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YERSINIA PESTISNING VIRULENTLIK OMILLARI VA PATOGENEZ XUSUSIYATLARI

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Annotatsiya. Ushbu maqolada Yersinia pestis bakteriyasining virulentlik omillari va patogenez mexanizmlari tahlil qilinadi. Y. pestis vabo kasalligining qo'zg'atuvchisi bo'lib, uning yuqori patogenligi bir nechta molekulyar omillarning o'zaro muvofiqlashgan faoliyati bilan belgilanadi. Maqolada III tip sekretsiya tizimi (T3SS), F1 antigeni, Pla proteazasi, V antigeni va sideroforlarning patogenezdagi o'rni yoritiladi. Odam qo'zg'atuvchilari Yersinia pseudotuberculosis va Yersinia enterocolitica enterokolitni, Yersinia pestis esa o'pka, bubon va septik o'latni keltirib chiqaradi. Uchalasi ham virusli omillar arsenaliga tayanadigan umumiy infeksiya strategiyasini o'z ichiga oladi, bu ularga xo'jayinga kirish, unga yopishib olish va mustamlaka qilish imkonini beradi, shu bilan birga o'z vaqtida tozalanishdan qochish uchun xo'jayin himoyalaridan qochadi. Ularning arsenalida bir qator adgezinlar mavjud bo'lib, ular bosqinchi patogenlarning xo'jayinda o'rnashib olishiga va keyinchalik infeksiya paytida ma'lum to'qimalarga yopishib olishiga imkon beradi. Xo'jayinning tug'ma immun tizimi faollashganda, barcha uchta qo'zg'atuvchi teri osti ignasiga o'xshash tuzilmani hosil qiladi. Shuningdek, bakteriyaning immun tizimni bostirish mexanizmlari, hujayra ichida va hujayradan tashqarida omon qolish strategiyalari hamda vaboning limfatik, septisemik va pnevmonik shakllarining patofiziologik asoslari ilmiy adabiyotlar asosida tahlil qilinadi.

Kalit so'zlar: Yersinia pestis, vabo, virulentlik omillari, patogenez, III tip sekretsiya tizimi, F1 antigeni, Pla proteazasi, immunomodulyatsiya.

ВИРУЛЕНТНЫЕ ФАКТОРЫ YERSINIA PESTIS И ОСОБЕННОСТИ ПАТОГЕНЕЗА

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Аннотация. Возбудители заболеваний человека Yersinia pseudotuberculosis и Yersinia enterocolitica вызывают энтероколит, а Yersinia pestis отвечает за пневмоническую, бубонную и септическую чуму. Все три имеют общую стратегию заражения, которая опирается на арсенал факторов вирулентности, позволяя им проникать в хозяина, придерживаться и колонизировать его, уклоняясь от защиты хозяина во избежание несвоевременного удаления. Их арсенал включает в себя ряд адгезинов, которые позволяют инвазирующим возбудителям закрепиться в хозяине и впоследствии при инфекции прикрепиться к определенным тканям. При активации врожденной иммунной системы хозяина все три возбудителя образуют структуру, аналогичную гиподермической игле. В данной статье анализируются факторы вирулентности и механизмы патогенеза бактерии Yersinia pestis. Y. pestis является возбудителем чумы, а её высокая патогенность обусловлена согласованным действием нескольких молекулярных факторов. В статье освещается роль системы секреции III типа (T3SS), F1-антигена, протеазы Pla, V-антигена и сидерофоров в патогенезе заболевания. Также рассматриваются механизмы подавления иммунной системы бактерией, стратегии выживания внутри и вне клетки, а также патофизиологические основы лимфатической, септицемической и пневмонической форм чумы на основе научной литературы.

Ключевые слова: Yersinia pestis, чума, факторы вирулентности, патогенез, система секреции III типа, F1-антиген, протеаза Pla, иммуномодуляция.

VIRULENCE FACTORS OF YERSINIA PESTIS AND FEATURES OF PATHOGENESIS

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Abstract. The human pathogens Yersinia pseudotuberculosis and Yersinia enterocolitica cause enterocolitis, while Yersinia pestis is responsible for pneumonic, bubonic, and septicaemic plague. All three share an infection strategy that relies on a virulence factor arsenal to enable them to enter, adhere to, and colonise the host while evading host defences to avoid untimely clearance. Their arsenal includes a number of adhesins that allow the invading pathogens to establish a foothold in the host and to adhere to specific tissues later during infection. When the host innate immune system has been activated, all three pathogens produce a structure analogous to a hypodermic needle. This article analyzes the virulence factors and pathogenic mechanisms of Yersinia pestis. Y. pestis is the causative agent of plague, and its high pathogenicity is determined by the coordinated activity of several molecular factors. The article highlights the role of the Type III secretion system (T3SS), F1 antigen, Pla protease, V antigen, and siderophores in the pathogenesis of the disease. In addition, the mechanisms by which the bacterium suppresses the immune system, its survival strategies inside and outside host cells, and the pathophysiological basis of the lymphatic, septicemic, and pneumonic forms of plague are analyzed based on scientific literature.

Keywords: Yersinia pestis, plague, virulence factors, pathogenesis, Type III secretion system, F1 antigen, Pla protease, immunomodulation.

Relevance. The host and the invasive bacterial pathogen compete for dominance during an infection timeframe. Both may be in the lead at any one moment, but the host's destiny ultimately depends on how this struggle turns out. Although the pathogen's infectivity will be reduced by the triggered host response, many bacterial species have developed sophisticated techniques to ensure they may successfully cause infection after colonization in order to stay one step ahead.A variety of virulence factors are used by the three human pathogens in the genus Yersinia to effectively cling to host cells and tissues and interfere with host cell activities. Cholera is an acute infectious disease that has caused three major pandemics in human history and remains endemic in some regions today. The high pathogenicity of Yersinia pestis, its ability to spread rapidly, and its potential as a bioterrorism agent make its study one of the priority areas of modern microbiology and epidemiology [14,15,16]. As noted in the literature, the mortality rate in untreated bubonic plague is 50-60%, while in the pneumonic form, the mortality rate reaches almost 100%. With timely antibiotic therapy, recovery is observed in the majority of patients, and mortality is recorded in less than 10% of cases [18]. In recent years, the discovery of antibiotic-resistant strains of Yersinia pestis (e.g., gentamicin and doxycycline resistance) has necessitated the development of new strategies for treating the disease [8]. In particular, a study conducted by Galimand et al. identified a strain of Y. pestis resistant to many antibiotics and demonstrated resistance to streptomycin, tetracycline, chloramphenicol, and other drugs [8]. Therefore, an in-depth study of the molecular mechanisms of virulence factors is an important basis for creating effective vaccines and therapeutic drugs against cholera [18]. Yersinia pestis is a gram-negative, facultative anaerobic rod-shaped bacterium belonging to the family Enterobacteriaceae. It evolved approximately 1500–20,000 years ago from Yersinia pseudotuberculosis, a relatively less pathogenic species.[1] The pathogenicity of Y. pestis is primarily determined by virulence factors encoded by plasmids (pPCP1, pCD1, pMT1) and chromosome-located genes [10]. Enterocolitis is caused by the human pathogens Yersinia pseudotuberculosis and Yersinia enterocolitica, whereas pneumonic, bubonic, and septicemic plague are caused by Yersinia pestis. In order to enter, adhere to, and colonize the host while eluding host defenses to prevent premature clearance, all three employ an infection strategy that depends on a virulence factor arsenal. Several adhesins in their arsenal enable the invasive

pathogens to take root in the host and stick to particular tissues at a later stage of infection. All three viruses create a structure that resembles a hypodermic needle when the host's innate immune system is triggered. Six "effector" proteins can enter the cytoplasm of the host cell through the channel that is created in conjunction with the translocon, which creates a pore in the host membrane. These proteins are more effective than their native counterparts at altering the host cell cytoskeleton and initiating the host cell suicide response, even though they imitate host cell proteins. Despite the host's greatest efforts to combat the invading virus, Yersiniae maintains the upper hand thanks to such a formidable arsenal. The main virulence elements that make up Yersinia spp.'s arsenal are highlighted in this mini-review, along with how these infections can overcome host defenses thanks to their highly developed biological weaponry. Three extremely versatile psychrotrophic main human pathogens include Yersinia pseudotuberculosis, Yersinia pestis, and Yersinia enterocolitica. Self-limiting stomach infections are caused by Y. pseudotuberculosis and Y. enterocolitica. With almost 98% DNA identity, Y. pestis is a recently developed nearly identical subclone of Y. pseudotuberculosis 1, 2. The colonization of rat fleas, which then transmit Y. pestis from the rodent host to humans, is its mode of transmission 3. Without antibiotic treatment, Y. pestis can produce septicemic, pneumonic, and bubonic plague once it has entered the human host, with fatality rates up to 100% 4. According to the World Health Organization, Y. pestis is a "re-emerging" virus that poses a significant risk of bioterrorism and, alarmingly, can develop resistance to several antibiotics 5. The two additional virulence plasmids that Y. pestis carries, along with slight genomic variations on the corresponding chromosomes, are the main causes of the lifestyle and virulence differences between Y. pseudotuberculosis and Y. pestis [20-26].

The main purpose of the presented manuscript is to provide a brief analysis of the virulence factors and pathogenetic features of Yersinia pestis based on the results of authoritative scientific works.

The main virulence factors of Yersinia pestis; several important factors are involved in the pathogenicity of Y. pestis. Among them, the most important are the type III secretory system (T3SS), capsular antigen F1, Pla protease, V/W antigens, structural features of lipopolysaccharide (LPS), and siderophores (yersiniabactin) [6]. The type III secretory system is one of the most important pathogenic factors of Y. pestis and is encoded by the pCD1 plasmid. Through T3SS, the bacterium sends "effector proteins" (Yersinia outer proteins) directly into the cytoplasm of the host cell [24]. These effector proteins are designed to suppress the activity of immune cells (e.g., macrophages and neutrophils). Specifically, the YopJ protein blocks the signaling pathways of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB), preventing the synthesis of pro-inflammatory cytokines. Thus, Y. pestis avoids phagocytosis and can reproduce in an extracellular environment [16].

F1 antigen (capsular antigen); F1 antigen is a capsule-forming protein encoded by the pMT1 plasmid, which plays an important role in Y. pestis' resistance to phagocytosis. The capsule forms a thick protective layer on the bacterial surface, making it resistant to lysis through the complement system and recognition and absorption by phagocytes [7]. The F1 antigen possesses high immunogenic properties, and antibodies formed against it play an important role in the defense reaction. Therefore, the main component of cholera vaccines used today is the F1 antigen [25]. F1 antigen (capsular antigen); F1 antigen is a capsule-forming protein encoded by the pMT1 plasmid, which plays an important role in Y. pestis' resistance to phagocytosis. The capsule forms a thick protective layer on the bacterial surface, making it resistant to lysis through the complement system and recognition and absorption by phagocytes [7]. The F1 antigen possesses high immunogenic properties, and antibodies formed against it play an important role

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B and W antigens; B antigen (LcrV) and W antigen (YopB/YopD) are also important factors encoded by the pCD1 plasmid. Antigen B acts as a regulator of T3SS while simultaneously modulating the host's anti-inflammatory response. Antigen B suppresses the immune response by reducing the production of interferon-gamma (IFN-γ) in macrophages [15]. The W antigen is a component of the T3SS translocation apparatus and participates in the transport of effector proteins across the host cell membrane. The combined activity of B and W antigens ensures the adaptation of Y. pestis to the intracellular environment [19]. As a gram-negative bacterium, Y. pestis has a lipopolysaccharide (LPS) on its outer membrane. The LPS of Y. pestis has lower endotoxin activity than that of other enterobacteria, which helps it survive in the host organism for a long time, escaping immune control [19]. The small number and relatively short acyl chains in the lipid A region of LPS lead to weak activation of the immune response via TLR4. This adaptation is an important part of Y. pestis' strategy to evade the host's initial immune control [20].

Ciderophores (yersinia bactin) Y. pestis requires iron ions to survive inside the body. In the host organism, iron is primarily found bound to proteins such as transferrin, lactoferrin, and ferritin. Y. pestis synthesizes a siderophore called yersiniabactin. This is a high-affinity chelator molecule that extracts bound iron from the host's proteins and delivers it to the bacteria [17]. The synthesis of yersiniabactin and its receptors are encoded by the ferric yersiniabactin uptake and iron-regulated protein genes. This system allows Y. pestis to reproduce even under conditions of iron deficiency [9]. Yersinia pestis is transmitted by the subcutaneous or mucosal bites of fleas (mainly Xenopsylla cheopis). The inoculated bacteria initially trigger a local inflammatory response, but they quickly avoid phagocytosis using the T3SS and F1 antigens. The bacteria travel through the lymphatic vessels to the regional lymph nodes, where they multiply intensively, forming an inflammatory focus called the "cholera bubo." This condition is characteristic of bubonic plague [21]. Necrosis and hemorrhagic inflammation develop in the lymph nodes as a result of the active release of Pla protease and inflammatory mediators produced by Y. pestis. The bacteria then move into the bloodstream, causing bacteriemia. This stage is called septicaemic cholera. In the septicemic form, endothelial cell damage, coagulopathy, and disseminated intravascular coagulation syndrome (DIC) may develop, leading to multi-organ failure [5]. Pneumonic cholera is considered the most severe form of infection. It can develop in two ways: first, as a result of infection spreading from the bubonic or septicemic form into the lungs (secondary pneumonic cholera); second, as a result of airborne transmission from an infected patient (primary pneumonic cholera). In the lungs, Y. pestis proliferates rapidly, causing hemorrhagic necrotic pneumonia. In this case, Pla protease enhances fibrinolytic and proteolytic breakdown in the alveoli, further accelerating the penetration of bacteria into the blood [2].

Mechanisms of immunomodulation; Y. pestis suppresses the host's innate and acquired immune response through several mechanisms. The aforementioned T3SS effectors (YopJ, YopH, YopE, YopT, etc.) directly block the phagocytosis, bactericidal, and antigen-presenting functions of macrophages and neutrophils. In particular, the YopH protein possesses tyrosine-phosphatase activity and disrupts the signaling pathways of cytoskeletal reorganization in phagocytes. As a result, phagocytes lose their ability to swallow and break down bacteria [4]. Furthermore, the LPS of Y. pestis weakly activates signal transmission via TLR4, inhibiting the maturation of dendritic cells and the secretion of inflammatory cytokines. This leads to a delay in the activation of the acquired immune response, especially T-lymphocytes [23]. Factors such as genotype, age, and immune status significantly affect the course of Y. pestis infection.

Individuals with weakened immunity have a high risk of developing septicaemic and pneumonic forms. Additionally, a more severe course of the disease is observed in childhood and old age [11]. When Y. pestis enters the body, local normal microflora can play a certain protective role in its colonization and the development of pathogenic effects. Symbiont microorganisms in the skin and mucous membranes provide colonization resistance, thereby limiting the proliferation of pathogenic bacteria. However, the high invasiveness and immunosuppressive properties of Y. pestis allow it to overcome these defense mechanisms [3].

Conclusions. Summarizing the above data, the pathogenicity of Yersinia pestis, the causative agent of cholera, occurs as a result of the combined activity of several complex and interconnected virulence factors. The high level of danger posed by this bacterium is directly linked to its ability to effectively evade the body's natural defense mechanisms. Specifically, the type III secretory system (T3SS) allows the bacterium to suppress the immune response and disrupt phagocytosis by delivering specific proteins to host cells. Capsular antigen F1 forms a protective layer on the bacterial surface, preventing it from being absorbed by phagocyte cells. Pla protease enhances invasion of body tissues, helping the bacterium spread rapidly through the lymphatic system and bloodstream. Antigens B and W suppress the activity of immune system cells, weakening the inflammatory response.

Furthermore, siderophore systems facilitate the metabolic activity of the bacterium by absorbing iron ions, significantly increasing its ability to survive and reproduce within the body. Although each of these factors is of particular importance, their complex and synergistic effect determines the high virulence of Yersinia pestis and causes a severe course and rapid development of the disease. Therefore, an in-depth study of the mechanisms of virulence at the molecular level of this pathogen is one of the most pressing areas of modern medical microbiology. Such research is of great scientific and practical importance in the development of next-generation vaccines, the creation of effective therapeutic drugs, and the prevention of the spread of antibiotic-resistant strains. Overall, a deep understanding of the virulence mechanisms of Yersinia pestis will play a crucial role in the future control of cholera and reducing its risk to global health.

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