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Pathogenicity Islands in Pathogenic Bacteria and Its Role in Severity and Survival in Diseases

Abstract

Research on the pathogenicity origin has always been and researchers. It was first performed on human and animal, and plant pathogens. Laboratory samples such as Escherichia coli Spp or the SacB gene in Bacillus subtilis and statistical analyses were extensively used for pathogenicity studies. Pathogenicity islands are large genomic regions. They code toxins and proteins and are affected by pathogenic factors that cause disease in the host. Pathogenic factors are coded by PAIs that have genes with high mutation frequency and the capability to transfer from one tRNA site to another. These studies showed that genetic changes occur in animals and plants in addition to humans. Genome evolution is the process in which the genetic information of strains changes during the time. The present study was conducted to examine the pathogenicity island phenomenon scientifically and identify the factors affecting this phenomenon and the diseases caused by it.

Keywords: *Pathogenicity Island, Genome, Plasmid, Pathogenicity*

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Introduction

Pathogenicity islands are large genomic regions that include about 10-200 kb in the chromosomes of bacteria that contain one or more pathogenic genes. They code toxins and proteins and are affected by pathogenic factors that cause disease in the host. Bacteria receive fragments of genes around them in the form of horizontal transfer. They cause disease in the host and are influential in their genetic richness and development. Several genes without a role are lost during evolution and based on selective processes and useful genes, which are called proportional islands, remain. These islands are saprophytic, symbiotic, and ecological based on the interactions between the bacteria and the host. Pathogenicity islands are formed when the bacterium harms the host through these genes to ensure survival. PAI is created from environmental and non-pathogenic ancestors during evolution and includes a subgroup of genetic islands with similar composition and organization. These fragments are formed from unstable regions of DNA and include small direct sequences removed through their ends or other homologs. Pathogenic factors are coded by PAIs that have genes with high mutation frequency and the capability to transfer from one tRNA site to another. The composition of these genes is different from the nuclear genome content. In other words, the content of guanine and cytosine bases is slightly higher than this content in the nucleus. The islanding of genes has a direct association with the bacteria stability in its genome; in some cases, changes are observed due to the effect of the type of phage. Infectious diseases do not necessarily cause genetic evolution in microbes.

The first report about the pathogenic center was a large gene region. In subsequent studies, the pathogenicity of islands with foreign virus origin was also observed in them [1]. An epidemic of vibrio cholera bacteria with a different antigen appeared in Indo-Bangladesh in people over 15 years of age in 1992.

It was created by a new strain in which a region coding for the lipopolysaccharide antigen was replaced by a region responsible for polysaccharide synthesis.

It was found that O1 immune factors did not confer immunity against the new strains. Many bacteria have been sequenced, and their genome sequence has been recorded in the Genome Bank. Direct repeats of DR (PAI) are usually used as identification sites for integrating bacterial phages. Figure 1 shows the general structure of pathogenicity islands. Figure 2 also shows the stages of pathogenicity development.

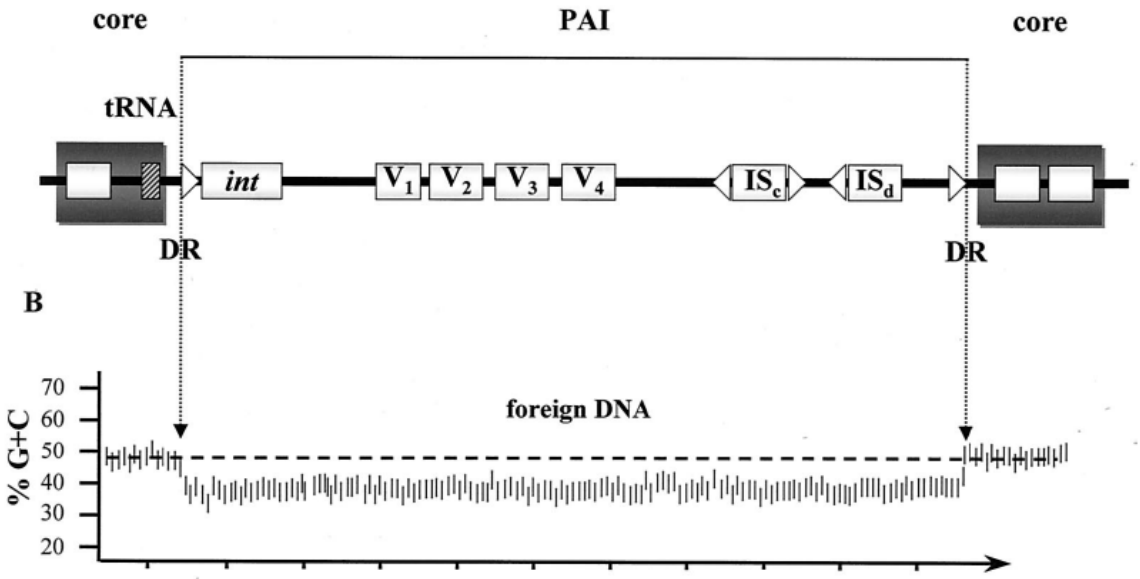

Figure. 1. General structure of PAI. (A) Typical PAI are distinct regions of DNA that are present in the genome of pathogenic bacteria but absent in nonpathogenic strains of the same or related species. PAI are mostly inserted in the backbone genome of the host strain (dark grey bars) in specific sites that are frequently tRNA or tRNA-like genes (hached grey bar). 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. PAI harbor one or more genes that are linked to virulence (V1 to V4) and are frequently interspersed with other mobility elements, such as IS elements (Isc, complete insertion element) or remnants of IS elements (ISd, defective insertion element). The PAI boundaries are frequently determined by DRs (triangle), which are used for insertion and deletion processes. (B) 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 PAI (see the text for details).

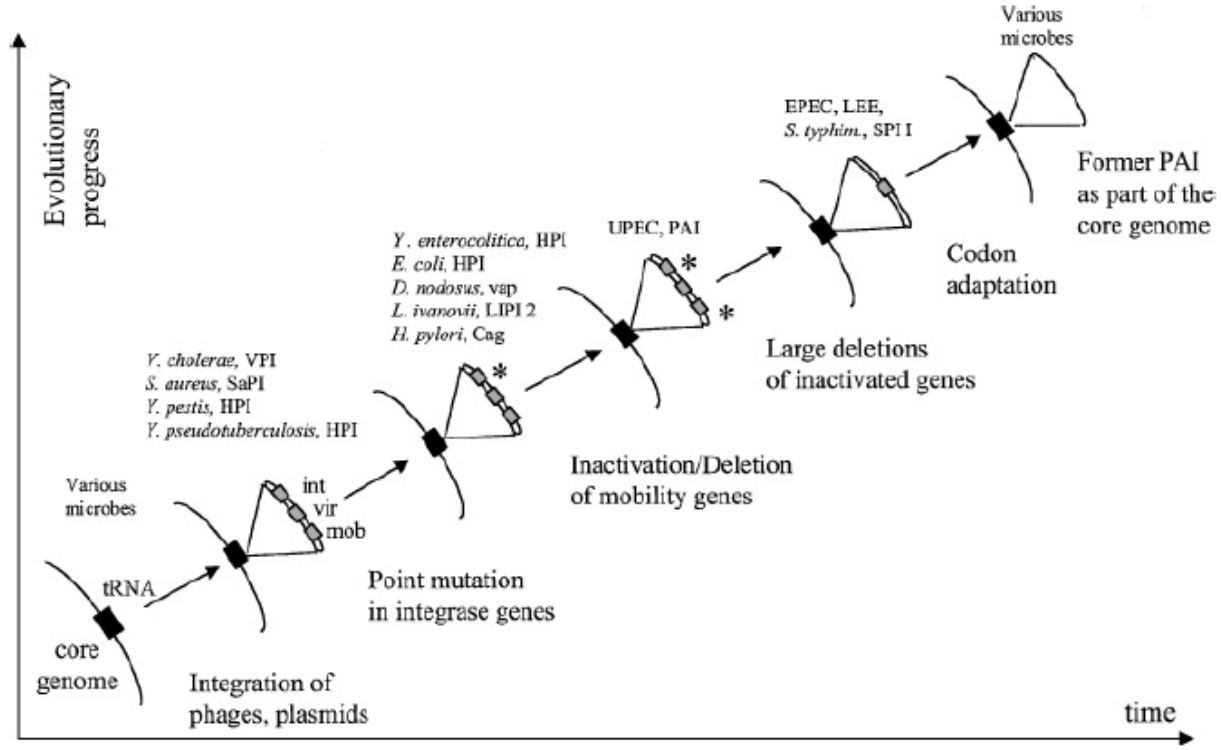

Figure 2: Evolutional stages of pathogenicity island formation. The *vertical line* represents the evolutionary progress; the *horizontal line* represents a time scale. The *thin line* represents parts of the core genome; the *double line* represents pathogenicity island-specific

DNA. The *boxes* indicate genes, and the *asterisks* indicate mutations. Abbreviations: tRNA, transfer RNA genes; int, integrase gene; vir, virulence-associated gene; mob, mobility gene (e.g. gene encoding transposase).

PAI

PAI can be considered a genetic residue due to its specific stages in the pathogen evolutionary process [1]. Certain PAIs tend to delete specific sequences or genetic elements. Such deletions occur longer to optimize PAI structure, eliminate genes whose Productionsare less efficient.

PAIs contribute to the development of a variety of macro-pathogens. However, the microevolution that produces new biotypes occurs in a shorter period. Both are involved in creating and adapting pathogenic microbes.

When PAIs adapt to the host's nuclear genome, evolutionary progress completes. When the new genes enter the host or the receiving bacterium finds other interactions, they cause the host's genetic richness and better ecological adaptation.

Pathogenic factors and genomic islands of bacterial genes are located on the plasmid, the main chromosome, or the bacteriophage.

The efficiency of the genome sequence obtained by the microorganism depends on its genetic composition and ecological location in the receiving bacterium. Thus, a genetic sequence may have different efficiency in different bacteria [2]. For example, the iron absorption system, namely Yersiniabactin, and the systems in pathogenic Enterobacteriaceae in soil bacteria act as a fitness island in non-pathogenic soil species, but it causes disease in pathogenic bacteria. The primary sequences in bacteria include specific ribosomal RNA genes that code essential metabolic proteins such as ATPase.

PAI function and activities

Pathogenicity islands have different functions in pathogens, some of which include the following:

A) They cause bacteria survival and facilitate their movement and transfer [2]

Example:

1) PAI in Pseudomonas spp and Enterobacteriaceae spp, which codes the iron absorption system and increases the growing capacity of bacteria.

2) PAI in Shigella flexneri, namely SH-I2, which synthesizes aerobactin and enables the bacteria to grow in unfavorable environmental conditions and iron deficiency.

b) They have genes coding the antibiotic resistance factor and their resistance to drugs.

Example:

1) MecA gene in Staphylococcus aureus bacteria increases the bacteria resistance in the host and creates resistance to methicillin in MRSA strains.

2) Shigella-resistant locus (SRL) in SPI causes resistance to streptomycin, tetracycline, and ampicillin antibiotics.

PAI (3) in bacteria (Salmonella. Typhimurium), i.e., SPI, causes multiple antibiotic resistances.

c) They are responsible for synthesizing proteins and binding agents in various secretory systems and producing toxins and enzymes.

PAI codes sucrose absorption in Salmonella senftenberg, which causes bacterial metabolic adaptation.

Similar islands show different effects on different bacterial agents due to environmental conditions.

Example: PAI in yersinia.spp causes the synthesis of Yersiniabactin, which helps bacteria survive in iron deficiency conditions and facilitates bacterial colonization in the host in other species.

Fas. fimbriae-specific genes are a part of PAI, which carry iron absorption system genes and were first found in salmon species.

PAI translocation and transfer

PAI is transferred in three ways:

1) Transfer by natural method

2) Transfer by plasmid

3) Transfer by transduction

1) In a natural method, a foreign genome is acquired through unique systems in bacteria, and the genes related to the native race remain inside the genome and are integrated there [1].

2) Transfer by plasmid method

Plasmids perform activities such as transferring information, coding resistance genes, and consuming unusual metabolites [1]. If the plasmid is extra-chromosomal and has a homologous sequence with the chromosome, it will be episomally placed with it and integrated into it and reproduces [2] like Staphylococcus aureus strains.

Example: In Shigella spp, the type 3 secretion system required for cell invasion is coded by spa and mxi genes in the plasmid. The same genes are present in PAI related to Salmonella enterica. Thus, conjugation is a crucial factor in the transfer by plasmid in bacteria.

3) Transfer by transduction method:

This process involves transferring gene blocks by bacteriophage to host bacteria. If the transferred gene fragment is accepted and expressed by the bacteria, the conditions for bacteria adaptation to the new conditions are provided depending on the environmental conditions in the evolutionary course of the bacteria [1]. Some pathogenicity islands are enormous, cannot be transferred by bacteriophages, and should be transferred through transformation.

Phage transport has been implicated in the transport of other PAIs and similar compounds.

Some PAIs do not have the capability of transferring from one strain to another..
They can be transferred in the genome of a bacterial pathogen or transferred during infection.

tRNA genes and their gene sequence

The tRNA-related genes are extensively used since they exist in multiple copies and have conserved sequences. The genomic fragments can be integrated into them as specific recombination sites.
Most of the islands and some phages are integrated into their third end.
The presence of translocation sequences in the pathogenicity islands facilitates the lysogenic bacteriophage genome to the host genome. It is performed by integrase-oxygenase enzymes and is coded by the bacteriophage genome of the pathogenicity island.
SeLc and Leux loci exist only in one copy and are used by pathogenicity islands as a suitable site for integration in some bacterial families such as Shigella and Escherichia coli in some bacterial families such as Shigella and Escherichia coli.
There is an overlap of 15 to 20 nucleotides between the pathogenicity islands and the tRNA coding locus. This site codes the TWC arm in the second structure of the tRNA molecule.
The genes in the tRNA site are effective in the overall movement order of the system. The CCA terminal in tRNA provides the primary place for integration by an internal group. For this reason, E.colik1 translocation is observed in a different range of catalytic materials. Some methods have been determined to remove chromosomal regions crucial for determining the pathogenicity island. About 75% of PAIs are related to tRNA. The translation of rare tRNAs has been proposed recently to regulate genes coded on certain PAIs. It is known as the minor codon hypothesis.

The main classes of pathogenicity agents in PAI:

- Adhesions
- Secretory system
- Toxins (on mobile genetic elements)
-Iron absorption systems
- Serum resistance

Table 1: presents the major pathogenicity characteristics coded by the pathogenicity islands.

Important virulence characteristics coded by pathogenicity islands

pathogenicity characteristics	Example
adhesion factors	Diarrheagenic *Escherichia coli* Uropathogenic *Escherichia coli* *Vibrio cholerae* *Listeria* spp.
- Toxin	Uropathogenic *Escherichia coli* *Staphylococcus aureus*
Iron absorption systems	Uropathogenic *Escherichia coli* *Shigella flexneri* *Yersinia* spp.
Invasion, influence	Diarrheagenic *Escherichia coli* *Salmonella* spp. *Shigella* spp. *Listeria* spp.
Type 3 secration system	Diarrheagenic *Escherichia coli* *Pseudomonas syringae* *Erwinia* spp. *Yersinia* spp. *Salmonella* spp. *Shigella* spp.
Type 4 secration system	*Helicobacter pylori* *Agrobacterium tumefaciens*

Adhesion: It is located in the PAIs in the genome of pathogenic species. It is the mediator for binding to specific receptor

molecules in eukaryotic cells, such as pap pili in bacteria. Ec to adhere to a specific receptor molecule, such as α-galactose 1-4, located on the epithelial cells in the urinary tract.
Removing adhesion-bearing PAI may cause a phase change in bacteria.
For example, Escherichia coli adhesions destroy the bacteria. Its colonization causes by some cells due to the host's immune response.
Iron absorption system: This process is coded by pathogenic and non-pathogenic members of a species, and these islands help their adaptation to a particular environment.

Two significant mechanisms for iron supply in bacteria:
1- Expression of iron carrier receptors (hemoglobin, lactoferrin, and transferrin)
2- Synthesis and secretion of low and high molecular weight siderophores
Iron-binding compounds for two different systems, yersinia bactin siderophore and aerobactin, form gene clusters and are part of the PAI.
The hemin iron absorption system in enterobacteria is part of an island coded by a 5 kb DNA fragment. The phenolate type of siderophore system (yersiniabactin) was described by HIP for the first time for pathogenic species.
Serum resistance: The proteins coded by PAI also mediate serum resistance, such as the sac_4 gene coding serum resistance in Neisseria gonorrhoeae in people with gonococcal infection. This region is absent in some strains.
Immunoglobulin A proteases can cleave IgA molecules by non-enterobacterial species and pic family protein-degrading toxins. Other organisms such as Haemophilus influenzae, E. meningitides, Neisseria gonorrhoeae, and Streptococcus pneumoniae synthesize IgA protease.

Capsule: The genomic location and genetic factors for capsule synthesis in pathogenic strains have not yet been elucidated.
Biofilm: Regarding the biofilm in the Staphylococcus epidermis strain, the exopolysaccharide coding source, namely the ica gene, is located on the DNA of more than 100 kilobytes in PAI.

HIP (High Pathogenicity islands)
The first case of these islands was observed in Yersiniabactin. However, this type of island is not limited to Yersinia species and can be found in other bacteria such as Klebsiella, Citrobacter, and Enterobacter.
These regions in different species and pathogenic species are suitable models for studying bacterial transfer.
HPI is located beside one of three tRNA positions of asparagine amino acid.
In extra-intestinal E. coli in strain K1, there is a 20 kb segment adjacent to phev tRNA.
There are other species in Y.pestis and highly pathogenic strains. It is responsible for coding the Yersiniabactin protein, which involves iron absorption and synthesis, siderophore absorption, and hemin absorption.
These islands are controlled by Yops proteins.
The activities coded by this bacterium:
1-Yersiniabactin synthesis
2- Siderophore synthesis and absorption
3- Hemine absorption
4- Pigmentation locus
5- Sifa protein synthesis in which type 3 secretory system is made and is used for its intracellular reproduction.

Pathogenicity islet:
There are genetic clusters that are not entirely adaptable and similar to characteristics of the pathogenicity islands [3]
These regions' length is usually less than 10 kilobytes, and their guanine and cytosine nucleotides level are less than the main pathogenicity islands. Genetic clusters may be considered ancestral PAI [3].
- Secretion system in bacteria [2]
- Secretion system in gram-positive bacteria: through general secretion pathways
- Secretion system in gram-negative bacteria: through particular secretion pathways

1) Type 1 secretion system (T1SS):
This system is used in transferring large proteins and was first identified in the alpha-hemolysin of Escherichia coli in upEc strains in the EHEc plasmid. It needs three types of proteins [1].
1) ATPasep in the inner membrane provides the necessary energy for the system.
2) The protein involved in bacterial hemolysin (HLYB protein for hemolysin in E.coli bacteria)
3) Mem, a branched protein in the UP.E coli, which includes the protoplasm and bacterial membrane
The hly operon is responsible for hemolysin synthesis, activation, and transfer.

2) Type 2 secretion system (T2SS):
The genes that code this system belong to the chromosomal genome and nucleus genes [2]. They are not found in PAI. There are at least ten or fourteen subunits in them. This system is located in the inner membrane, periplasm membrane, plasma membrane, etc. It mainly plays a role in the extracellular secretion of protein-degrading enzymes. Enzymes such as

cellulase, elastase, chitinase, amylase, phospholipase C, protease, and pullulanase are secreted by this system.

3) Type 3 secretion system (T3SS):

It includes 20 different genes. Some of its subunits are involved in pathogenesis [1].

In this system, the secretion of pathogenic agents to the outside and their transfer in the eukaryotic host cell membrane is done directly and requires contact between pathogen and target cell.

In extracellular pathogens, it is performed by the cytoplasmic membrane and other organisms. This system activity disrupts the host's natural function and intracellular transfer, phagocytic, and apoptosis.

SPI-1 and SPI-2 in Salmonella enterica and Locus of enterocyte effacement (LEE) in EPEC have this system. In Yersinia.pestis, this system neutralizes the host's body cells. The secretion of yopD and yopB molecules results in microorganisms' reaction with macrophages and destroys them. YSCN protein is involved in ATP hydrolysis and energy supply for bacteria. In Yersinia, which includes invasin, the intimin protein binds to its receptor in the host, which is secreted through a type 3 secretion system on the LEE PAI.

SPI1_2 in Salmonella enterica and Locus of enterocyte in Escherichia coli EPEC

4) Type 4 secretion system (T4SS):

It has a structure with more than 10 subunits that can transfer proteins to target eukaryotic cells.

The transfer is done by cytoplasmic ATPase. Example:

1) Transfer of protein complex to DNA in Agrobacterium tumefaciens

The plant cell induces tumor formation by activating this system [1].

2) The secretion system in PAI of Helicobacter pylori bacteria, cagA, has a cytotoxic property and induces vacuole in the epithelial of the target cell and cell death.

The following bacteria have this secretion system:

Bordetella pertussis

Bartonella spp

Legionella pneumophila

Brucella spp

Helicobacter pylori

Cm/dotergion genes are involved in this system activity in Legionella pneumophila.

5) Type 5 secretion system (T5SS)

In this secretion system, protein transfer occurs spontaneously in large gene clusters.

It is a polypeptide chain with an N-terminal sequence signal at its end. The proteolytic separation of the signal sequence and the formation of secretion pores guide the protein outside through this system.

This type of secretion system is present in the following bacteria:

1-LPA and the EspC PAI of pathogenic E. coli

2-SPI-3 of Salmonella enterica

3-SHI-1 of Shigella flexneri

- Pertactin in Bordetella Pertussis
- Vacuolating cytotoxin (in Helicobacter pylori)
- Sep A in Shigella flexneri
- In Salmonella enterica, the gene encodes MgtcB, which is crucial for the intracellular phenotypic property of Salmonella to replicate, but its exact role is not known.

Pathogenicity islands in Gram-positive bacteria [2,3]

Staphylococcus.spp

Staphylococcus aureus

- PAI in it is Sap-1 and Sap_2.
- It has genes causing resistance to bleomycin, kanamycin, methicillin, and erythromycin antibiotics
- The Tsst gene in it causes toxic shock synthesis.
- The mecA gene in MRSA strains causes resistance to methicillin.

Sterep spp

1) Group A: Streptococcus pyogenes

A bacteriophage does horizontal gene transfer, but PAI does gene transfer.

However, it has a chromosomal region like PAI, and about 10% of its genome contains bacteriophage and transposons.

This type of bacteria causes skin infection, pharyngitis, and necrotizing fasciitis.

2) Group B: Streptococcus pneumoniae

This species often exists in infants and causes pneumococcal septic infections in the upper respiratory tract, pneumonia, and otitis media.

These two types of bacteria code the iron absorption system by pit1 and pit2 genes

Listeria spp

Only six species of this bacterium have been known

- PAI in them is a pathogenic genetic cluster (prf virgne cluster)
- Listeria monocytogenes species
- Contaminating humans and some mammals and birds
- It causes blood cell lysing and phagocytic vacuole disorder
- It spreads bacteria into the cytoplasm.

This bacterium synthesizes the following proteins:

1) The plcb gene, which codes phospholipase and metalloproteinase.

2) Regulator protein

3) Listeriolysin protein, which causes listeriosis

Listeria ivsnobia
- PAI is LIPI1 and LIPI2 in it and has a genetic cluster.
- This bacterium is mainly pathogenic for ruminants, and infection is usually associated with no symptoms.
- It codes phospholipase, metalloproteinase, regulator protein (ActA), internalin (Inl), and sphingomyelinase (SmLc)
Listeriolysin (LLO): Complications caused by it include sepsis and meningitis and are often observed in patients whose immunity is reduced, such as diabetic patients, liver patients, infants, elderly, chemotherapy patients, pregnant women, and people with viral infections.
Yersinia spp: It has three pathogenic species
Y.pestis: It causes plague and widespread epidemic in the human population and is a dangerous option for bioterrorism.
Y. enterocolitica and Y. pseudotuberclosis cause intestinal infections. HPI is the Pathogenicity Island in them.
Clostridium difficile: It has a Pathogenicity locus, and the coding of tcf A, B-E toxin genes causes the synthesis of enterotoxin and cytotoxin. PAI has not been detected in perfringens and tetani species yet.
Enterococcus faecalis: Its PAI is NPM, involved in cytolysin (cyl) synthesis and biofilm formation.

Pathogenicity islands in Gram-negative bacteria [4,5]

Esch spp

Uropathogenic Escherichia coli (UPEC)

UPEC Ecoli 536:

It includes different PAIs:
- It has 4 PAIs that perform the following actions:
-Alpha-hemolysin synthesis, siderophore synthesis in iron absorption (Iro siderophore system), Yersiniabactin synthesis, P-fimbriae and Sfa-fimbriae synthesis (P-fimbriae causes infection in the urinary tract).

UPEC Ecoli j96:

-A, B, and D operon cause the synthesis, transfer, and activation of hemolysins and alpha-hemolysin in them, the synthesis of P_fimbriae and P_pilus.
- Cytotoxin necrotizing factor 1(CNf1) synthesis
-The synthesis of heat resistance hemagglutinin is done in them.

UPEC Ecoli cFT073:

UPEC Ecoli cFT073:
-It has a PAI called PAI CFTO73I_Ii.
- It codes P-fimbriae, alpha-hemolysin and aerobactin synthesis.
- It has iron-regulated genes.

E.Coli K1:

- It lacks the gene for coding the toxin.
- It codes the genes necessary for the secretion of the biosynthesis capsule.
- In some UPEC strains, it was found that the pressure caused by the antibiotic may cause the release and change of PAI by causing changes in DNA topology.

Enteropathogenic Ecoli (EPEC)

EPEC Ecoli E348/69:

- Its PAI is LEE (Locus of enterocyte effacement).
Its functions include:
-Coding type 3 secretion system, cell invasion, and Tir transporter.
- EPEC RW137
- Its PAI is LEE.

Enterohemorrhagic Ecoli 0157:H7 (EHEC):

-PAI is LEE in it
- Its functions are synthesizing type 3 secretion system, cell invasion, and transporting Tir receptor
• This serotype causes food poisoning and diarrhea in humans.

Enterotoxigenic Ecoli (ETEC):

- Its PAI is Tia PAI, codes Tia and Leo genes, and is involved in cell invasion.
- It is one of the significant causes of diarrhea in Iran.
- It binds to the intestinal mucosa and damages its epithelial cells, especially the small intestine.
- It is resistant to heat and produces an enterotoxin
-Espc protein: This 110 kilodalton protein is in the group of autotransporter proteins (T5ss).
-It is a serine protein that can separate human clots
-This protein is not to interfere in A/E lesion formation (base formation by bacteria and destruction of microvillous membrane of intestinal cells) and is not transported by T3ss LEE.
- The Espc gene is in a fragment of 15195 bp with 40% CG content and is located adjunct to the ssrA tRNA gene, which is related to pathogenicity.

E.Coli enterovasiv (EIEC)

This strain is related to the Shigella species.
It contains aerobactin, whose genes are located in PAI in tRNA selc.

Helicobacter pylori

-It usually exists in the stomach and causes disease and damage to it
-It can cause stomach cancer and produces carbon dioxide, urease, and ammonium, and it becomes resistant to the acidic environment of the stomach.
-The pathogenicity island of this bacterium is cag and can move through other sequences.

- There are two cytotoxins in this bacterium, cagA, and vacA, which disrupt the cytoskeleton system by irregular binding in actin strands.
-CagA produces cytokines, chemokines, and interleukins.

Pseudomonas aeruginosa

-It is an opportunistic pathogenic bacterium in animals, humans, and plants.
-This bacterium has about ten pathogenicity islands with various proteins such as ExoTo and ExoS. ExoT destroys the structure of the cell skeleton and has the property of ADP ribosyltransferase
- ExoS protein disrupts the transduction pathway.
- PAG1 contains several ORFs, and the function of the proteins coded by it is unknown. PAG1_3 is involved in urinary tract infections in cystic fibrosis patients.
- PAG2: This type of PAI is found in Type C Pseudomonas aeruginosa.
- PAG3: This PAI is found in the SG-17M strain of these bacteria.

Glycosylation Island:

- This pathogenicity island is found only in the PAK strain of this bacterium, and its role is to glycosylate the flagellin protein.
- The protein coded by it connects glycosyl to flagellin through a covalent bond.

Shigella spp

The bacterium is pathogenic and aerobic and has approximately five pathogenicity islands; its exact role is unclear.
Shigella species have a PAI called she locus (SHI).
It is a crucial viral agent derived from an ancestral bacteriophage that has lost the ability to leave the bacterial chromosome. A part of the phage genome has been deleted.
It is a viral agent derived from a bacteriophage that has lost the ability to leave the bacterial chromosome.
It has three ORFs that produce proteins similar to bacteriophage integrase in site recombination.
This bacterium has many pathogenic factors, the most crucial of which is LPS (lipopolysaccharide), which has an O antigen and an A fat.
Glycosylation and acetylation of antigens cause antigenic changes, which causes the host's immune response to change and become neutral.
Bacteriophages code the agent of these changes.
Bacteriophages and pathogenic bacteria code enzymes that cause changes in antigens.
There are four types of Shigella bacteria:
S.sonnei
S.Boydii
S.Desenteriae
S.Flexneri

SHI_1 was discovered for the first time in Shigella flexneri and contains bacteriophage p4.
Pathogenicity island SHI_O in Shigella flexneri, as a result of its glycosylation and acetylation, causes antigenic changes in it.
The island contains several ORFs.
The difference between Shigella serotypes is in the o antigen in them.
PAI inhibits the following factors:
1- Lipopolysaccharide biosynthesis
2- Bacterial penetration into epithelial cells as a result of replacement and formation of a colony in bacteria
3- Aerobactin synthesis and transfer enables the bacterium to grow under iron deficiency conditions and in unfavorable environmental conditions and compete with other microorganisms.
4- Production of anthraxin and protease enzyme
5- Ferric dicitrate absorption
The sigA protein, a protease, has a cytotoxic effect on HEP-2 cells.
SHI-2: It contains the aerobactin operon and the immunity gene to colisin V and some other ORFs. Their primary function is to facilitate the survival and durability of bacteria in a stressful and iron-deficient environment.
SHI-3: It has been detected only in S.boydi, has the aerobactin operon and prophage genes, and is responsible for synthesizing the lysine decarboxylase enzyme, which has been deleted in the coding part of the cadaverine enzyme.
- It has enterotoxin activity and is effective against Shigella pathogenicity
- It contains a p4-like integrase gene.
- In this group of bacteria, there is a Shigella resistance locus to ampicillin, tetracycline, and streptomycin.
- Type 3 secretion system synthesis is performed in these pathogens.
- Shigellosis symptoms: Diarrhea, mucous and bloody secretions in stool, fever, testicular inflammation, attack on colon epithelial cells and lymphoid cells, causing apoptosis.
- The body's immune response to Shigella is antigen 0

Vibrio cholera:

- It has VPI (Vibrio cholera pathogenicity islands)
-This island codes TcP (Toxin regulates pilus), a pili-regulated toxin that is the fourth type of pili and is a phage receptor (CTX) and plays a role in bacterial colonization.
- The island contains a gene that codes the ToxT protein that activates the transcription of the cholera toxin gene and codes

the MoP protease, which can change the virulence of Vibrio cholera.
-Other proteins coded by it are acf and inf.
- This bacterium codes utilization of amino sugar and neuraminidase.
VPI2:
- This pathogenicity island has recently been identified in this bacterium.
- Its crucial role is the production of light amidase enzyme, and it produces molecules similar to ganglioside GM-1 in the cell by removing sialic acid from carbohydrate groups.

Salmonella spp
PAI in these bacteria is SPI (Salmonella pathogenicity islands) and includes SPI1-5.
The invasive gene of Salmonella is inv.
SPI-1 is responsible for invading non-phagocytic cells and creating structures on the bacteria's surface to allow bacteria to enter the host cell. The activity of other proteins plays a role in causing diarrhea and absorbing iron.
SPI-2 plays its role in the secondary stages of infection for the intracellular multiplication of bacteria and its toxic effects.
The proteins coded by this island protect the bacteria inside the phagosome and helps the bacteria survive inside the phagosome by inhibiting the oxidase and nitric oxide synthetase enzymes.
SPI-3: Its organization and genetic efficiency are different from other loci. The most crucial virulence factor coded by it is the magnesium transport system with high activity, which is necessary for the bacteria's survival and reproduction in the phagosome environment.
SPI-4: Its products play a role in the bacteria's survival inside the macrophage.
SPI-5: It codes the effective proteins for SPI-1, 2 islands.
Spi in enterica and bongori types causes their multiple resistances to antibiotics and is involved in type 3 secretory system, invasion of epithelial cells, and cell apoptosis.
It acts as enterophattogenesis in the Dublin type and creates effective proteins for PAI types 1 and 2.
Other activities performed in this bacterium:
1- Monocytosis cell invasion
2- Secretion system synthesis types 1 and 3
3- Coding bacteriocin pseudogenes protein

Regulation of pathogenicity islands
The process in which regulators regulate a group of genes in PAI that another PAI codes are called cross-activation.
The best PAI regulatory systems have a regulatory cascade in which pathogenic genes encoded by PAIs are regulated.
Two sets of regulators:
1- Arac-like proteins
2- Two-component response regulators and alternating sigma factors and histone-like proteins.
Two-component response regulators and alternating sigma factors and histone-like proteins.
A sigma factor regulates the hro gene cluster in the plant pathogen p.syringae.
Hrp codes a type 3 secretion system and is regulated by four proteins.
Hrpl is an alternative sigma factor and is necessary for the transcription of all hrp regulon genes, except hrps and hrpR.
Its transcription depends on the alternative sigma factor Q54.
Hrps and hrpR lack the N-terminal domain
Its activity is negatively regulated by the phosphorylation of the fourth Hrpv protein through hrps and hrpR genes in the hrp regulon.

Conclusion
The investigations on Pathogenicity islands describe the characteristics and role of crucial pathogenic factors in pathogenicity. Currently, the information about this issue is increasing.
The availability of the genome sequence of bacteria causes the identification of genetic islands in them. Only about 4000 species of prokaryotes have been described so far. It is impossible to analyze their genomes due to the non-possibility of culturing some of them in the laboratory. Pathogenic organisms should overcome environmental limitations to survive and reproduce. Pathogenic islands are selected to stimulate their survival and reproduction in the natural environment of microbes. Since the ecological reservoir of many pathogens is not clear, the selected pressure does not entirely lead to PAI creation. Further ecological development of microbes will identify new ways to approach the specific DNA source in PAI.
One question in PAI studies is where the specific parts of DNA in PIA enter that region. There is currently no answer to this question. For example, in the case of HPI origin in the Yersinia pathogenic bacterium, it has been suggested that this DNA may have entered them from the Pseudomonas family. However, this hypothesis has not been confirmed yet. Acquiring PAI by microbes will cause most of them to become aggressive. In this regard, if their host is destroyed, their evolution will be unsuccessful. Multiple levels of the genetic pathogenicity islands can be controlled by identifying the relationship between the microbe and the human body. Thus, several changes should be made in the genes in the host to interact with each other, although its strategies are still unknown. These investigations revealed that PAI originated from non-pathogenic and environmental ancestors and can be related to external factors such as viruses and phages.

Analyzing PAIs provides new insight into the evolution of pathogens and helps to formulate the evolutionary principles of prokaryotes.

The disease is sometimes caused by the genes in the protein secretion systems of pathogens, which can be used in cell biology for providing antigens and vaccination processes. Resistance islands in pathogens make them resistant to antibiotics, such as those found in crucial human pathogens Shigella spp and Salmonella enterica.

Information about pathogens coded by PAIs is helpful in better-understanding bacteria, and their effects on the eukaryotic host can have crucial practical messages. They can identify pathogens in clinical samples and differentiate pathogenic agents from non-pathogenic agents. Microbiologists can identify the characteristics of pathogens and their evolution, the severity of the disease they cause, and diagnosis of newly emerging strains by understanding the basic concepts of PAI in bacteria.

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Conflict of interest

The authors declare that they have no competing interests

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Ethical considerations

The Ethics Committee of Payam Noor University of Hamadan has approved the present study. This manuscript has not been published elsewhere..

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