *E. coli* lambda lysogens is discussed above (see "Lysis and lysis" inhibition).

As detailed above (see "mRNA and tRNA turnover"), another cryptic DNA element of certain *E. coli* strains, *prr*, encodes the PrrC protein that excludes mutants deficient in T4 RNA ligase/polynucleotide kinase. The PrrC RNA endonuclease is activated by the small T4 Stp protein to cleave the anticodon loop of an essential host lysine tRNA (515, 1021). T4 RNA ligase (*rnlA* or gene *63*) and polynucleotide kinase (*pseT*) can repair this damage, but in the absence of RNA ligase the cleavage of the tRNA is lethal to T4 protein synthesis. Intriguingly, the *prrC* gene is located between three genes of a type IC restriction cassette. The corresponding proteins are thought to inhibit PrrC RNase activity in uninfected cells.

Two additional exclusion mechanisms involving T4 can be cited. Phage P2 lysogens exclude T4 by two mechanisms: the Tin protein poisons gp32, which is essential for all T4 DNA replication and recombination (794), and the P2 Old protein degrades T4 and lambda DNA from ends, nicks, and gaps unless they are protected by specific proteins (125). It seems more than likely that many other cell-, phage-, and plasmid-encoded mechanisms of T4 exclusion remain to be discovered.

PREDICTED INTEGRAL MEMBRANE PROTEINS

One approach to exploring the function of the many uncharacterized T4 ORFs is to determine the cellular localization of their products. A number of early T4 studies used cell fractionation and gel electrophoresis to identify membrane-associated phage proteins during infection (reviewed by Harper et al. [385]). There is evidence that the cell envelope continues to be synthesized after infection. The optical density of the infected culture continues to increase substantially under a variety of growth conditions. Freedman and Krisch (291) demonstrated ongoing cell enlargement coupled with gradual arrest of cell division after infection of *E. coli* B in M9 by using a combination of Coulter Counter and dry-weight measurements. The rate of incorporation of diaminopimelic acid remained equal to that of uninfected cells for at least 50 min after infection, supporting the presence of ongoing growth and repair of the peptidylglycan layer. The total phospholipid content continues to rise as rapidly in T4 infected cells as in the uninfected control (as reviewed in reference 385). The rate at which phosphatidylglycerol is synthesized actually increases markedly after infection, while that of phosphatidylethanolamine diminishes, suggesting some changes after infection in basic membrane properties. Synthesis of host membrane proteins appears to be shut off along with that of other host proteins, as observed on two-dimensional gels (189), implying that most new protein in this expanded membrane is either phage encoded or the result of continued processing of already-synthesized host membrane proteins (385).

In recent years, an alternative (bioinformatic) approach to exploring protein function has been developed on the basis of primary sequence data. Computer programs are now available that use various algorithms to predict localization of proteins to the membrane or periplasm. Boyd et al. (105) optimized a statistical approach to determine the probability of an individual protein being integrated into the bacterial inner cell membrane. The calculation of these so-called MaxH values gives two very distinct peaks for proteins from a variety of organisms. These calculations were carried out for the complete set of T4 proteins and ORFs (D. Boyd, E. Thomas, and E. Kutter, Evergreen Int. Phage Biol. Meet., abstr. 11, 1998), using normalization constants determined with the training set of known *E. coli* proteins (105). MaxH values above 1.505 are considered to have a >50% probability of being integral inner membrane proteins. Using this approach, two very distinct peaks are also obtained for T4, with 15 T4 proteins predicted to be integrated into the inner membrane with a probability of over 99%. Three proteins are given a probability of 45 to 95%, three are given

TABLE 6. Potential T4 membrane proteins and their cellular locations

Protein	P-SORT predictions[a]			Membrane domain[b]	Size (aa)	Cut site[c]	MaxH (%)	Comments[d]
	Inner membrane	Periplasm	Outer membrane					
Inner membrane								
t	0.516	0.000	0.000	30–46	218		100.0	
rI	0.210	0.000	0.000	2–18	97			Not M
7	0.297	0.000	0.000	890–906	1,032		99.6	
29	0.425	0.000	0.000	237–253 327–343	590		96.0	
Ac	0.700	0.000	0.790	5–27 29–48	51	32, 19	100.0	M, SOSUI: IM lpp
Imm	0.000	0.926	0.181	7–29 41–63	83	54	100.0	M, SOSUI: IM
52.1	0.359	0.000	0.000	23–39	46	15	1.3	
Ndd.3	0.196	0.000	0.000	3–19	26		100.0	
Ndd.4	0.750	0.000	0.000	16–32	42		100.0	
e.2	0.219	0.000	0.000	82–98	102		100.0	
e.3	0.230	0.000	0.000	32–48 57–73	120	25	100.0	
e.4	0.650	0.000	0.000	26–42 57–73	130		100.0	
tRNA.4	0.624	0.000	0.000	38–54 9–31	61	22	100.0	
55.8	0.561	0.000	0.000	26–42	70	24	100.0	
PseT.3	0.387	0.000	0.000	8–24	117		100.0	
PseT.2	0.000	0.000	0.000	1–21	98			Not M, P
47.1	0.338	0.000	0.000	30–46	46	19	100.0	Not S
NrdC.7	0.200	0.000	0.000	110–126	133	23	16.0	
Imm.1	0.700	0.000	0.790		125	19, 14	1.0	lpp
Outer membrane/periplasm								
sp = rIV	0.000	0.935	0.274		97	22		Not M
MotA.1	0.000	0.765	0.191		49	31	45.0	
Ndd.6	0.000	0.926	0.174		28	23		
Ndd.2a	0.000	0.753	0.146		40	17		
Ndd.2	0.000	0.266	0.934		36	32		Not M
Ndd.5	0.000	0.132	0.922		32	25	93.0	

[a] The PSORT predictions for each site are given in a decimal form, 0 to 1.0, that is related to the strength of the prediction but is not an actual probability; for a given protein, they never add up to 1 for the sum of the different sites. All of these proteins show a "0" prediction for the cytoplasm.
[b] Amino acids in the predicted membrane domain of each protein are listed.
[c] Cut site refers to the position(s) at which the predicted leader peptide would be cleaved.
[d] not M, P, S: not predicted by MaxH, PSORT or SOSUI, respectively. M, SOSUI, inner membrane location predicted by these programs. lpp, lipoprotein. See the text for the URL and description of the output for each program.

a probability of 1 to 16%, and the rest are given probabilities generally well below 0.001%.

Additional programs that predict cellular localization have been applied to all T4 proteins (Kutter, unpublished). TMPred (www.ch.embnet.org/software/TMPRED_form.html), SignalP (www.cbs.dtu.dk/services/SignaIP/), SOSUI (sosui.proteome.bio.tuat.ac.jp/sosuiframe0.html), and PSORT (psort.ims.u-tokyo.ac.jp/) variously predict the presence of transmembrane domains; the presence of leader sequences, their cleavage sites and lipid modification sites (lipoproteins); and whether the protein should be localized to the cytoplasm, cytoplasmic membrane, outer membrane, or periplasm. We summarize the major conclusions from these analyses in Table 6. In most cases the programs agree, but there are some interesting exceptions.

Integral Membrane Proteins of Known Function

Some of the high-scoring proteins from the predictive programs have long been considered to be membrane proteins. For example, Imm, holin (t), rI, and Ac have recognized physical and functional cell envelope associations. The additional proteins having predicted membrane-related properties either are encoded by uncharacterized ORFs or are proteins that have not previously been considered to be membrane associated. We first summarize the predicted properties of the better-recognized T4 membrane proteins.

The immunity protein, Imm (83 aa) plays a primary role in the exclusion of superinfecting phage (3, 1113). Various programs predict it to be a typical membrane protein, with two transmembrane (TM) domains and its N and C termini probably external to the cell. However, PSORT and SignalP both suggest that Imm is periplasmic or possibly in the outer membrane. The site of localization needs to be determined experimentally; any of the three sites are consistent with its known function. The gene adjacent to *imm* encodes Imm.1 (125 aa), which is predicted by PSORT to be a lipoprotein with equal probability of being in the inner or outer membrane; it may well work together with Imm in superinfection exclusion.

The T4 holin (218 aa, encoded by gene *t*) is predicted to have a single TM domain, but with an unusual charge distribution for a membrane protein. It has very different properties from

other known phage holins, as extensively reviewed (886, 1145). Analysis of *t* mutants with a rapid-lysis phenotype (*rV* mutants) indicates that various segments throughout much of gpt are involved in the phenomenon of lysis inhibition (discussed above) (236). Biochemical confirmation has been provided that gpt has a single N-terminal transmembrane domain and that the bulk of the protein lies in the periplasm (886, 887). Thus positioned, T4 holin apparently receives a signal that additional phage are trying to enter the already-infected cell; lysis inhibition is thus an effective strategy to promote exclusion of other phages and optimal accumulation of T4. This extra role for gpt in receiving the signal for lysis inhibition may explain why it is larger than other holins.

gp rI (97 aa), the other T4 product required for lysis inhibition, is the apparent signal transducer (851, 888). Cloned *rI* can produce lysis inhibition in lambda-infected cells if the lambda holin gene has been replaced by the T4 *t* holin gene. It is classified by both PSORT and TMpred as an inner membrane protein with one TM domain at residues 1 to 22, but its MaxH value of 1.40 puts rI slightly below the threshold of membrane proteins, with a probability of 10^{-7} of being in the inner membrane. The SignalP program was used to predict that gprI is a periplasmic protein (851), and SOSUI assigns the one potential TM domain as a signal peptide. The uncertainty revolves around whether or not this signal peptide is cleaved. Unpublished experiments (E. Ramanculov and R. Young, personal communication) were inconclusive in determining whether it is in the membrane or in the periplasmic space, due to the extreme instability of the rI protein; clearly, more experimental work is needed.

Ac (51 aa) confers resistance to acridine dyes, and its gene served as an important genetic marker in early phage crosses (894). It is a clear, if not typical, membrane protein according to MaxH and SOSUI analysis. However, PSORT suggests that the potential signal peptide is cleaved so as to add an N-terminal lipid and classifies it as a lipoprotein, giving it equally high probabilities of being in the inner or outer membrane. SignalP suggests it may be cleaved between residues 18 and 19.

Two baseplate proteins, gp7 (1032 aa) and gp29 (590 aa), have MaxH values predicting a 99.6% and 96% probability, respectively, of being integral membrane proteins. PSORT, SOSUI and TMPred all predict that gp7 has a single C-terminal TM domain and that gp29 has a pair of TM domains in the middle (Table 6). As mentioned above, the baseplate is assembled on the membrane. gp7 and gp29 are involved in initiating wedge and hub assembly, respectively, and gp29 later becomes the tail-length calibrator. The baseplate remains attached to the inner cell surface (via 300Å fibers from the six corners) throughout tail morphogenesis and the start of lysis (1003), and antibody studies have localized gp7 to the outer corners of the baseplate. This location is consistent with the C-terminal region of gp7 being the observed fibrous attachment structures; at 1,032 aa, gp7 is the second largest T4 protein, comparable in size to the two main tail fiber proteins.

Hypothetical Proteins with Predicted Cell Membrane Associations

The T4 genome has three apparent gene clusters that encode predicted envelope proteins (Table 6). One of these lies between *rIIB* and *52*, a region of very short genes and ORFs, including *ac*, where it was difficult to determine gene and ORF assignments using standard computational methods. Other proteins encoded by this region and predicted by MaxH to be membrane proteins include 52.1 (51 aa, N inside the cell), Ndd.2a (40 aa, C inside but atypical in its structure), Ndd.4 (42 aa, N inside), and possibly MotA.1, Ndd3 (26 aa), Ndd.5 (32 aa, N inside), and Ndd.6 (28 aa, C inside). Ndd.2a, Ndd.6, and MotA.1 are characterized by PSORT as probable periplasmic/possible outer membrane proteins, while PSORT gives Ndd.2 and Ndd.5 over a 90% chance of being in the outer membrane.

The experimental work of Harper et al. (385) suggested that at least two genes in the *ac* region are required for the stimulation of phosphatidylglycerol biosynthesis following T4 infection; one of them is required for ongoing phospholipid synthesis after infection. Their identity has yet to be determined, but some of these predicted membrane proteins may well be involved. Ndd (for "nuclear disruption deficient") has often been assumed to be a membrane protein, due to its observed role in binding the bacterial DNA to the membrane. However, its MaxH score is only 1.22, and PSORT and SOSUI localize it to the cytoplasm. Nucleoid binding may actually involve the combined function of multiple proteins from this transcriptional unit, which extends from *ndd.4* through *motA.1.*

The second cluster consists of significantly larger predicted membrane proteins and is located in the *e* (lysozyme)-*tRNA* region, the general region where the still-unpositioned "star" plaque mutants *stI* and *stII*, affecting lysis timing, were mapped (583, 1208). gpe.3 (120 aa) and gpe.4 (130 aa) both clearly have two potential TM domains, with N and C inside the cell; gpe.4 is one of the few T4 proteins that looks like a typical membrane protein. PSORT calls the N-terminal helical domain of gpe.3 a cleavable signal peptide, which would leave only one transmembrane domain in the final protein. gpe.2 (102 aa) is predicted to be an integral inner membrane protein, although it is otherwise very hydrophilic. gptRNA.4 (61 aa) is also predicted by all four programs to have two transmembrane regions.

The third possible cluster is a compact eight-gene operon that starts with *cd.3.* PseT.3 (117 aa, with an apparently uncleavable signal peptide TM) is encoded in this cluster and is predicted by all programs to be an integral membrane protein. The adjacent ORF, *pseT.2* (99 aa), is also predicted by SOSUI (but not the other programs) to encode a membrane-associated protein, with a potential signal peptide at residues 1 to 21. PSORT, SOSUI, and TMPred all suggest that the Cd.3 protein may also be in the inner membrane, although the scores are barely above the cutoff in each case.

Three other isolated ORFs are also generally predicted to encode integral membrane proteins. These are 47.1 (46 aa), 55.8 (70 aa, very hydrophobic) and NrdC.7 (133 aa, with a cleaved signal peptide as well as one C-terminal TM domain). ORF *47.1* overlies a middle promoter and encodes a protein of only 46 aa. Because gp47.1 has a correlation coefficient of only 0.30, it was earlier dropped from the list of probable T4 proteins. It has been reinserted on the basis of this analysis. It could function as the membrane anchor for the gp46/47 nuclease earlier reported to be a membrane protein (345, 731).

Missing Membrane-Associated Proteins

Notable by their absence from this list of predicted integral membrane proteins are several proteins that were classified as

membrane associated on the basis of early experimental work (reviewed in reference 385). Huang (446) performed the most extensive gel analysis to date of proteins that are enriched in the membrane fraction following differential centrifugation. Most that were observed have not yet been identified genetically. The MaxH and PSORT scores and other predicting programs all give zero integral membrane probabilities for most known proteins that were identified as membrane associated in those studies, including gprIIA, gprIIB, Ndd, and gp46. gp52 has a slight potential for one TM domain near the center but is still classified by all of the programs as cytoplasmic. It is important to test more carefully the connection that these proteins have to the membrane, a relationship that was observed by several groups. The current analysis would predict that they are likely to be bound peripherally, perhaps through other proteins, lipid, or DNA. Some of the small membrane proteins cotranscribed with *46*, *ndd*, and *52* could be involved in such attachments, as suggested above.

The use of multiple programs provides complementary insights when using predictive algorithms. Experimental work is required to assess the significance of the predictions by the various programs for TM domains and other membrane associations for these T4 proteins. However, the analysis suggests a starting point for determining the functions of a number of otherwise uncharacterized ORFs and should aid the study of cell expansion and membrane changes during T4 infection. The clustering of many predicted membrane-associated proteins is consistent with the organization of other functional groups of T4 genes.

EVOLUTIONARY PERSPECTIVES: T4 PROTEINS AND THE GENOME

Extensive functional, mutational, and structural data on a number of the T4 proteins provide an excellent framework for advancing the study of protein evolution. Many of the DNA metabolism and replication enzymes of T4 have orthologous proteins represented in all domains of life, which is why the biochemical and structural studies of T4 proteins have been so broadly relevant. Growing knowledge about specific genes, complete genomes, and the proteomes of at least a few T4-related bacteriophages are beginning to make possible comparative genomics studies that impact our understanding of the well-studied T4 systems and broaden our perspectives for other organisms. In the sections below, we briefly summarize the reported structural and evolutionary relationships of T4 proteins and provide some evolutionary reflections on the T4 genome and that of its relatives. A more thorough discussion of the evolutionary relationships among T4-related phages will appear elsewhere (E. Thomas, F. Zucker, and E. Kutter, unpublished data).

T4 Protein Structures

Structural studies of T4 proteins began with the crystallization and three-dimensional structure determination of gpe (lysozyme) (705, 1158). T4 lysozyme is an excellent example of structural analysis and targeted amino acid replacements used hand-in-hand to unravel an enzyme's catalytic properties and protein conformation (594, 1193). Solving the structure of the T4-related RB69 phage DNA polymerase (1146), when the T4 enzyme has been refractory to crystallization, has permitted a full appreciation of the structural and catalytic effects of the numerous available mutations in T4 gene *43* (DNA polymerase) (40, 507, 827, 906). Currently, the structures of 23 T4 proteins, protein domains, and protein complexes are deposited in the Protein Data Bank (Table 7; http://www.rcsb.org/pdb/). In addition to protein structure studies, an RNA-folding model (pdb entry 1SUN) predicts how the 3′-terminal domain of the RNA stabilizes the intron core (468, 730). Each of these structures provides a framework for functional and evolutionary analysis of the respective protein or molecular machine in which it participates. Evolutionary relationships between macromolecules, whether phage or cellular, will be fully appreciated only in the context of their structures, so that the yield from structural studies of additional T4 proteins would appear to be high.

TABLE 7. T4 proteins in the structure database

Protein	Description	Protein Data Bank entry
AsiA	Anti-σ^{70} regulatory protein	1JR5, 1KA3
β-gt	β-Glucosyltransferase	1QKJ
DenV	Pyrimidine-dimer excisionase	2END, 1VAS
gpe	Lysozyme	1LYD
I-TevI	Intron-homing endonuclease	1I3J
MotA	Transcription regulatory factor	1BJA, 1I1S
NrdC	Glutaredoxin, thioredoxin	1ABA, 1DE1
NrdD	Anaerobic NTP reductase, large chain	1H77
RegA	Translation regulatory protein	1REG
Rnh	RNase H	1TFR
TS	Thymidylate synthase	1TIS
Wac	Fibritin deletions E and M	1AAO, 1AVY
gp1	dNMP kinase	1DEK
gp5/27	Tail-associated lysozyme	1K28
gp9	Long-tail fiber connector	1QEX
gp11	Baseplate–short-fiber connector	1EL6
gp12	Short tail fiber	1H6W
gp31	Cochaperone	1G31
gp32	ssDNA-binding protein	1GPC
gp42	dCMP-hydroxymethylase	1B5D
gp43	T4 DNA polymerase fragment, RB69 DNA polymerase	1NOY, 1WAF
gp45	Processivity clamp	1CZD
gp49	EndoVII	1E7D
gp59	Helicase assembly protein	1C1K
nrdD intron	Group IA intron RNA/ribozyme	1SUN

Orthologous T4 Proteins

T4 proteins involved in nucleotide and nucleic acid metabolism typically show sequence similarity to functionally related enzymes of other organisms (69). Proteins that have orthologs in the database are often members of multientry clusters of orthologous groups (COGs) curated at the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/COG). The T4 genome page (NC_000866) provides access to each protein and its respective COG. Proteins involved in DNA transactions (UvsX, Topo II, NrdD, Td, and many others) are present in organisms across the phylogenetic tree and have dozens if not hundreds of entries. However, only 28 of 274 T4 proteins can be grouped into clusters of related

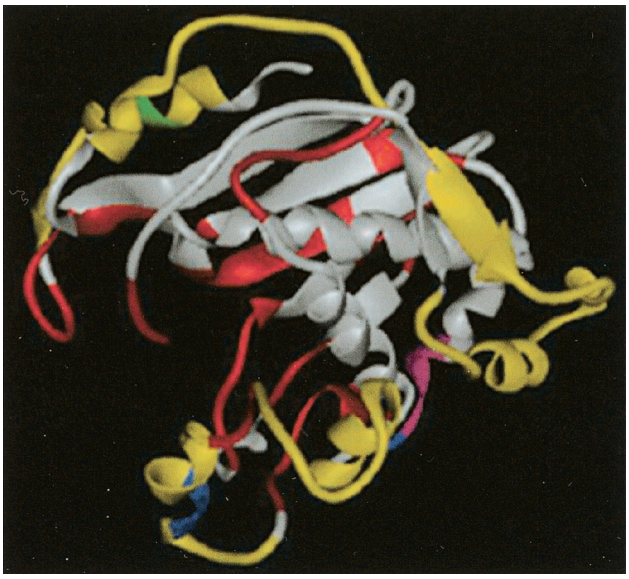

FIG. 10. Structure of T4 thymidylate synthase. The T4 sequence was aligned with other available thymidylate synthases, with the invariant regions colored in red and the regions in which the T4 enzyme is different from all others colored in yellow. The latter regions are largely hydrophilic for most thymidylate synthases but are hydrophobic for the T4 enzyme (which may facilitate its incorporation into the nucleotide-synthesizing complex). These regions were not included for the predicted evolutionary tree in Fig. 11. Structural coordinates are from reference 274 and were used to create this figure. Also see reference 143.

phage proteins. These relationships among viral and phage proteins, including proteins of T4, are now cataloged by NCBI at a dedicated website (http://www.ncbi.nlm.nih.gov/PMGifs/Genomes/crp_start.html).

One of the most interesting and potentially instructive examples of an orthologous protein is thymidylate synthase (td or TS). A number of stretches of amino acids are highly conserved between *Bacteria, Eucarya* and T4, facilitating precise alignment and analysis; these are indicated in red on the crystal structure of the T4 enzyme shown in Fig. 10 (also see pdb 1TIS). The two stretches indicated in yellow are totally different between the T4 enzyme and all other thymidylate synthases; these regions are largely hydrophobic in T4 but hydrophilic in other members of the family. They lie on the surface of the enzyme, where presumably they are involved in the interaction between thymidylate synthase and other enzymes of the nucleotide synthesis complex described above. When these two segments are excluded and the core regions are used for alignment, the phylogenetic relationship shown in Fig. 11 is obtained. The tree suggests that the T4 enzyme branched off somewhere before the split between *Eucarya* and *Bacteria.* The apparently ancient branch point is not just due to faster evolution of viral proteins than of proteins of their hosts, since, for example, herpesviruses appear to branch off much later in the *Eucarya* lineage, just before the separation between the human and rat-mouse lines. Also, T4 TS has several regions that are characteristic of the eukaryotic enzymes, intermixed with others that seem to be unique to the bacterial sequences. T4 TS also has one sequence near the N terminus that is otherwise unique to archaeal thymidylate synthases, which are sufficiently different from those of bacteria and eukaryotes that they are more difficult to align unequivocally. Figure 11 also shows the distant relationship between thymidylate synthases and T4 HMase (gp42; also see pdb 1B5D). This is not too surprising since both enzymes catalyze the transfer of methyl (or hydroxymethyl) to the same position on a pyrimidine monophosphate (dUMP and dCMP, respectively).

The T4 dihydrofolate reductase and the three topoisomerase II components (gp39, gp52, and gp60) also appear to have diverged before the separation of prokaryotes and eukaryotes. This is seen in both the clade patterns and the clear interspersion of sequences uniquely conserved among eukaryotes between ones that are characteristic of prokaryotes.

Other T4 proteins are more closely related to bacterial proteins. These include thymidine kinase (tk), DNA adenine methylase (dam), and the ribonucleotide reductases. The T4 anaerobic NTP reductase (NrdD) and its copeptide, NrdG, are most closely related to the *E. coli* proteins; however, even these two enzymes appear to have diverged from their host counterparts well before the separation between the *Haemophilus influenzae* and *E. coli* enzymes.

T4 DNA polymerase aligns with the B family of DNA polymerases, which includes archaeal, eucaryal, bacterial, and viral enzymes (273). Included in this group are pol II enzymes of γ-proteobacteria (such as *E. coli*), involved in DNA repair, and DNA polymerases of *Saccharomyces*, herpesvirus, and chlorella virus. Interestingly, the T4 DNA polymerase is most closely related to polymerases of the archaeal halophile *Halobacterium* sp. and two of its viruses, HF1 and HF2 (273). These relationships also emerged in the crystal structure of the DNA polymerase of the T4-related phage RB69 DNA (507, 1146) and have been functionally confirmed. A mutation introduced into yeast DNA polymerase (POL3) on the basis of the mutator properties of an altered T4 DNA polymerase gave a yeast mutator phenotype (370). Moreover, gp44, a subunit of the DNA polymerase clamp loader, is orthologous to eukaryotic replication factor C, as discussed above (see "DNA metabolism, replication, recombination, and repair"). Its highest-scoring homology is 29% identity, over its entire 319-residue length, to the *Archaeglobus fulgidus* replication factor.

Primary sequence homologies to eukaryotic viruses are also observed. For example, T4 DNA ligase (gp30) is most homologous to the DNA ligase of the African swine fever virus (25% identity over a conserved region of 229 of its 487 aa). It also shares smaller conserved regions with archaeal DNA ligases (such as 27% identity over 154 aa for *Methanobacterium thermoformicicum*). Two T4 proteins have a particularly interesting homology to an insect viral protein. PseT (the 5′ polynucleotide kinase-3′ phosphatase) and RnlA (gp63 RNA ligase) are similar in amino acid sequence to the two halves of ORF86 in the *Autographa californica* nuclear polyhedrosis virus (246). Together, *rnlA* and *pseT* look somewhat like the tRNA splicing machinery in eukaryotes. The *A. californica* nuclear polyhedrosis virus ORF86 protein has been named Pnk/Pnl to reflect its relationship to the T4 enzymes and its motifs that are characteristic of polynucleotide kinase and RNA ligase. There is generally no need for tRNA splicing machinery in T4, since its tRNA genes contain no introns. However, the ligase and

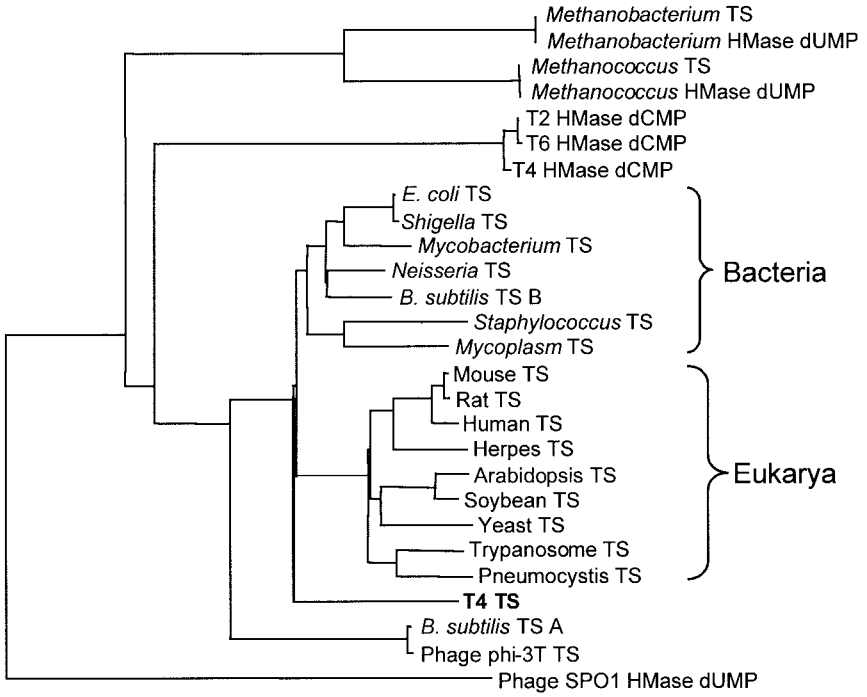

FIG. 11. Phylogenetic tree of thymidylate synthases and deoxynucleotide hydroxymethylases. All protein sequences were obtained from the public databases. Alignment and tree construction were done by the methods of Feng and Doolittle (271).

kinase activities are both required in host strains with the restriction system carried by the cryptic DNA element, *prr* (see above) (515).

Paralogous Genes in the T4 Genome

The T4 genome contains a few apparent duplications that have evolved into separate functional genes. These include *modA-modB* (781) and genes *9–10* and *23–24* (225), as well as a duplication of lysozyme (gene *e*) found inserted into the baseplate protein gp5 (787). This lysozyme insertion, although present in gp5 of coliphages RB49 and RB69, is not seen in gp5 of the *Vibrio* phage KVP40 (Miller et al., submitted). Duplications in the T4 genome have also been explored by evaluating structural similarities in proteins with low-level sequence homologies (T. Kawabata, K. Nishikawa, F. Arisaka, and E. Kutter, unpublished data). Potential duplications were identified in the pairs of proteins encoded by the adjacent genes *26–51*, *rnh-34*, *49-nrdD*, *dexA.1-dexA.2*, and *tk.1-tk.2.* FASTA alone indicated relationships between gpe.3 and gpe.4 and between gpAlt.-1 and Alt.-2 and the N-terminal region of Alt, the latter apparently reflecting an ancient duplication followed by insertion of a new internal start codon to generate this pair of ORFs. Noted similarities were also seen between gp34, gp37, and gp12, all of which form trimeric β-helix fibers. Internal repeats were seen in gp34 (40 aa, 7 *X*), gp12 (25 aa, 5 *X*), hoc (94 aa, 3 *X*) and gp46 (100 aa, 2 *X*), where *X* indicates the number of times each motif is repeated.

A Glimpse at Genome Diversity and Evolution in T4-Type Phages

Bacteriophages may well be the most numerous living entities on Earth; about 10 times as many phages as bacteria have been seen in ocean samples, leading to a total estimate of about 10^{32} phages on Earth (62, 1184). There is interest in how viruses arose, how they acquire their special properties and genes, and how they relate to each other and to cellular genomes.

Botstein (100) presented evidence that lambdoid phages are a mosaic of ordered sets of modules, each of which may have come from a particular host, plasmid, or other phage. This concept has since been extended to other temperate phages, and a lambdoid "supergroup" seems to extend even into gram-positive bacteria (128, 149, 209, 400). For example, L5- and ψM1-like phages, which infect mycobacteria and *Archaea*, respectively, and are members of the Siphoviridae family, show a distant but still detectable similarity in their genome organization with lambdoid phages (209). Another genus of Siphoviridae, the c2-like *Lactococcus* phages, differs a good deal from the lambda pattern of structural gene organization but could still be aligned with the lambda-like *Lactococcus* phage sk1 when allowing for two genome rearrangement events (117, 118).

Nonetheless, "modular mosaicism" does not appear to be an appropriate characterization for the genomes of T4-like phage. Genome sequence surveys of T4-like phages (210, 700, 702, 919, 1067, 1069) suggest that T4 and its relatives are largely in a group by themselves, undergoing few exchanges with other phage families. Sequence homology is observed between the

receptor-binding region of the tail fibers of the T-even group and other phages, apparently reflecting the selection for new receptor-binding capabilities and the special recombinogenic properties of this region (1067). BLAST analysis between T4 and P1 proteins (M. Lobocka and M. Yarmolinsky, personal communication) reveals some homologies in the tail tube, baseplate, and two DNA metabolism enzymes. Nonetheless, there is no evidence for ongoing exchange events between T-even phages and other phages that involve entire gene cassettes or modules; exchanged segments are usually the size of single genes or smaller. The high frequency of recombination observed for T4, its lytic developmental program, and the presence of multiple promoters throughout the genome allow for many independent exchanges of smaller genome segments, apparently precluding extensive selection for large modular genetic units.

The DNA endonucleases or "homing enzymes" in group I introns of T-even phage could afford one mechanism for gene dissemination. However, Edgell (251) discusses reasons why this appears not to occur. The related T4 Seg and Mob endonucleases may also either disseminate or exclude targeted regions of the phage genome (51, 335). The presence in phages of gram-positive bacteria of ribonucleotide reductase genes (*bnrdE* and *bnrdF*) with T4-like group I introns (626) may suggest that introns and genes with introns (see the discussions above on homing endonucleases) can be transferred between phage of major phylogenetic divisions.

Phages with T4 morphology have been isolated from a variety of sources throughout the world: sewage plants, coastal and offshore seawater, zoos, and diarrhea patients in the former Soviet Union and the United States (8, 247, 379, 596, 703, 946, 1233). Members of the family have been found infecting several different gram-negative bacteria (8). The T4-like phages infecting a range of host genera generally show conservation in gene order and protein sequence for the essential units—capsid and tail structures and DNA replication proteins. Since T4 has until very recently been the only fully sequenced member of its myovirid subgroup, with just short genomic regions of sequence data obtained from other phage by PCR analysis or localized cloning (485, 748, 919, 1217), the evolutionary relationships of only a few specific genes (e.g., *56* and the head and tail genes) have been studied in detail (777, 1069).

During the completion of this review, progress on genomic sequencing of T4-type phages has been achieved. The genomes of phage that infect γ-proteobacteria (*E. coli* phage RB69 and RB49; *Aeromonas* phages Aeh1, 44RR2, and 65; *Vibrio* phage KVP40; *Acinetobacter johnsonii* phage 133 β-proteobacteria), (*Burkholderia cepacia* phage 42), and cyanobacteria (*Synechococcus* phage S-PM2) (210, 379, 700, 1069; H. Krisch, J. Karam, et al., personal communication; Miller et al., submitted) are all under study. Many have dsDNA genomes similar in size to T4, while some, such as KVP40 (Miller et al., submitted) have longer heads, filled by substantially larger genomes (e.g., 245 kbp). For these different T4-like phages, ClustalW and neighbor-joining bootstrap analysis of capsid and tail tube proteins led to similar phylogenetic trees with relationships paralleling those of the host bacteria (379, 1069).

Current sequencing projects reveal that the genomes of some T4-type phage infecting *E. coli* are arranged much like that of T4 (such as RB69; see http://phage.bioc.tulane.edu), although group I introns, *seg* genes, and other characterized nucleotide metabolism genes are absent. For other T4-like coliphages (such as RB49), there are yet fewer of the "nonessential" T4 genes and more hypothetical, uncharacterized ORFs (210). For RB49, conservation of the DNA replication and viron structural proteins is most evident. A related situation is seen for the *Vibrio* phage KVP40. The DNA replication and structural proteins most closely align with those of T4 (ca. 35 to 70% similar), but this represents only about 20% of the ORFs, with more than 60% still having no characterized function (Miller et al., submitted). The same pattern was observed in the genome sequence of *Bacillus* phage SPβc2; 75% of its predicted ORF products have no significant homologies to proteins in the databases (625). One of the more extreme examples to date is the 280,334-bp genome of *Pseudomonas aeruginosa* myoviridae phage phiKZ, with only 59 of its 306 ORF products aligning with proteins of known function in the database (727); fully 80% of the proteins it encodes appear not to have been characterized in any organism. It seems likely that the more conserved DNA replication and virion genes of T4-like phages are the ancient genes. The few complete phage genome sequences that are available, which can have 50 to 80% of the ORFs as unique, suggest the presence of a separate, more variable group of genes in each genome. However, our overall view of phage genomes is still very limited, where the small number of BLAST hits with phage proteins in part reflects the paucity of complete phage genome sequences in the databases.

No phages morphologically identical to T4 have been identified as infecting gram-positive bacteria. *Bacillus subtilis* phage SP01, containing dsDNA (ca. 140 kbp) with HMU in place of thymine, somewhat resembles T4 (47-nm-diameter head and 142-nm-long sheathed, contractile tail) and has several DNA metabolism and replication enzymes similar to those of T4. The sequenced dsDNA genome of the temperate *Bacillus* phage SPβc2 (accession no. NC_001884 and AF020713; 134,416 bp) (625) has a few DNA metabolism enzymes that are present in T4, and its ribonucleotide reductase genes harbor the T4-like group IA2 introns (624). Clearly, genomic sequences of large lytic phages infecting gram-positive bacteria and others from across the phylogenetic tree are of great interest. The return on phage genome sequencing would appear to be highest for comparative functional and structural biochemistry on the individual gene products and for new protein and RNA resources for biotechnology, such as novel antimicrobials, therapeutics, and diagnostic reagents.

OUTLOOK

T4, with its legions of investigative disciples over the last 50 years, has provided us with a beautifully integrated system of biological machines and networks (506, 697). The otherwise elaborate biochemical perspective on the fully sequenced T4 genome provides a vast resource for phage genomics and the future of phage biology. Among the large, ubiquitous group of tailed, T4-like phages found on Earth (8), phage T4 has been the most extensively studied. T4 biology will "bootstrap" us to the recognition of similar biochemical processes in related phage while identifying genes and proteins that are novel to

each. It is already clear from emerging genome sequences that although some of the uncharacterized ORFs in T4 are shared in other phages (i.e., RB49, RB69, and KVP40), each has a relatively large proportion of individually unique ORFs. Just in the past year, the identities of uncharacterized T4 ORFs have been revealed: gene *69* (*segF*) and ORF *32.1* (*segG*) encode DNA endonucleases (51, 655), ORF *e.1* (*nudE*) encodes a Nudix hydrolase (1204), and ORF *24.1* (*rnlB*) encodes a second T4 RNA ligase related to the RNA-editing enzymes of trypanosomes and those present in sequenced *Archaea* (426). T4 will be a handy genetic and biochemical tool for detailed studies of their respective enzymatic activities. As with any fully sequenced genome, strategies (beyond BLAST alignments) are needed to explore the function of the novel phage ORFs. T4 should be a sound model for dissecting the emerging genome sequences of related phages while itself continuing to provide new insights into gene function and phage metabolism with relevance across phylogenetic domains.

Many of the unresolved problems in T4 biology reflect the subtlety of the process or the demands on the researcher for sample preparation, timing, or control of growth conditions. We still do not fully understand the process of DNA entry during infection, the very early shutoff of host gene expression, and the relevance or mechanism of T4-directed disruption of the host nucleoid. Moreover, the effects of hydroxymethylated and glucosylated cytosines in T4 DNA on DNA-protein interactions important for transcription, DNA replication recombination, repair, and restriction remain to be determined. To achieve this, the availability of T4-like modified phosphoramidites and of α and β glucosyltransferases for synthesis of modified DNA would be a major asset in addressing the recognition of early, middle, and late promoters by variously modified RNAP and the relevant activator proteins. Similarly, the potential roles of ModB modifications of the host translation proteins and the genetically still unidentified ribosomal alterations and the role of the membrane in transcription, replication, and capsid assembly are all in need of additional biochemical studies.

One of the more elegant aspects of T4 biology has been the elucidation of the assembly mechanism of its supramolecular structure. To construct such a huge, complicated and intricate structure, a number of intriguing molecular tricks have evolved, such as a scaffold, DNA-packaging apparatus, a ruler molecule, and phage-encoded molecular chaperones (e.g., gp31). Details of this process are still probably hidden in the genome. Additional study on the high-resolution structure of the particle will eventually elucidate how a series of structural changes (conformational change of the baseplate, contraction of the tail sheath, and DNA ejection) take place at atomic resolution.

Practical applications of phage and phage gene products should continue to emerge. In an era of increasing bacterial antibiotic resistance, there is renewed interest in the therapeutic applications of phage in the treatment of infectious disease (37a, 83, 141, 725, 866, 1052a; www.evergreen.edu/phage). It was Delbrück and the initial American phage group who selected three of the seven virulent coliphages—T2, T4, and T6—from among early, largely "therapeutic" isolates. Even today, one of the best sources of T-even-like phages is the stools of patients recovering from dysentery (L. Gachechiladze and H. Brussow, personal communication). Specific proteins, phage lysins in particular, have been proposed as useful enzymes for killing troublesome bacteria (66, 759). Recently, purified PlyG lysin (an *N*-acetylmuramoyl-L-alanine amidase), produced by gamma phage of *Bacillus anthracis*, was shown to effectively kill the bacterium (967). T4 and its relatives will probably yield novel products that target various cellular processes, inhibiting or killing their host bacteria.

Many of the major enzymes of molecular biology came onto the scene with T4, yet there are few laboratory reagents that derive from other phages beyond the well-studied isolates. There is every reason to expect that enzymes with unique catalytic parameters will emerge from genome sequences of other phages.

Phage are also an excellent teaching tool. They are easy to work with, so students can learn the simple methods required and get meaningful results quite easily. Phage research also calls for integrating broad areas of microbial physiology, biochemistry, biophysics, genetics, and molecular biology. The analysis presented here of the T4 genome and its relationship to phage biochemical processes, ecology, and evolution is based on the work of many students of many ages and countries. One can only hope that the scientific community will continue to take advantage of the historically large investment of intellectual and fiscal resources committed to T4 and will continue to explore the vast, wonderful world of phage biology.

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