

Cross-Resistance Between Bacteriophages and Colicins in *Escherichia coli* K-12

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Cross-resistance between bacteriophages and colicins was studied using collections of bacteriophage- and colicin-resistant mutants of *Escherichia coli* K-12. No new examples were found of highly specific one-to-one cross-resistance of the type suggestive of common receptors. However, several groups of mutants showed tolerance to colicins and resistance to bacteriophages. Mutants known to be very defective in lipopolysaccharide composition were found to commonly show tolerance to certain colicins in addition to their bacteriophage resistance. Another group of mutants showed varying patterns of resistance to colicins E2, E3, K, L, A, S4, N, and X and bacteriophages E4, K2, K20, K21, K29, and H⁺. However, many bacteriophage-resistant mutants were fully colicin sensitive, and most colicin-resistant mutants were fully sensitive to bacteriophages.

Cross-resistance between bacteriophages and colicins were first reported in 1949 (7) and several examples are known (1-3, 6, 8, 9, 11). Recent surveys on the resistance of *Escherichia coli* K-12 to a wide range of bacteriophages (10) and colicins (4, 5) have provided the basis for a more extensive study of the phenomenon of cross-resistance between bacteriophages and colicins.

The bacteriophages and bacteriophage-resistant mutants used have been described before (10), as have the colicinogenic strains and colicin-resistant mutants (4, 5). All of the bacteriophage-resistant mutants were tested for their colicin resistance pattern against the 19 colicins used previously, using the triple-layer plate test and a electrophoretic technique (4). The colicin-resistant mutants were tested for insensitivity to bacteriophages, using a multiple-syringe bacteriophage applicator (10) and 41 bacteriophages representative of the 56 used previously (10). Only T1, T5, BF23, Ac4, M3, K3, T7, and W31 were used from the T1-like, T5-like, BF23-like, K3-like, and T7-like bacteriophages (10). The results are shown in Tables 1 and 2.

The TonA, TonB, Bfe, Tsx-1 and Con mutants are previously described and well-defined mutant classes resistant to specific bacteriophages and colicins (1-3, 6, 8, 9, 11, 12). We found all mutants within each class to have identical bacteriophage and colicin resistance

patterns, whether isolated as colicin-resistant or as bacteriophage-resistant mutants. This paper does not significantly add to our previous knowledge of these classes of mutants.

This study revealed similarities between the Ktw bacteriophage-resistant mutants and the Tol Ia, Tol Ib, Tol X, Tol XIV, and Tol XV colicin-tolerant mutants (Table 1). Ktw-1 and Ktw-2 are very similar to Tol Ib and Tol Ia mutants, respectively, whereas the Tol X mutant has a resistance pattern similar to those of Ktw-1 and Tol Ib mutants. These five mutations all map near *gal* (4; unpublished data) and show tolerance to colicins K, L, A, S4, and sometimes N, as well as resistance to bacteriophages K2, K20, K21, K29, and sometimes E4. Thus, they appear to be quite similar and may carry mutations in the same or linked loci. The Ktw-3 mutant has a bacteriophage resistance pattern similar to Ktw-1 and Ktw-2 mutants (10) but is distinguishable from the latter mutants on the basis of altered sensitivity to bacteriophage U3 (R. E. W. Hancock and P. Reeves, *J. Bacteriol.*, in press) and its lack of cross-resistance to colicins. Tol XIV and Tol XV mutants exhibit a similar cross-resistance pattern to the five mutants described above, but are, in addition, resistant to colicins E2, E3, and X and map elsewhere (4). P456 and P457 (Ktw-1) are the only mutants of this group for which we have information on the lipopolysaccharide; they both have a minor change in the sugar composition (Hancock and Reeves, in press).

Another complex set of interrelations is shown by the Bar and Wrm groups of bacterio-

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TABLE 1. Cross-resistance between the bacteriophages that fail to lyse *Ktw* mutants and various colicins

Class or group ^a	Representative mutant	Bacteriophage resistance pattern ^b						Colicin resistance pattern ^c							Corresponding group or class		
		E4	K2	K20	K21	K29	H ⁺	E2	E3	K	L	A	S4	N		X	
Ktw-1	P457																
	P456	—	IP	R	R	R	—	—	—	R	R	R	R	R	R	—	Tol Ib
Tol Ib	P210	—	I	I	IP	R	—	—	—	R	R	R	R	R	—	—	Ktw-1
Tol X	P661	—	I	I	I	I	—	—	—	P	R	R	R	R	—	—	Ktw-1
Tol XIV	P530	—	I	R	R	R	—	R	R	R	R	R	—	R	R	—	Ktw-1
Tol XV	P686	—	I	I	R	R	—	R	R	R	R	R	R	R	R	—	Ktw-1
Ktw-2	P476	SL	IP	R	R	R	—	—	—	R	R	R	R	—	—	—	Tol Ia
Tol Ia	P218	SL	I	I	I	R	—	—	—	R	R	R	R	—	—	—	Ktw-2
Ktw-3	P240	—	SL	IP	IP	IP	I	—	—	—	—	—	—	—	—	—	—

^a As defined previously (4, 10).

^b Resistance patterns of *Ktw* mutants are as described previously (10). I, Bacterial inhibition; IP, partial resistance with inhibition; SL, slight resistance; R, full resistance; —, sensitivity. For the basis of differentiation, see reference 10.

^c Resistance patterns of colicin-resistant mutants are as described previously (4). R, Resistance; P, partial resistance. For colicins E2, E3, K, L, S4, and N, it was due to tolerance in all cases; for colicins A and X, the technique used does not distinguish between receptor loss or tolerance (4).

phage-resistant mutants and some of the group A colicin-tolerant mutants. Tol VII, Tol VIII, and Tol XI are the only mutants among those selected as colicin resistant which, on the basis of altered sensitivity to bacteriophages C21 and U3, are thought to have altered lipopolysaccharide (4). They have bacteriophage resistance patterns (Table 2) that superficially resemble those of *Wrm* mutants, which have substantially altered lipopolysaccharide (Hancock and Reeves, in press). The Tol VII, Tol VIII, Tol XI Bar, and *Wrm* mutants show resistance to various combinations of colicins A, L, and S4; the partial resistance to K which occurs with the Tol VII, Tol VIII, and Tol XI mutants would not have been detected by the plate method used in this study. However, the Tol VII, Tol VIII, and Tol IX mutants (4) and the Bar group of mutants (Hancock and Reeves, in press) map at different loci; furthermore, the Tol VII mutant is partially resistant to colicin E2, and Tol VII mutants resist colicin E1, whereas none of the Bar or *Wrm* mutants is resistant to colicins E1 or E2. The Tol XI mutant P220 is mucoid, which may account for some of its properties. Thus, there seem to be at least four different loci that can affect lipopolysaccharide structure and give rise to a bacteriophage-resistance pattern similar to that of Bar or *Wrm* mutants. It should be noted that the Tol mutants were isolated from strain AB1133, whereas the bacteriophage-resistant mutants were isolated from a *non* derivative which cannot produce the capsular polysaccharide and, hence, none of its derivatives will be mucoid.

Apart from the above-mentioned bacteriophage-resistant mutants, only one miscellaneous group mutant (P495, Misc-5) which is lipopolysaccharide altered (unpublished data) shows resistance to any colicins, and this only to colicin L. The Tol XVII mutant is remarkable in being resistant to almost all bacteriophages, including T1, T5, BF23, H3, and many related bacteriophages, which we had so far found to be affected only by the very specific TonA, TonB, Bfe, or Tsx mutants (10).

The type strains of each of the remaining colicin-resistant mutants (Rcx, Tol Iib, Tol Iic, Tol III, Tol IV, Tol IX, Tol XII, Tol XIII, Tol XVI, Cir, ExbB, ExbC, Cbt, Cmt, Ivt, and Cvt) and bacteriophage-resistant mutants (Tsx-2, Ktn, Efr, Ttk, Misc-1, Misc-2, Misc-3, Misc-4) described previously (4, 5, 10) were tested and found to be sensitive to all of the bacteriophages or colicins, respectively. Thus, while substantial cross-resistance between bacteriophages and colicins has been demonstrated, a large number of bacterial cell alterations that lead to colicin resistance fail to protect the cell against the attack of a wide range of virulent bacteriophages and vice versa.

The reasons for the cross-resistance documented in Tables 1 and 2 is not yet known, but the colicin tolerance of Bar and *Wrm* mutants shows that alterations in the lipopolysaccharide core can affect sensitivity to colicins A, L, and S4, and the pattern of cross-resistance shown in Table 1 suggests a rather specific interaction between one group of bacteriophages and some colicins.

TABLE 2. Cross-resistance between bacteriophages and colicins (bacteriophage-resistant mutants that are resistant to a set of colicins not fitting into any previously defined class and vice versa)

Class or group ^a	Representative mutant	Colicin resistance pattern ^b	Bacteriophage resistance pattern ^c
Tol VII	P689	pE2, pK, L, A, S4	T5, BF23, M3, K10, H3, H1, H8, K18, K31, Ox1, K9 _R , Ac3, Ox3, Ox2, Ox4 _R , E4 _R , K2 _R , K20 _R , K21 _R , K29 _R , Ox5 _{SL} , K16 _{SL} , F27, H ⁺ _R , V _R , E7, K17 _{IP} , A _{SL} , T3 _{IP} , T4, K19 _{SL} , T7 _{IP} , W31 _{IP} , H _P
Tol VIII	P602	E1, pK, A	H3 _{SL} , H8 _R , K18, K31 _R , Ox1 _R , K9 _R , K3 _R , Ac3 _R , Ox3 _{SL} , M1 _{IP} , Ox4 _R , E4 _R , K2 _{IP} , K20 _R , K21 _R , K29 _R , Ox5 _{SL} , H ⁺ _R , V _R , A _R , T4, T2
Tol XI	P220	pK, L, pA, pS4	Ac4, M3, K10, H3, H1, H8, K18, K31 _{IP} , Ox1, K9 _{IP} , Ac3, Ox3, M1 _{IP} , Ox2 _{IP} , Ox4 _{IP} , E4, K2, K20 _P , K21 _P , K29 _P , Ox5 _R , K16 _{IP} , F27, H ⁺ _R , V, E7, K17 _{IP}
Tol XVII	P652	E1, E2, pE3, K, L, A, S4, N	Shows partial resistance to T6, Ox1, Ox2, Ox4, Ox5, Ac3, Ac4, H1, M1, K2, K20, K21, K29, K3, K4, and K5; resistant to all others
Misc-5	P493	L	Ox5 _{SL} , K16 _{SL} , K17 _{SL} , E4
Bar-1	P455	L	Resistant to between 10 and 19 specific bacteriophages (10)
Bar-2	P492	Not done	
Bar-3	P494	—	
	P409	L	
	P404, P413	ALS4	
	P415, P495	ALS4	
	P496, P497	ALS4	
Bar-4	P405, P428	L	
	P436, P490	L, S4	
Bar-5	P402	A, L, S4, N	
Bar-6	P451	A, L, S4	
Bar-7	P487	A, L	
	P488	A, L, S4	
Bar-8	P489	A, L	
Wrm-1	P435	L, S4	Resistant to between 30 and 33 specific bacteriophages (10)
	P479	A, L	
Wrm-2	P416	L	
	P424	—	
	P239	A	

^a As defined previously (4, 10).

^b Resistance patterns of colicin-resistant mutants are as described previously (4). Resistant to indicated colicins; pK, partial resistance to colicin K; —, sensitive to all colicins.

^c I, Bacterial inhibition; IP, partial resistance with inhibition; SL, slight resistance; P, partial resistance; R, full resistance. For the basis of differentiation, see reference 10.

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