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ScienceDirect
Infection, Genetics and Evolution 8 (2008) 217–226
Infection, Genetics and Evolution
www.elsevier.com/locate/meegid

Discussion

Molecular evolution of *Salmonella enterica* serovar Typhimurium and pathogenic *Escherichia coli*: From pathogenesis to therapeutics

Jean-Philippe Lavigne [a,b], Anne-Béatrice Blanc-Potard [a,c,*]

[a] *Institut National de la Santé et de la Recherche Médicale, Espri 26, Avenue J.F. Kennedy, 30908 Nîmes Cedex 02, France*
[b] *Laboratoire de Bactériologie, Groupe Hospitalo-Universitaire de Carémeau, Place du Professeur Robert Debré, 30029 Nîmes Cedex 09, France*
[c] *Université Montpellier 1 EA4204, UFR de Médecine, Avenue J.F. Kennedy, 30908 Nîmes Cedex 02, France*

Received 18 August 2007; received in revised form 20 November 2007; accepted 22 November 2007
Available online 15 January 2008

Abstract

Salmonella enterica serovar Typhimurium (*S.* Typhimurium) and certain *Escherichia coli* are human pathogens that have evolved through the acquisition of multiple virulence determinants by horizontal gene transfer. Similar genetic elements, as pathogenicity islands and virulence plasmids, have driven molecular evolution of virulence in both species. In addition, the contribution of prophages has been recently highlighted as a reservoir for pathogenic diversity. Characterization of horizontally acquired virulence genes has several clinical implications. First, identification of virulence determinants that have a sporadic distribution and are specifically associated with a pathotype and/or a pathology can be useful markers for risk assessment and diagnosis. Secondly, virulence factors widely distributed in pathogenic strains, but absent from non-pathogenic bacteria, are interesting targets for the development of novel antimicrobial chemotherapies and vaccines. Here, we summarize the horizontally acquired virulence factors of *S.* Typhimurium, enterohemorrhagic *E. coli* O157:H7 and uropathogenic *E. coli*, and we describe their use in novel therapeutic approaches.

Keywords: Antimicrobial therapy; EHEC; Horizontal gene transfer; Pathogenicity island; Prophage; *Salmonella enterica* serovar Typhimurium; UPEC; Vaccine; Virulence gene

1. Introduction

Commensal bacteria, as *Escherichia coli*, have adapted to coexist with the human host without causing disease. Pathogenic bacteria have adapted to colonize the human host and have acquired the ability to cause clinically significant pathologies. *Salmonella enterica* and *E. coli* are closely related enterobacteria that diverged from a common ancestor 100–150 million years ago (Doolittle et al., 1996). The genomes of the two species are essentially superimposable and genome sequencing demonstrated that the median homology between non-pathogenic *E. coli* and *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) genomes is 80% (Blattner et al., 1997; McClelland et al., 2001). Both species have evolved into intestinal pathogens. In addition, *E. coli* strains have also evolved as extraintestinal pathogens. The molecular evolution of virulence of human pathogens *S.* Typhimurium and pathogenic *E. coli* is driven by the acquisition of multiple genetic elements (pathogenicity islands, plasmids, and prophages) by horizontal gene transfer. These horizontally acquired elements encode virulence factors necessary for colonization and replication within the host, neutralization of host defences and spread into new hosts. Main virulence determinants used by *S.* Typhimurium and/or *E. coli* include adhesins, type III secretion systems (T3SS) that inject effector proteins into host cells, toxins and iron acquisition systems.

Both non-typhoidal *S. enterica* and pathogenic *E. coli* are increasingly resistant to multiple antibiotics. For example, the resistance of uropathogenic *E. coli* strains to trimethoprim–sulfamethoxazole and fluoroquinolones, the drugs of choice for the treatment of urinary tract infections (UTI), has become a major concern both in hospitals and in the community (Gupta et al., 2001). Hence it is urgent to develop better prevention and treatments against these infections. The implication of horizontally acquired virulence factors in clinical issues is

* Corresponding author at: Institut National de la Santé et de la Recherche Médicale, Espri 26, UFR de Médecine, CS 83021, Avenue J.F. Kennedy, 30908 Nîmes Cedex 02, France. Tel.: +33 4 66 02 81 47; fax: +33 4 66 02 81 48.
E-mail address: ablancpotard@univ-montp1.fr (A.-B. Blanc-Potard).

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doi:10.1016/j.meegid.2007.11.005

multiple. First, genes that have a sporadic distribution, associated with specific pathology and/or epidemic features, can be used as markers of infection to improve molecular epidemiology and diagnostic methods. Secondly, genes that are stable in pathogenic strains, and absent from non-pathogenic strains, can provide novel therapeutic targets and novel vaccine strategies. Here, we present a brief overview of horizontally acquired genetic elements from *S*. Typhimurium and pathogenic *E. coli* that play a role in virulence and we provide examples of the implications of these studies for the development of novel therapeutic approaches.

2. Human pathologies associated with non-typhoidal *Salmonella* and *E. coli*

Non-typhoidal salmonellosis is one of the most common food-borne bacterial diseases in humans in industrialised countries (Schlundt et al., 2004), with an incidence rate of about 20–40/100,000, which is similar to the one of campylobacteriosis. Humans are infected through contaminated food and water. The most commonly *S. enterica* serotypes in humans are *S*. Typhimurium and *S*. Enteritidis, which account for more than 75% of reported cases. Non-typhoidal salmonellosis is characterized by gastroenteritis, associated with intestinal inflammation and diarrhea. The infection is usually self-limited to the intestine, but bacteria can also spread beyond the intestine and cause bacteraemia and focal systemic infections, especially in compromised patients.

E. coli is a commensal bacterium of the facultative anaerobic colonic microflora. However, some strains have acquired virulence determinants to produce intestinal or extraintestinal diseases (Kaper, 2005). There are at least six well-characterized classes or pathotypes of *E. coli* that can cause intestinal diseases in humans and that are associated with diverse pathologies (Kaper et al., 2004): enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), and enteroinvasive *E. coli* (EIEC) are responsible for severe and acute diarrhea; enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC) and diffusely adhering *E. coli* (DAEC) are associated with chronic and mild diarrhea. In the present review, we will focus on EHEC O157:H7, a food-borne pathogen that causes hemorrhagic colitis and hemolytic uremic syndrome mainly in industrialized countries. Pathogenic *E. coli* are also an important cause of extraintestinal infections. Extraintestinal pathogenic *E. coli* (ExPEC) possesses virulence traits that allow it to invade, colonize, and induce disease in body sites outside the gastrointestinal tract. A pathotype known as uropathogenic *E. coli* (UPEC) is the major cause of community-acquired UTI. UPEC are responsible for both lower infections of the urinary tract (cystitis) and upper infections (pyelonephritis). Another extraintestinal pathotype, which will not be described in this review, is the meningitis/sepsis-associated *E. coli* (MNEC).

3. Virulence determinants encoded by horizontally acquired genes in *S*. Typhimurium, EHEC O157:H7 and UPEC strains

S. Typhimurium and pathogenic *E. coli* genomes are characterized by the presence of virulence determinants that have been acquired by lateral gene transfer (Boyd and Brüssow, 2002; Porwollik and McClelland, 2003; Schmidt and Hensel, 2004). In both species, these genetics elements, which are mobile or formerly mobile, include pathogenicity islands, prophages, and plasmids. The term pathogenicity island (PAI) has been initially used to describe large unstable regions carrying virulence determinants on the chromosome of UPEC (Hacker et al., 1990). Currently, this term is commonly used to describe chromosomal regions that contain virulence genes and that are absent from non-pathogenic strains of the same or closely related species. Although PAIs differ in structure and

Table 1
Main pathogenicity islands and prophage encoded of *S*. Typhimurium, EHEC O157:H7 and UPEC strains CFT073 and 536

Name	Size (kb)	Insertion site	Main virulence determinants
S. Typhimurium LT2			
SPI-1	40	*fhlA*	T3SS-1, T3SS-1 effectors (SptP, SipA, SipB, AvrA)
SPI-2	40	tRNA *valV*	T3SS-2, T3SS-2 effectors (SpiC, SseF, SseG)
SPI-3	17	tRNA *selC*	MgtC, T5SS (MisL)
SPI-4	25	*ssb*/*soxSR*	T1SS, SeeI
SPI-5	7	tRNA *serT*	SopB (T3SS-1 effector), PipB (T3SS-2 effector)
EHEC O157:H7 EDL933 and Sakai			
LEE	43	tRNA *selC*	T3SS, T3SS-1 effectors (EspFGHZ, Map, Tir), Intimin (*eae*)
UPEC CFT073			
PAI I_{CFT073}	123	tRNA *pheV*	Alpha-hemolysin, P-fimbriae (*pap* operon), T5SS (Sat), Iha, IutA, Iuc, Kps
PAI II_{CFT073}	52	tRNA *pheU*	P-fimbriae (*pap* operon)
PAI III_{CFT073}	100	tRNA *aspV*	T5SS (PicU)
$PAI_{CFT073\text{-}serX}$	113	tRNA *serX*	S/F1C fimbriae, IroN
HPI_{CFT073}	32	tRNA *asnT*	Yersiniabactin sytem (FyuA, Irp, Ybt)
UPEC 536			
PAI I_{536}	77	tRNA *selC*	Alpha-hemolysin
PAI II_{536}	102	tRNA *leuX*	Alpha-hemolysin, P fimbriae
PAI III_{536}	68	tRNA *thrW*	S fimbriae, IroN, Sap adhesin
PAI IV_{536} (HPI)	30	tRNA *asnT*	Yersiniabactin sytem (FyuA, Irp, Ybt)