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Review Article

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The Virulence Factors of Yersinia: A Review

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Abstract

Yersiniosis is the most common food borne disease around the worldwide. The disease is caused by the genus *Yersinia* under the *Enterobacteriaceae* family and consisting of 18 species. Yersinia is gram negative, facultative and rod-shaped bacteria. The most common pathogens are: *Yersinia pestis* which causes plague, *Yersinia enterocolitica* and *Y. pseud- tuberculosis* that causes enteric yersiniosis in human. *Yersinia enterocolitica* is one of the pathogenic species and has six biotypes (1A, 1B, 2, 3, 4, and 5). The biotypes are grouped into non-pathogenic biotypes (1A), weakly pathogenic biotypes (2–5), and highly pathogenic biotypes (1B). *Yersinia* species have numerous major virulence markers with different functions. The pathogenicity is therefore influenced by a number of structures. Plasmid and chromosomal are virulence markers. The chromosomal is genetically stable virulence markers and used for diagnostic purpose.

1. Introduction

The genus *Yersinia* belonging to the *Enterobacteriaceae* family consists of 18 species and, only three species are pathogenic to Humans and Animals which includes *Yersinia pestis*, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis* (1). Yersinia enterocolitica is one of the pathogenic species which has been identified and six biotypes (1A, 1B, 2, 3, 4, and 5) as well as more than 70 serotypes (2). Those biotypes are divided into non-pathogenic biotype 1A, weakly pathogenic biotypes 2–5 and highly pathogenic biotype1B based on their pathogenic properties (1). On the other hand Y. pestis, the causative agent of the plague, Y.pseudotuberculosis and Yersiniaenterocolitic, responsible for human enteric yersiniosis (2).

Enteric yersiniosis is a food borne disease caused by consumption of contaminated food or water (3). They are influenced by several structures, that is plasmid and chromosomal which are virulence markers or virulence determinants (4). The proteins encoded by these genes are able Yersinia to invade a susceptible organism and evade the immune response. The plasmid of Yersinia virulence (pYV) is the most known and virulence marker of Y. enterocolitica (5).

The biotypes of Y. enterocolitica has the ability to invade intestinal mucosa, but only strains with a plasmid can migrate from Payer's patches to mesenteric lymph nodes. They multiply in an internal organs and lead to the necrotic abscesses formation (1).The Biotype 1B of Y. enterocolitica strains having pYV and carrying the chromosomal high pathogenicity island (HPI) is associated with the iron acquisition system. This facilitates the uptake and utilization of iron by Y.enterocolitica as well as promotes their growth under iron-limiting conditions (6). Numerous genes that are directly responsible for the pathogenicity of Y.enterocolitica are placed within the pYV, like yadA encoding the Yersinia adhesin (YadA), or the yop virulon encoding Yersinia outer membrane proteins (Yops) and determination of the pathogenicity of Y. enterocolitica strains are not based on plasmid markers alone because a spontaneous loss of pYV by bacteria results false negative due to prolonged strain storage, frequent passaging and temperatures higher than the optimum range (6).
Physicochemical parameters like temperature, the concentration of calcium iron ions, pH, and osmolality play a role during infection (7). So the expression of many plasmid-encoded virulence genes, selected genes of the flagellar regulon and chromosomal virulence genes is strictly regulated by temperature and the genes of the flagellar regulon. Early virulence genes (invA) are expressed below 30◦C. where plasmid-encoded virulence genes (ysc, yop, yadA) are expressed at 37 ◦C (7). The expression of virulence markers is again regulated by regulatory genes that are virF, encoding the transcriptional activator of the Yersinia virulence regulon (8). The mechanisms of virulence factors expression are generally complicated. So; the main objective this paper is to highlight the common virulence factor of Yersinia.

2. Etiology

Yersiniosis is caused by the Genus *Yersinia* belongs to the family of Enterobacteriaceae which composed of three pathogenic species: Yersinia pestis, *Yersinia enterocolitica* and *Y. pseudotuberculosis* (9).It can be transmitted between humans through the faecal-oral route. The disease is characterized by a self-limiting acute infection beginning in the intestine and limited to the ileo-cecal junction for *Y.enterocolitica*. In contrast, *Y.pseudotuberculosis* often disseminates deeply to the mesenteric lymph nodes (10).

3. Epidemiology

3.1. Distribution

Yersinia pestis is not widespread throughout the entire world as it preferable dry land of the earth (11). The disease has several hosts: swine, horses, ovine, humans and non-humans primates and have public implication (11).

3.2. Transmissions

3.2.1. Food borne Transmission

Yersinia Enterocolitica and *Yersinia Pseudotuberculosis are* food borne entero-pathogen that causes sporadic illness and isolated from many foods like beef, pork, liquid eggs, soft cheese, raw milk, pasteurized milk, fish, raw oysters, shrimps, crabs, chocolate milk, turkey, chow mein (chop suey served with fried noodles), powdered milk, bean sprouts (especially mung beans, lentils, or edible soybeans), and tofu (cheese-like food made of curdled soybean milk) (12). Whereas transmission of plague by fleas depends on infection of the periventricular valve in the insect's foregut by a dense aggregate of *Yersinia pestis (*13).

3.3. Virulence factors

3.3.1. Type III secretion systems (T3SS)

Type III secretion systems are complex bacterial structure. This provides pathogens with unique virulence mechanism enabling them to inject bacterial effector proteins into the host cell cytoplasm. This virulence factor helps bacteria to evade host innate immunity and to enable the

pathogen to replicate and propagate extracellular (5).Virulence of plasmid in which a set of genes whose transcription is activated by temperatures of 37 °C in the presence of concentrations of calcium, conditions representing the mammalian host (5).

3.3.2. Plasmid of Yersinia virulence (pYV)

The virulence plasmid (pYV) encodes a type III secretion system (Ysc and Icr genes) essential for delivery of additional plasmid-borne anti-host factors known as Yops (Yersinia outer proteins (14). It is associated with genetic determinants that include low-calcium response, pinpoint colony, colony morphology, crystal violet (CV) binding (dark-violet colony), Congo Red (CR) uptake (red pinpoint colony, auto agglutination (AA = cells agglutinate), and hydrophobicity (HP = clumping of cells) (14).

3.3.3. Mucoid yersiniae Factors (MyfA)

The mucoid yersiniae Factor plays an important role at the beginning of infection. It is closely resemble CS3 of enterotoxigenic Escherichia coli. This Suggest that MyfA promotes the adhesion to enterocytes. It is also immunogenic at the commencement of disease (19).

3.3.4. Yersinia Adhesin (YadA), Invasin (invA) and Attachment-Invasion Locus (Ail) protein

The proteins encoded by three genes, yadA, invA, and ail, are mostly involved in the processes of adhesion and invasion. Yersinia adhesin (formerly YopA) protein is encoded by the structural gene yadA, found extra-chromosomally on pYV (21). It is a member of the trimeric auto-transporter adhesin (TAA) family. This (YadA) forms fibrous, lollipop-like structures on the cell surface that mediate binding to epithelial cells (21).

3.3.5. Yersinia Outer Proteins (Yops)

A yersinia outer protein is Plasmid virulence that is either intracellular effectors or membrane proteins that create a delivery system for these effectors (22). There are six effector proteins of Yops (YopE, YopH, YopJ/P, YopM, YopT, and YpkA/YopO). They are transported into eukaryotic cells to inactivate the host immune response. The four effector proteins are (YopE, YopH, YopT, and YpkA) doing at different mechanisms to prevent phagocytosis of the bacterium (22). The YopJ inhibits the production of certain inflammatory cytokines by blocking the mitogen-activated protein kinase (22).

3.4. Pathogenesis

Yersinia enters the body per os with contaminated water or food and colonizes palatine tonsils, multiply and reach further segments of the gastrointestinal tract. Before come into contact with enteric epithelial cells, they penetrate the layer of gastrointestinal mucus which is secreted by goblet cells. Gastrointestinal mucus contains mucins which are responsible for its gel-like properties (15).They attach to mucin of animals and humans to a greater extent which do not possess pYV and the Lipopolysaccharide (LPS) is encoded chromosomally, which is integral component of the external cell membrane that forms complex structures with proteins and phospholipids, protects bacterial cells against bile (16). Follicle-associated epithelium (FAE) is the primary site of host–pathogen interactions in penetrating microfold cells (M cells) and, subsequently, induces the destruction of Peyer's patches and abdominal lymph nodes are target site where the microorganism multiplies and causes inflammatory changes and ulcerations, and from where it can invade internal organs (17).

3.5. Clinical Signs

The Symptoms vary with age and are commonest in young animals and children which include fever, diarrhea, often bloody in young children, abdominal pain, cramps, symptoms similar to appendicitis and joint pain occurs in half of affected animals (17).

3.6. Diagnosis

The chromosomal genetically-stable virulence markers like ail, invA, myfA, and yst genes,

which encode the production of Ail (attachment-invasion locus) protein, primary internalization factor invasin InvA, mucoid Yersiniae factor MyfA and Yst (Yersinia-stable toxin) enterotoxin, respectively, is more justified for the diagnostic (16,18). The signs of yersiniosis are often difficult to distinguish from other diseases like Salmonellosis, Shigellosis and Appendicitis (23). As a result, diagnosis of Yersiniosis can be performed by Multiplex polymerase chain reaction (PCR), Pulsed-field gel electrophoresis (PFGE), Antigen capture enzyme-linked immune-sorbent assay (ELISA), and Cell Culture. Finally, the chances of successful laboratory confirmation of yersiniosis are completely aligned with Samples required for laboratory testing which includes: Faecal samples, Whole blood, lymphoid tissue including tonsils, Tongue, Liver, Heart and Contaminated food (23).

3.7. Impacts of Disease Agent beyond Clinical Illness

The disease is risk to public health and zoonotic disease that infect humans via ingestion of faeces-contaminated foods (raw meat, undercooked meat and sewage-contaminated water) (20). Again if the livestock facilities are infected by the disease, severe economic loss due to decreased thriftiness (meat production, milk production) and mortality are take place (20).

3.8. Treatment

Care in patients with *Yersinia* is primarily supportive with good nutrition and hydration being supports of treatment and First-line drugs used against the bacterium include aminoglycosides and trimethoprim-sulfamethoxazole as well as other effective drugs includes third-generation like cephalosporin are needed (15).

4. Conclusion and Recommendation

The Overall review indicates that how the yersiniae colonise tissues and combat host defences during infection. The T3SS is the best system which helps for evading host innate immunity and enabling the pathogen to replicate. Moreover clarifying the function of YopM will offer an important step change, as will understanding more clearly the global molecular mechanisms that support the regulatory relationships that must exist between the T3SS system and the adhesins. It is also important that the relationships that exist between the different adhesins, how they compensate for each other, and which environmental signals dictate their site-specific expression. Finally, the structures of many of the adhesins have been explained, there is certainly a need to better understand how they interact with different host ligands. Based on the above conclusion the following recommendations were forwarded

- Significant progress has been made in defining this sophisticated virulence determinants.
- Much more work is required to fully appreciate the success of the sophisticated diagnostic kit and tools.

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