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ABSTRACT

Pathogenicity islands (PAIs) are a group of mobile genetic elements that play a pivotal role in the virulence of bacterial pathogens of humans. Typical PAIs are distinct regions of DNA that are present in the genome of pathogenic bacteria. PAIs are mostly inserted in the backbone genome of the host strain at specific sites. Pathogenicity islands are considered as a subset of horizontally-acquired genomic islands. Acquisition of PAIs by horizontal gene transfer (HGT) is an important mechanism in the development of disease-causing capability and the evolution of bacterial pathogenesis. Protein secretion systems encoded by PAI include 5 different types of secretion systems: type I, II, III, IV and V which are general requirements for pathogenic and nonpathogenic bacteria. Pathogenicity islands have been described in different Gam-negative and Gram-positive bacteria. The acquisition of knowledge about PAIs, their structure, mobility and pathogenicity factors not only is helpful in gaining a better understanding of bacterial evolution and pathogen interaction with eukaryotic host cells.

Keywords: pathogenicity island, genomic, virulence, integration.

Introduction

Pathogenicity islands (PAIs) are a group of mobile genetic elements that play a pivotal role, not only in the virulence of bacterial pathogens of humans but also in pathogens of animals and plants **(Dobrindt *et al*., 2002 and Schmidt & Hensel, 2004)**.

Typical PAIs are distinct regions of DNA that are present in the genome of pathogenic bacteria, but absent in nonpathogenic strains of the same or related species. PAIs are mostly inserted in the backbone genome of the host strain at specific sites that are frequently tRNA or tRNA-like genes. Mobility genes, such as integrases (*int*), are frequently located at the beginning of the island, close to the tRNA locus or the respective attachment site. PAIs harbor one or more genes that are linked to virulence and are frequently interspersed with other mobility elements, such as insertion sequence (IS) elements. The PAI boundaries are frequently determined by direct repeats (DRs), which are used for insertion and deletion processes. A characteristic feature of PAI is a G+C content different from that of the core genome. This feature is often used to identify new PAIs **(Hacker *et al.*, 1997).**

Pathogenicity islands are considered as a subset of horizontally-acquired genomic islands (GIs) that are present in various microbial pathogens and contain virulence-associated genes **(Nakamura *et al.*, 2004 and Schmidt & Hensel, 2004).** Bacterial pathogenicity/virulence determinants that can be found in PAIs include the type III secretion system (e.g. LEE PAI in pathogenic *Escherichia coli* and Hrp PAI in *Pseudomonas syringae*), superantigen (e.g. SaPI1 and SaPI2 in *Staphylococcus aureus*), colonization factor (e.g. VPI in *Vibrio cholerae*), iron uptake system (e.g. SHI-2 in *Shigella flexneri*) and enterotoxin (e.g. *espC* PAI in *E.coli* and *she* PAI in *S. flexneri*). Widespread presence of PAIs in pathogens is due to their efficient mechanisms of horizontal transfer **(Dobrindt *et al.*, 2004).**

Acquisition of PAIs by horizontal gene transfer (HGT) is an important mechanism in the development of disease-causing capability and the evolution of bacterial pathogenesis **(Hacker *et al.*, 2004).**

Although PAIs are loosely defined entities, many of them can be identified by features such as the presence of virulence genes, biased G+C content and codon usage and association with tRNA genes, mobile sequence elements or repeated sequences at their boundaries **(Hacker *et al.*, 1997).**

Transfer of PAIs may occur through natural transformation, plasmids and transduction **(Schmidt & Hensel, 2004)**. However, integration of PAIs into the bacterial chromosome is a site-specific event. Most PAIs have inserted at the 3' end of tRNA loci. Moreover, phage attachment sites are frequently located in this region **(Hou, 1999)**.

Protein secretion systems encoded by PAI include 5 different types of secretion systems: type I, II, III, IV and V which are general requirements for pathogenic and nonpathogenic bacteria **(Stathopoulos *et al*., 2000 and Thanassi & Hultgren, 2000)**.

Like other virulence genes, PAI genes are usually not constitutively expressed but respond to environmental signals. PAIs are frequently part of complex regulatory networks that include regulators encoded by the PAI itself, regulators encoded by other PAIs and global regulators encoded elsewhere in the chromosome or by plasmids. PAI regulators, in turn, can also be involved in the regulation of genes that are located outside the PAI **(Schmidt & Hensel, 2004)**.

Pathogenicity islands have been described in different Gam-negative and Gram-positive bacteria, including *Helicobacter pylori*, *Pseudomonas aeruginosa*, *Shigella* spp., *Yersinia* spp., *E. coli*, *Listeria monocytogenes*, *Staph .aureus*, *Enterococcus faecalis* and *Clostridium difficile* **(Schmidt & Hensel, 2004)**.

The reasons for the absence of PAIs in certain species have not been understood, but comparison of the life-style of pathogens; with and without PAI; might give some hints about the underlying principles. This led to some groups of pathogens lacking PAI show an extreme adaptation to a specific host environment that is also accompanied by reduction of the genome size and loss of the ability to replicate outside a host. In contrast, most pathogens harboring PAIs show a high degree of flexibility in the utilization of different hosts or body sites of a host for their proliferation. In addition, pathogens containing PAIs are often able to live in natural environments. These observations suggest that PAIs extend the spectrum of habitats that can be colonized by a bacterial species **(Schmidt & Hensel, 2004)**.

The acquisition of knowledge about PAIs, their structure, mobility and pathogenicity factors not only is helpful in gaining a better understanding of bacterial evolution and pathogen interaction with eukaryotic host cells, but also can have important practical implications. Genes located within PAIs have been used as diagnostic markers for the

identification of pathogens in clinical specimens and for the differentiation of pathogenic strains from closely related non-pathogenic relatives. Toxins encoded by PAI genes can be used as tools in cell biology **(Schiavo & van der Goot, 2001)**. Protein secretion systems can be used to deliver heterologous antigens for vaccination strategies with live carrier strains. Virulence determinants encoded on PAIs, such as secretion systems, may be interesting as targets for novel forms of therapeutic intervention of bacterial infections. The availability of microbial genome sequences has provided an extremely useful platform for future work. When this is combined with the understanding of the basic concepts of evolution of bacterial virulence and the crucial role of PAIs in this process, microbiologists will be able to identify virulence traits of new emerging pathogens or strains very efficiently **(Rüssmann *et al.*, 1998 and Gentschev *et al*. 2002).**

Aim of the work

The aim of the present work is to review the pathogenicity islands, their structure, mobility, the encoded virulence factors, besides, their important contributing role in bacterial pathogenesis and disease development. Moreover, new aspects in the regulation of PAI-encoded virulence, their integration sites and new approaches to the identification of new PAIs and proposed clinical implications will be covered.

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