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Author's Affiliation:
Health information Technology Department, The Applied College King Abdulaziz University - Saudi Arabia

Corresponding Author:
Ibrahim Alotibi
Email: ialotibi@kau.edu.sa

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The role of bacteriophages transferring virulence factors to *Escherichia coli* species

Ibrahim Alotibi

Abstract

Bacteria develop in order to adapt to new surroundings, colonize new niches, and become pathogenic. The presence of mobile genetic elements MGEs in *E. coli* can be increasing the genome size of a pathogenic strain by up to 1 Mb when compared to a commensal strain. Phage satellites make up one subset of MGEs they are linked to specific temperate phages, named as helper phages, which parasite bacteria for their own induction. In fact, various pathogenic *E. coli* differ in the presence of a subset of genes produced by MGEs that are crucial in hijacking host cell machinery and subverting host responses. Phages not only provide genetic variability through prophage integration, they can also mediate horizontal genetic transfer HGT within bacterial populations through the transfer of either bacterial DNA or other MGEs, such as phage satellites. The phage-mediated transfer of bacterial DNA is known as transduction and plays a crucial role in bacterial biology, diversity and evolution. Recently, it has been noticed that phage transduction occurs at an astonishing magnitude, much higher than previously anticipated. Importantly, some of the genes transferred by transduction are virulence and antibiotic resistance genes, highlighting the impact that this process has in driving evolution of pathogenic bacteria.

Introduction

Escherichia coli belongs to the Proteobacteria phylum and is a facultative anaerobic Gram-negative bacterium that not sporulate. *E. coli* forms rod-shaped colonies that can be grouped singly or in pairs, and it is motile due to peritrichous flagellae. *E. coli* can be a harmless bacterium or a clinically important opportunistic pathogen [1]. *E. coli* colonizes the gastrointestinal system of new-borns, with the colon, notably the mucous layer, as its habitat. To become an adapted pathogen, *E. coli* just needs to acquire one or a combination of various mobile genetic elements (MGEs).

MGEs have the capability to adapt to new niches and cause a wide range of illnesses, including gastroenteritis (diarrhoea), dysentery, bloodstream infections, sepsis, and urinary tract and central nervous system infections (meningitis). Furthermore, virulent *E. coli* strains can arise from deletions, point mutations, and genomic rearrangements [2].

Different criteria can be used to divide *E. coli*, including type, serotype, pulsotype, phage type, and biotype4. The pathotype, which refers to the various disease that pathogenic *E. coli* may cause, is the most prevalent characteristic used to categorize pathogenic *E. coli*.

Eight several pathotypes have been extensively characterized, as intestinal (diarrheagenic) or extraintestinal *E. coli* (ExPEC) [2,3]. Six different pathotypes are included as intestinal: i) enteropathogenic *E. coli* (EPEC), ii) enterohaemorrhagic *E. coli* (EHEC), iii) enterotoxigenic *E. coli* (ETEC), iv) enteroinvasive *E. coli* (EIEC; including also *Shigella*), v) enteroaggregative *E. coli* (EAEC); and vi) diffusely adherent *E. coli* (DAEC) [2,5-16]. On the other hand, the two most common pathotypes categorised as extraintestinal are: i) uropathogenic *E. coli* (UPEC); and ii) neonatal meningitis *E. coli* (NMEC) [17-26]. Other pathotypes have been proposed, although they have not been adequately defined. They include the following: necro toxigenic *E. coli* (NTEC) or adherent invasive *E. coli* (AIEC) [27-30].

MGE acquisition or loss is essential for pathogenic bacteria to adapt to new or changing environmental conditions, in reality, each pathotype is distinguished by the presence of a group of genes involved in the hijacking of host cell machinery and the subversion of host responses [3,10]. Despite the fact that the same host machines or processes are attacked, the mechanisms and results are different. When compared to commensal *E. coli*, virulence-associated genes expressed by MGEs can increase the genome size of pathogenic *E. coli* by up to 1 Mb. (Table 1) [18]. For example, in the UPEC strain CFT073, A total of 13 genomic islands have been discovered, consisting of up to 13% of the bacterial genome [31].

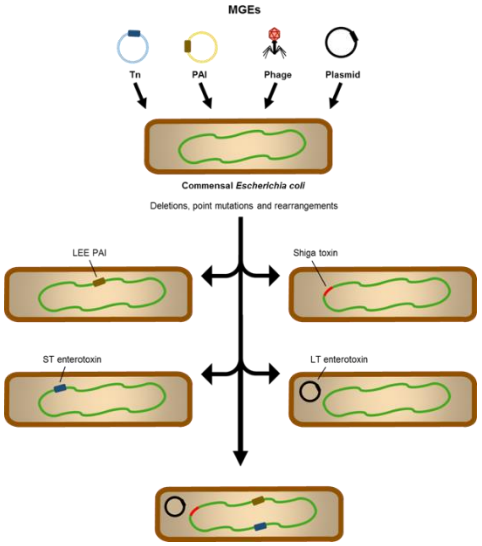

Figure 1: Contribution of MGEs to pathogenic *E. coli*. Virulence factors are encoded by distinct MGEs. Transposons (Tn) encode the heat-stable enterotoxin (ST) of ETEC, plasmids encode the heat-labile enterotoxin (LT) of ETEC or invasion factors of EIEC, bacteriophages encode the Shiga toxin of EHEC, and pathogenicity islands (PAIs) encode the locus of enterocyte effacement (LEE) of EPEC, EHEC, and UPEC. Deletions, point mutations and/or DNA rearrangements can also lead to acquisition of virulence traits in commensal *E. coli*. Adapted from James B. Kaper *et al.* 2004 [2].

Methods

Literature Search and Selection Criteria

Raw data was organized using Microsoft® Excel® 2010. The NCBI BLAST server program www.ncbi.nlm.nih.gov235 has been used to compare sequences with the GenBank database for homology. Assembling sequences to a reference, multiple nucleotide or protein sequence alignments were performed using CLC Genomics Workbench 7.

Discussion

Temperate phages have an impact the genomes of their hosts, causing genetic variation in their cognate cells [32]. In the genome of the *E. coli* strain O157:H7, for example, 18 distinct prophages have been discovered. This strain belongs to the EHEC pathotype and can contain phages that encode the Shiga toxin protein (Stx) [34]. This difference is important in virulent strains because lysogenic conversion (phage integration into the bacterial genome) provides the host bacterium with virulence proteins and other phage-encoded genes that are necessary for colonization of new habitats. As a result, prophages constitute a significant source of genetic diversity that contributes to the pathogenicity of bacteria [35-38]. Toxins, adhesion factors, invasion factors, and superantigens, among other phage-encoded

virulence factors, are included in Table 2 [32,39]. Toxin-mediated illnesses, including as botulism, cholera, diarrhoea, diphtheria, and scarlet fever, are caused by toxins encoded by phages [40]. Virulence genes at *E. coli* phage specially Stx, can causes attaching and effacing (A/E) lesions, bloody diarrhoea and haemolytic uremic syndrome (HUS) [2].

Feature	Name of element	Key virulence factors or function
EPEC		
PAI	LEE	T3SS, Tir, Map, EspB, EspF, EspG, EspH and EspZ
Plasmid	EAF (pMAR2)	BFP
Phage	PP2	EspJ, Cif and NleH
Phage	PP4	NleD, NleC, NleB and NleG
Phage	PP6	NleF, NleH and NleA
PAI	IE2	NleE and LifA-like
PAI	IE5	EspG and EspC
PAI	IE6	NleE, NleB, EspL and LifA-like
EHEC		
PAI	LEE	T3SS, Tir, Map, EspB, EspF, EspG, EspH and EspZ
Plasmid	pO157	EspP, toxinB, LifA/Efa, StcE, HlyA and EhxA
Phage	Sp3/CP-933K	NleB, NleC, NleD and Cif
Phage	Sp5/CP-933W	Stx2
Phage	Sp9/CP-933P	NleA (EspI), NleF, NleG, EspM, NleH and EspO
Phage	Sp14/CP-933U	TccP and EspJ
Phage	Sp15/CP-933V	Stx1
PAI	SpLE3/O122	NleE, NleB1 and EspL2
ETEC		
PAI	Tia	Tia and TibA
Plasmid	pCoo (pCS1)	CFA/a, LT and STIb
Plasmid	pJY11	LT and STIa
Plasmid	pTRA1	Mobilises pCoo and pJY11
Transposon	Tn	ST
EIEC/*Shigella*		
Plasmid	pINV	T3SS, IpaA, IpaB, IpaC, IpaD, IpaH, IcsABP, IpgB1, IpgB2, IpgD, OspF, OspB, VirA ans SepA
PAI	SHI-1 (*she*)	Pic, ShET1 and SigA
Antivirulence loci	Deletion (blackhole)	*cad*BA and *nad*AB
EAEC		
Plasmid	pAA	AAF, Pet and EAST1
PAI	*she*	Pic and ShET1
DAEC		
Plasmid	Various names	AAF/Dr adhesins (some chromosomal)
UPEC		
PAI	PAI-CFT073-pheV	Hly, Pap, Sat and polysialic acid transport (Kps) proteins
PAI	PAI-CFT073-pheU	Pap2
PAI	PAI-CFT073-aspV	PicU, CdiA and TosA (exotoxin)
PAI	PAI-CFT073-serX	IroNEDCB and MchBCDEF
NMEC		
Phage	CUS-3	O antigen modification
PAI	RDI 4	S fimbriae
PAI	RDI 16	K1 capsule
PAI	RDI 21	P fimbriae, F17-like fimbriae, CNF1 and Hyl
PAI	RDI 22	IbeA

Table 1: MGEs and virulence traits in pathogenic *E. coli*. Adapted from Matthew A. Croxen *et al,* 2010 [3].

The expression, release, and mobilization of these toxins are all linked to the phage lytic cycle in some situations. This is relevant in the treatment of prophage-containing pathogenic bacteria because certain antibiotics can cause the SOS response and, as a result, the phage lytic cycle to begin. Finally, phage induction will increase toxin expression, and the toxins will be released once the cells are lysed by the phage. The Stx encoded by *E. coli* EHEC phages is one example of toxin production associated to prophage induction. Stx expression raises the risk of A/E lesions, diarrhea, and HUS when EHEC strains are treated with antibiotics such fluoroquinolones [33].

Temperate phages have an impact the genomes of their hosts, causing genetic variation in their cognate cells [32]. In the genome of the *E. coli* strain O157:H7, for example, 18 distinct prophages have been discovered. This strain belongs to the EHEC pathotype and can contain phages that encode the Shiga toxin protein (Stx) [34]. This difference is important in virulent strains because lysogenic conversion (phage integration into the bacterial genome) provides the host bacterium with virulence proteins and other phage-encoded genes that are necessary for colonization of new habitats. As a result, prophages constitute a significant source of genetic diversity that contributes to the pathogenicity of bacteria [35-38]. Toxins, adhesion factors, invasion factors, and superantigens, among other phage-encoded virulence factors, are included in Table 2 [32,39]. Toxin-mediated illnesses, including as botulism, cholera, diarrhoea, diphtheria, and scarlet fever, are caused by toxins encoded by phages [40]. Virulence genes at *E. coli* phage specially Stx, can causes attaching and effacing (A/E) lesions, bloody diarrhoea and haemolytic uremic syndrome (HUS) [2].

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Bacteria	Phage	Gene	Protein
C. botulinum	Phage C1	C1	Neurotoxin
C. diphtheriae	B-Phage	*tox*	Diphtheria toxin
E. coli	H-19B	*stx1, stx2*	Shiga toxins
E. coli	φFC3208	*hly2*	Enterohaemolysin
E. coli	Unnamed	*cdt*	Cytolethal distending toxin
E. coli	Sp4, 10	*sodC*	Superoxide dismutases
E. coli	λ, λ-like	*bor, eib*	OMP
P. aeruginosa	φCTX	*ctx*	Cytotoxin
P. multocida	Unnamed	*toxA*	Mitogenic factors
V. cholerae	CTXφ	*ctxAB*	Cholera toxin

Table 2: Selection of toxins and virulence factors encoded by phages.

Conclusion

Bacteria develop in order to adapt to new surroundings, colonize new niches, and become pathogenic. HGT and MGEs are important participants in this evolutionary process because they can transmit advantageous characteristics or virulence factors between bacterial species [41, 42]. The presence of MGEs in *E. coli* can increase the genome size of a pathogenic strain by up to 1 Mb when compared to a commensal strain [18]. Indeed, in the UPEC strain CFT073, 13 distinct genomic islands have been found, accounting for 13% of the bacterial genome [31]. As fact, various pathogenic *E. coli* differ in the presence of a subset of genes produced by MGEs that are crucial in hijacking host cell machinery and manipulating host defences [3,10]. Phage satellites are one type of MGE. They are associated with special temperate phages known as helper phages, which parasitize bacteria for their own induction, allowing transmission to a new host bacterium.

Competing Interest

The authors declare that there is no conflict of interest.

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