



Review article

Staphylococcus aureus: Immunopathogenesis and Human Immunity

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SUMMARY

Considering a large number of pathogen factors that enable high virulence of a microorganism such as *Staphylococcus aureus* (*S. aureus*), it is essential to see them through the continuous adaptation to the newly acquired mechanisms of the host immune response and efforts to overcome these, allowing the bacteria a perfect ecological niche for growth, reproduction, and location of new hosts. Past efforts to create a vaccine that would provide effective protection against infections caused by *S. aureus* remained without success. The reasons for this stem from the outstanding adaptability skills of this microorganism to almost all environmental conditions, the existence of a numerous virulence factors whose mechanisms of action are not well known, as well as insufficient knowledge of the immune response to *S. aureus* infections. This review article deals with this issue from another perspective and emphasizes actual knowledge on virulence factors and immune response to *S. aureus*.

Key words: Staphylococcus aureus, virulence factors, immunity

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INTRODUCTION

S. aureus was discovered by Alexander Ogston (1844 - 1929), a Scottish surgeon in 1880, as the major cause of pus: "My delight may be conceived when there were revealed to me beautiful tangles, tufts and chains of round organisms in great numbers, which stood out clear and distinct among the pus cells and debris...", but its "godfather" was Anton J. Rosenbach (1842 - 1923), also a surgeon, a German, who isolated two strains of staphylococci in 1884, which he named after the pigmented colonies (1).

Staphylococcus aureus (old Greek: staphyle - "grape" and kokkos - "granule"; From Latin aureus - "golden"), Gram-positive cocci (GPC), is probably one of the most important pathogenic species because of its natural virulence, that is, the ability to cause a variety of life-threatening infections, as well as the adaptive capacity to different environmental conditions (2). An average of the mortality rate of *S. aureus* bacteremia is still 20-40%, despite the availability of effective antibiotics (3). As the leading cause of nosocomial infections, and occasionally the cause of infections in seriously ill outpatients, *S. aureus* raises the possibility of isolation of methicillin-resistant staphylococci (4).

S. aureus is a ubiquitous microorganism that resides in the surrounding area, animals, and as a colonizer of the superficial regions of the skin and mucosa in adults it occurs in 20% to 40% of cases. The other sites of colonization include intertriginous areas of the skin, perineum, axilla, and vagina. Although these organisms constitute part of the normal human microflora, under certain conditions, they can cause significant opportunistic infections (5). The individual risk factors of contracting severe infections caused by *S. aureus* can be a disturbance in leukocyte chemotaxis (congenital origin, such as the Wiskott-Aldrich syndrome, Down syndrome, and Job syndrome) or acquired risk factors (such as diabetes mellitus, rheumatoid arthritis); defect in opsonization caused by antibodies (hypogammaglobulinaemia); disruption of intracellular killing of bacteria during phagocytosis (in chronic granulomatous disease); skin injuries (burns, surgical wounds, eczemas); the presence of foreign bodies (sutures, intravenous catheters, plastic materials); other infectious agents, especially viruses (such as influenza); chronic non-communicable diseases (malignancy, alcoholism and heart disease).

Under the above mentioned conditions, *S. aureus* can cause various infectious processes starting from

relatively mild skin infections to systemic life-threatening diseases. Skin infections may appear in the form of folliculitis, impetigo, furuncle and carbuncle. *S. aureus* is often isolated from infected surgical wounds that are the cause of the development of systemic infections. Staphylococcal bronchopneumonia is usually seen in the elderly population, and it is associated with viral pneumonia as a predisposing factor. Malignant disease is considered important risk factor for developing *S. aureus* bacteremia (6). *S. aureus* is able to disseminate to distant sites in the host provoking endocarditis, osteomyelitis, and pyogenic arthritis and to form metastatic abscesses in the skin, subcutaneous tissue, lungs, liver, kidneys, and brain. Staphylococcal meningitis occurs in patients with an abnormality of the central nervous system that is caused by trauma, surgical procedure, malignancy, or hydrocephalus. This microorganism is the second leading cause of meningitis in patients with ventriculoperitoneal shunt (7). *S. aureus* can be the cause of peritonitis in patients on CAPD (continuous ambulatory peritoneal dialysis) (8). Staphylococcal toxins are also responsible for staphylococcal epidermal necrolysis (staphylococcal scalded skin syndrome) and toxic shock syndrome (9). Additionally, production of staphylococcal enterotoxins in food can lead to food poisoning because they are resistant to acidic stomach pH.

VIRULENCE FACTORS

S. aureus virulence factors are numerous. They can be classified as parts of bacterial cells included in pathogenesis and substances that bacteria excrete into the environment. Structures of bacterial cell involved in pathogenesis are: capsule, protein A, and teichoic acid. Also, nearly the all strains of *S. aureus* excrete a group of extracellular products such as exoproteins: nucleases, proteases, lipases, hyaluronidase, and collagenase, as well as exotoxins: α -hemolysin, β -hemolysin, γ -hemolysin, leukocidin, and Panton-Valentine leukocidin (PVL)(10). Their ability to produce β -lactamases provides an efficient defense against antimicrobial drugs. Very important feature of *S. aureus* is its ability to multiply with only few synthesizing enzymes necessary for growth. That ability which enables surviving in unfavorable conditions unfortunately lead to the loss of enzymes' machinery necessary for the synthesis of virulence factors and resistance to antimicrobials (11).

Also, there are nucleotide signaling pathways that allow rapid alteration of cellular physiology to promote *S. aureus* survival. This is of particular importance when bacteria are faced with unfavorable environmental conditions. In that case, it is necessary to acquire the alternative sugar sources and to adapt during stresses such as amino acid deprivation, carbon source starvation, fatty acid depletion, or osmotic stress. In *S. aureus*, the main role have small nucleotides such as cyclic diadenosine monophosphate (c-di-AMP) and pentaphosphate (p)ppGpp. Examination of the transcriptional profile of *S. aureus* with under stress conditions provides evidence that high levels of c-di-AMP lead to an activation of the stringent response through a RelA/SpoT homologue (RSH) enzyme-dependent increase in the (p)ppGpp levels. Also, this activation is indirect as c-di-AMP does not interact directly with the RSH protein (12).

Bacterial cell structures

Cell wall of *S. aureus* as a Gram-positive bacterium contains glycopolymers including wall teichoic acid (WTA) that is a part of peptidoglycan and capsular polysaccharide (13).

Capsule

Some strains of *S. aureus* produce exopolysaccharide that can prevent polymorphonuclear cells to destroy microorganisms by phagocytosis. This exopolysaccharide can be found in strains of *S. aureus* that cause infections in people with pacemakers, peritoneal catheters or intravenous catheters, and can be demonstrated using in vitro methods. The exopolysaccharide-producing strains are called Smith strains (14). Exopolysaccharide can accelerate the bacterial adherence to both a host cell and plastic materials. Based on capsular polysaccharide immunotype, *S. aureus* clinical isolates are classified into eight types, and 70% to 80% belong to serotype 5 or 8 (15). These two capsular serotypes, mainly serotype 8, can be associated with other virulence factors of *S. aureus*, such as toxigenesis, leading to toxic shock (toxic shock like syndrome, TSLS). The most of oxacillin-resistant *S. aureus* isolates belong to capsular serotype 5 (16, 17). Capsular polysaccharide serotypes 5 and 8 are also found in many *S. aureus* isolates taken from animals.

Wall teichoic acid (WTA)

WTA of *S. aureus* was originally described as 4-O- β -N-acetyl-n-glucosaminyl-n-ribitol units joined by 1,5-phosphodiester linkages (18). It is glycopolymer that forms peptidoglycan by covalent bonding. *S. aureus* WTA, a cell wall glycopolymer, can be defined as ribitol phosphate substituted with α - or β -ON-acetyl-D-glucosamine (GlcNAc) and D-alanine, which can be recognized by serum anti WTA IgG and mannose-binding lectin (MBL), important host defense factors for host specific and non-specific immune response, respectively (13).

This polymer whose molecules (40 - 50) are comprised of repetitive ribitol-phosphate units, allows *S. aureus* to adhere in a specific way to the mucous membranes, and thus to the nasal mucous membrane. WTA is responsible for resistance to lysosomes and antimicrobial peptides as well as for evading host immune response (13). Besides giving firmness and elasticity of the cell wall, both peptidoglycan and WTA have other biological activities: complement activation, inhibition of chemotaxis, and stimulation of antibody production (5).

During an immune response, inflammatory chemokine receptors on the macrophage surface (chemokine, CC chemokine receptors), CCR1, CCR2, and CCR5, are involved in the accumulation of blood monocytes in the infected tissue. Toll-like receptors (TLRs) on the surface of host cells allow identification of pathogenic microorganism by the accumulated cells. In the case of Gram-positive bacteria such as *S. aureus*, one of these pattern recognition receptors (PRR), the Toll-like receptor 2 (TLR2), is responsible for the recognition of bacterial cell-wall components and is essential for protective innate immune responses. Triggering TLR2 activation can induce diverse cell responses through different signaling pathways. The data indicate that TLR2, after contact with *S. aureus* lipoteichoic acid (LTA), negatively regulates the activity of monocytes through CCR1, CCR2, and CCR5, helping in chemokine-dependent down regulation and ensuring molecular mechanisms that inhibit monocytes migration after *S. aureus* identification (19).

Protein A

The cell wall of *S. aureus* contains a unique protein A that has the ability to bind to the Fc region of immunoglobulin G (IgG). The protein A is bound to the peptidoglycan of the bacterial cell wall, but it is released into the culture medium during growth. This protein inhibits microorganism opsonization and phagocytosis by polymorphonuclear cells and the complement activation (5).

Besides that, the protein is an immunogen, stimulates B lymphocytes, and is responsible for the formation of antibodies that are found in patients with severe *S. aureus* infections (20).

EXOPROTEINS, EXOTOXINS AND β -LACTAMASE

Exoproteins

S. aureus produces several enzymes that may contribute to its virulence: catalase, coagulase, fibrinolysin, hyaluronidases, lipases, phosphatidyl inositol - specific phospholipase C.

Catalase

This microorganism produces catalase that inactivates the toxic hydrogen peroxide and free radicals formed under the action of myeloperoxidase in the process of phagocytosis after ingestion has taken place. Catalase can be considered as a one of the main virulence factors, since its activity in bacterial cell protects intraphagocytic microbes by destroying hydrogen peroxide produced by the phagocyte cells. In addition, good correlation is established between staphylococcal catalase activity and mouse lethality (21). In human, it is shown that *S. aureus* catalase in children receiving pneumococcal vaccine combat for the same niche since *S. pneumoniae* produces H_2O_2 . *S. aureus* catalase contributes to the survival of this pathogen in the presence of *S. pneumoniae* both in vitro and in vivo (22).

Coagulase

Both free and bound coagulase (also called the clumping factor) can coat bacterial cell surface with fibrin to make it resistant to opsonization and phagocytosis. During infection, *S. aureus* secretes two types of coagulase (Coa) and von Willebrand factor binding protein (vWbp) that, after binding with fibrinogen and prothrombin, create fibrin clot that protects the microorganism and enables the development of infection. The genetic basis of these may vary allowing the classification of different types. It has been shown that antibodies affect the variable part of coagulase allowing the acquisition of the type-specific immune system, thereby disabling *S. aureus*

protection, that eventually provides protection from infection. The scientists were able to develop the vaccine that is expected to provide protection against different types of *S. aureus* coagulase by combining variable parts of the isolates from North America and creating the Coa hybrids and vWbp proteins (23).

Fibrinolysin

Fibrinolysin can degrade fibrin thus facilitating the spread of infection to the surrounding tissue. Plasminogen and C3 / C3b can bind simultaneously to the bacterial surface proteins, and these are immunoglobulin-binding protein (Sbi) and extracellular fibrinogen-binding protein (Efb). Accumulated plasminogen remains accessible to the human activator (uPa) or bacterial plasminogen activator staphylokinase (SAK), which enables its conversion into active plasmin. Plasmin bound to Sbi or Efb degrades and inactivates the C3 and C3b. Degradation of C3a results in inactivation of its antimicrobial activity. The proteins originating from *S. aureus* (Sbi and Efb) are believed to inhibit the progression of the complement cascade, opsonization, antimicrobial activity and inflammatory reaction (24).

Hyaluronidase

Hyaluronidase cleaves the β -1,4 glycosidic bond of glycosaminoglycans – GAGs in intercellular matrix of tissue, allowing the microorganisms to spread in the immediate surroundings. Investigation on experimental animals showed that *S. aureus* hyaluronidase is a CodY-regulated virulence factor. Mice infected with mutant strains carrying mutation of the CodY binding box exhibited a 4-log-unit reduction in bacterial burden in their lungs, reduced lung pathology and increased levels of pulmonary hyaluronic acid, compared to mice infected with the wild-type, parent strain. These results can give insight into the possible reduction of the strain virulence, especially in patients with lung infection (25).

Lipase

Lipase is an enzyme that allows the *S. aureus* to spread through the skin and subcutaneous tissue, causing chronic furunculosis. Although the production of the lipase varies among different sources, especially non-human, in one investigation

86% of the isolates from human wounds were positive for lipase production, indicating its importance in tissue damage (26).

Phosphatidylinositol-Specific Phospholipase C

Phosphatidylinositol-Specific Phospholipase C (PI-PLC) is found in adults with respiratory distress syndrome and disseminated intravascular coagulation. Tissues affected by this enzyme become much more sensitive both to the complement components and to the products formed during the reaction of the complement activation. In one investigation of MRS, potential links between *S. aureus* responses to the host innate immune system and to oxidative stress were identified and supported the PI-PLC contribution to the pathogenesis of *S. aureus* infections (27).

Exotoxins

S. aureus toxins exhibit several biological activities. *S. aureus* produces exotoxins that possess cytolytic activity. Cytolytic toxins (Cytolysin) form β -cylindrical pore in the plasma membrane causing a leakage in the cell and thus lyse the target cell (15). *S. aureus* secretes several cytolysins, including α -hemolysin, β -hemolysin, γ -hemolysin, leukocidin, and Panton-Valentine leukocidin (PVL) (10).

Alpha-toxin (α -toxin) expresses cytotoxic activities on a wider range of cell types, including human polymorphonuclear cells, and it is able to lyse the red blood cells of several different animal species. The toxin causes necrosis of the dermis when administered subcutaneously, and for animals, it is lethal when injected intravenously. It is also a powerful neurotoxin. This toxin is responsible for the formation of the hemolytic zone around a colony of some *S. aureus* types on a blood agar supplemented with sheep blood.

Beta-toxin (β -toxin) is a neutral sphingomyelinase that affects different cells. The activity of this hemolysin is temperature-dependent (28). *S. aureus* Gamma toxin (γ -toxin) belongs to the group of pores forming toxins (PFTs) and causes lysis of various cells. In contrast with the α -hemolysin, for the pore-forming activity, the γ -toxin requires the presence of two polypeptides entitled slow (S) and fast (F) on the basis of their electrophoretic mobility. There are various *S. aureus* two-component PFTs that exhibit

significant similarity to the amino acid composition (28).

Delta-toxin (δ -toxin) acts primarily as a surfactant, and also is able to activate adenylyl cyclase causing the production of c-AMP. The δ -hemolysin is a small amphipathic (has both hydrophobic and hydrophilic ends) peptide with α -helical structure consisting of 26 amino acids. The toxin causes cell lysis by three different mechanisms: by binding to the cell via formation of transmembrane pores; the binding causes destabilization of the cytoplasmic membrane; in high concentrations acts as a detergent that dissolves the membrane (28).

Some of these toxins are classified in the phenol soluble modulins (PSMs) peptide class produced by both *S. epidermidis* and *S. aureus* (29). Furthermore, the PSMs are classified into two families based on their size. In the first are those of up to 26 amino acids (AA) (PSM α) and the second includes other proteins up to 40 AA (PSM β 1 and PSM β 2) (28).

Leukocidin stands out as an exotoxin that is directly toxic to the cell membrane of human polymorphonuclear, causing degranulation of the cytoplasm and lysis. It consists of two components that act synergistically causing severe granulocytopenia in experimental animals. This toxin also forms pores that modify the permeability of the cell membrane to potassium and various cations (30).

PVL is a two-component cytotoxin. This virulence factor is associated with serious illnesses (31). Synthesis of PVL is encoded by the genes lukS-PV, lukF-PV (integrated into *S. aureus* chromosome, LukED, and LukGH (synonym LukAB) (32). The structure and method of operation are similar to other binary toxins, as well as the mechanism of pore creation (33). Each water soluble component binds sequentially to the cell surface, as a monomer, before the oligomerization with four S components and possibly also with four F components. The newly created hetero-octamer forms a transmembrane pore in the plasma membrane leading to lysis of cell. These toxins are largely secreted into the external environment. Protein LukGH/AB can either be secreted into the environment, or be the one of the dominant surface protein of *S. aureus* in the late exponential phase of growth (32).

Perhaps a moment of binding to the cell surface is of importance when it comes to leukotoxin, the moment in which it binds to immune cells, that is, when they are in direct contact with bacterium, as it is in the phagocytosis (28).

The importance of leukotoxin binding to the cell surface might be in its binds to immune cells when they are in direct contact with bacterium, as it is in the phagocytosis (28).

Exfoliatin or epidermolytic toxin is produced by certain strains of staphylococci. There are two exfoliatins labeled ET-A and ET-B, each of them with a relative molecular mass of 24kDa (5). These two molecules are immunologically and biochemically different but share the same biological activity. ET-A is a thermostable protein with the genes encoded on the chromosome, while ET-B is thermolabile and originates from plasmid. These proteins have a proteolytic activity and separate glycosaminoglycanic matrix of epidermis, resulting in separation of intraepithelial cell connections of the stratum granulosum (granular layer) (33). Strains producing either one or both of these toxins are responsible for scalded skin syndrome. Both toxins are antigens and stimulate production of host-protective antibodies.

Enterotoxin, marked by big Latin letters A, B, C, D, and E, are thermostable and responsible for the clinical presentation of staphylococcal food poisoning. The exact mechanism of action of these enterotoxins is not clear, but it is known to accelerate peristalsis. Consumption of food contaminated by enterotoxins created during the propagation of staphylococci result in diarrhea within next 2-8 hours. Their presence can be proven by immunodiagnostic methods as well as molecular biology techniques (34).

Toxic shock syndrome toxin-1 (TSST-1), leads, as its name says, to toxic shock syndrome, which was first described by Todd and his associates in 1978, and soon after that, in 1981, two groups of researchers isolated this unique *S. aureus* toxin in these patients and announced its structure (35,14). The toxin is denoted as TSST-1. Although this toxin has a wide range of biological activities, its role in the formation of toxic shock syndrome remains unclear. Toxic shock syndrome is a multisystem disease characterized by: fever, hypotension, erythrodermia, vomiting, diarrhea, renal failure, headache and conjunctivitis. The disease was first observed in women using hyper-absorptive tampons during their periods. Afterwards, the disease was found in both sexes in patients with staphylococcal abscesses, osteomyelitis, after surgery wound infections, and post viral pneumonia (9).

TSST-1, staphylococcal enterotoxin and exfoliatin can act as superantigens. Superantigens do not present the professional antigen-presenting cells

(APC) such as mononuclear cells, do not bind to the receptor sites of cells (T cell receptor TCR) on CD4 + T lymphocytes, but to the V β domain of the TCR, and directly activate a large number of nonspecific T lymphocytes clones, leading to the release of large quantities of TNF into the circulation along with emergence of the systemic complications and shock (36).

Beta-lactamase

Drug and multidrug resistance mechanisms have recently been considered as virulence factors in pathogenic bacteria. The emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) infections in individuals with no predisposing conditions suggests an increased pathogenicity of the bacterium, which may be related to acquisition of novel genetic elements. *S. aureus* has developed the various strategies to evade obstacles laid out by the human host during colonization and infection. There are many controversies related to MRSA since acquisition of the novel genes could explain the increased incidence and severity of CA-MRSA diseases (37).

Numerous studies indicate that *S. aureus* produces at least three different types of β -lactamases. The production of these enzymes may be inducible (they produced only in the presence of β -lactam antibiotics) or constitutive (continuously produced), making these organisms resistant against β -lactam antibiotics. The synthesis of the enzyme encoded by genes is mainly found on the plasmids that often carry the gene for resistance to several other antibiotics such as erythromycin and tetracycline (5).

Most β -lactamases belong to the family of serine peptidase. These enzymes are produced by some bacteria and are responsible for the resistance to β -lactam antibiotics, although the cephalosporins are relatively resistant to their action. Beta-lactamases catalyze the hydrolysis and opening of the β -lactam ring resulting in its deactivation. Beta-lactamases can be divided according to the mode of action and chemical (molecular) structure. According to the mode of action, that is, based on the enzyme substrate specificity, β -lactamases were divided into four groups. The first group includes molecular class C cephalosporinases that are not inhibited by clavulanic acid (38). The second group that can be divided into several sub-groups (2a-2f) includes clavulanic acid-inhibitable penicillinases and cephalosporinases. By

the chemical structure they belong to the molecular class A, with the exception of sub-2d that belongs to both classes A and D. Group 3 consists of molecular class B zinc metalloenzymes that are not inhibited by clavulanic acid. The fourth group contains penicillinases that, for now, are not classified, whose activity is not inhibited by clavulanic acid (38).

Extended-spectrum beta-lactamases (ESBLs) are divided into: class A beta-lactamases, TEM SHV, CTX-M, class D beta-lactamases, OXA and other beta-lactamases (PER, VEB, GES, and IBC). For the long time, OXA beta-lactamases are known as relatively rare but plasmid-localized, capable of hydrolyzing oxacillin. These enzymes are responsible for ampicillin and cephalothin resistance, and have a pronounced hydrolytic activity against oxacillin and cloxacillin. They are poorly inhibited by clavulanic acid (39).

IMMUNOPATHOGENESIS OF *S. AUREUS* INFECTION

Bacterial surface molecule identifies a series of similar receptors located on the surface of the host cell and whose role is the recognition of pathogenic bacteria (pathogen recognition receptors, PRRs). When it comes to the recognition of lectin components, these receptors are mannose-binding lectin (MBL). MBL binds mannose functioning both as an opsonin and lectin-mediated complement activator. Activation of classical pathway of the complement along with anaphylatoxin formation results in the generation of proinflammatory signals and piling up of phagocytes. It is believed that the immune complexes induce phagocytosis via of *S. aureus* cell-surface Fc receptors (FCRs). Considering that *S. aureus* has a thick peptidoglycan layer, opsonization by serum antibodies is necessary to prevent phagocytosis of *S. aureus*. MBL deficiency on the surface of susceptible cells increases susceptibility to *S. aureus* infection in laboratory animals. In this way, the phagocytosis plays an important role in host defense, particularly against *S. aureus* MRSA strains (13).

Immune evasion

Important role in immunity to microbes are the mechanisms of immune evasion. In *S. aureus*, several proteins take part in those mechanisms: staphylokinase (encoded by *sak*), chemotaxis

inhibitory protein (*chp*), and staphylococcal complement inhibitory protein (*scn*), as well as particular enterotoxin encoded by genes such as *sea*, *sep*, *sek*, and *seq* (40). It seems likely that the expression of superantigens promotes the survival of *S. aureus* in the host by undermining the neutrophil response, leading to formation of a protective niche. In response to antibiotic usage in livestock farming, as well as human therapy of severe disease and gene accumulation in nosocomial strains, adaptation to the animal and human host is often accompanied by the acquisition of resistance genes such as *tet(M)* and *mecA* (41).

After the adherence to a target cell, *S. aureus* can be found within professional or non-professional phagocytes, such as epithelial or endothelial cells, both within membrane and cytoplasm, thanks to the surface structures and penetration into tissue or circulation.

The bacteria can escape into the cytoplasm due to the activities of δ -toxin or synergistic action of $\text{PSM}\beta$ and β -toxin. The explanation for the presence of *S. aureus* in the phagocytes of patients with cystic fibrosis is probably that the α -hemolysin is included in the lysis of the phagosomal membrane (42).

Intracellular bacteria may also lead to dissemination within migrating phagocytes. Further, *S. aureus* lyses host cells with a cytolytic toxins. Phenol-soluble modulins (PSM) comprise a genus-specific family of cytolytic peptides which are implied in killing polymorphonuclear leukocytes. In non-professional and professional phagocytes, $\text{PSM}\alpha$ mutants are unable to escape from phagosomes. Fortunately, offspring of *S. aureus* producing $\text{PSM}\beta$, δ and β -toxins, and Pantone Valentine leukotoxin escaped as efficient as the parental strains (43).

Local immunization or infection

Recruits of neutrophils from the blood to lymph nodes occur in waves where neutrophils infiltrate the medulla and interfollicular areas. Neutrophils interact with B cells and plasma cells, leading to production of antigen-specific IgG and IgM. In response to a local bacterial challenge, mobilized neutrophils dampen the early humoral response in the lymph node (44).

β -hemolysin inhibits IL-8 whose main activity is the accumulation of neutrophils and this is the important mechanism for immune evasion. The inhibition of IL-8 which is synthesized by endothelial

cells leads to the reduction in neutrophil migration through the endothelial barrier. This fact indicates that β -hemolysin can act as one of the chemotaxis inhibitors produced by *S. aureus* (45).

Virulence gene expression

S. aureus gene expression is under the regulation of the surrounding bacterial milieu, protein synthesis, mRNA up or down regulation.

Environmental factors such as nutrient availability, temperature, pH, osmolarity, and oxygen tension have the greatest potential to influence the expression of virulence factors. Protein synthesis can influence virulence gene expression, too. Therefore, virulence gene regulators could affect the expression of target genes directly, by binding to their promoters, or indirectly, via other regulators (10). Several global regulatory loci determine the production of *S. aureus* virulence factors: accessory gene regulator (*agr*), which controls at least 15 *S. aureus* products such as extracellular toxins and enzymes: alpha-, beta-, and delta-hemolysin, leucocidin, lipase, hyaluronate lyase, and proteases. For those reasons, *agr* system of *S. aureus* is an important virulence determinant in the induction and progression of septic arthritis experimental animals (46). One investigation emphasized that *arl* positively regulates capsule production at the transcriptional level primarily through an *mgrA*-dependent pathway. The *sigB* gene *S. aureus* mutant was deficient in clumping factor, coagulase, and pigment synthesis, indicating its possible contribution in virulence regulation although in three models on experimental animals, the mutant showed no reduction in virulence (47).

Important feature of *S. aureus* gene regulation is that several regulator proteins can influence one target virulence gene. That "cross talk" is to ensure that the specific gene is expressed only when it is necessary and conditions are favorable (10). E.g., *agr* negatively regulates the expression of *spa*, which encodes SpA protein by suppressing the expression of its activator, *sarS* (10).

Regulation of virulence on messenger ribonucleic acids (RNAs) mRNA level can lead to down or up-regulation of several virulence genes. In *S. aureus*, there are expression patterns of at least 250 different regulatory RNAs. So far, physiological functions are described in only few of them. One of them, RNAIII, combines quorum sensing with virulence gene regulation. RNAIII acts as a messenger

RNA (mRNA), encoding the δ -haemolysin peptide. Its regulatory functions are: participating in activation of translation of α -haemolysin and repressing the translation of several virulence factors and toxins reducing early expression on virulence. One of RNAIII target is the SpA immune evasion molecule, whose expression is downregulated at both transcriptional and translational levels. Small pathogenicity island RNA D (SprD), is a horizontally acquired pathogenicity island from the converting phage that is a repository for many toxins, adherence and invasion factors, superantigens and secretion systems. However, SprD downregulates the translational expression of the immune evasion molecule. SprD may significantly contribute to disease incidence in a mouse model of staphylococcal infection (48).

Biofilm formation

Biofilm synthesis enables the survival of *S. aureus* and other pathogens in harsh conditions. The locus termed *ica*, described first in *S. epidermidis*, is responsible for biofilm formation in *S. aureus*, too. This locus was found widespread present in biofilm producing *S. aureus* strains responsible for catheter and implant infections (49).

Chemical compounds of the main exopolysaccharide component of biofilm matrix in *S. aureus* and *S. epidermidis* clinical strains are similar and some of them are even identical e.g. poly- β (1-6)-N-acetylglucosamine (PIA/PNAG) (50). It seems that many bacteria, among them Gram-negative ones, produce the very same biofilm matrix such as *Escherichia coli*, *Yersinia pestis*, *Pseudomonas fluorescens*, *Bordetella spp.*, *Xenorhabdus nematophila*, *Aggregatibacter actinomycetemcomitans*, and *Actinobacillus pleuropneumoniae*, suggesting a convergent evolution of some adaptation mechanisms. In *S. aureus*, there are alternative forms of biofilm that are PIA-independent. The observation that a minor proportion of *S. aureus* strains can form biofilm even in the absence of the *ica* locus and that certain strains carrying such locus continue anyway to produce biofilm even after deletion of the locus suggested the existence of *ica*-independent pathways (51). Also, surface proteins such as SasG, SasC, Protein A, and two fibronectin-binding proteins, have been documented to contribute to biofilm formation in *S. aureus*. However, *S. aureus* clinical strains involved in severe infections are all generally endowed with the *ica* locus. The existence of alternative mechanisms

of biofilm formation provide better adaptation of *S. aureus* to the surrounding milieu and ensures the mechanisms for survival, in order to colonize and establish the infection in host tissues, while evading the immune response and the effects of antibiotic treatments.

Against the biofilm formation in *S. aureus*, humans apply several approaches: (a) biofilm disaggregating enzymes that attack the PNAG (Dispersin B); (b) the extracellular DNA (DNase I); (c) proteinase K; (d) quorum quenching (QQ), intercellular bacterial communications, with the aim of artificially inducing bacteria to assume sessile phenotype; (e) the prostaglandins reduce biofilm formation and stimulate clearance of the microorganism (52).

In *S. aureus*, some of newly detected phenol soluble modulins (PSMs), family of short, amphipathic, α -helical peptides, are the key virulence determinants, especially in invasive *S. aureus* diseases. Their role is to facilitate neutrophil lysis after phagocytosis, biofilm structuring and the dissemination of biofilm-associated infection. PSMs possess the surfactant properties which enable the growth on epithelial surfaces. They are able for strict and direct control by quorum sensing. It is possible that targeting PSMs for anti-staphylococcal drug development may be a promising approach to overcome the problems associated with widespread antibiotic resistance in staphylococci (53).

Quorum sensing

Quorum sensing (QS) system is on signal molecules often referred to as pheromones or autoinducers. The QS system enables bacteria to sense their own density in the milieu and modify their phenotype accordingly. This involves ruling the expression of distinct traits for the specific cellular phase of growth and/or milieu colonization. It seems that QS play an important role in surviving of *S. aureus* and causing infection. QS in *S. aureus* is involved in biofilm formation causing severe diseases. There is evidence that accessory gene regulator (*agr*) quorum-sensing system plays an important role in QS. Generally, *agr* expression enhanced biofilm formation. Expression of the *agr* quorum sensing cascade induces *S. aureus* to synthesize an extensive battery of exoproducts: enzymes, hemolysins and immunomodulators essential to its ability to disrupt intercellular matrix through and spread to the host tissues causing disease (54).

In *S. aureus* biofilm, under some conditions, influenced by environmental factors, cells changed their behavior. Those strains were very sensitive to rifampin but not to oxacillin. Biofilm expression of an *agr*-dependent reporter occurs in patches within cell clusters and oscillates with time. Detachment of cells expressing *agr* from biofilms may have important implications to disease severity and outcome especially with concomitant antimicrobial therapy (55).

Vaccines

Among all bacterial vaccines still missing, *S. aureus* is probably one of the most difficult to develop for a number of reasons. So far, there is no clear evidence of natural protective immunity against *S. aureus*, and there are no correlates of protection established yet. Vaccination attempts against *S. aureus* have not been successful so far and there must be numerous important reasons. One of them is the synthesis of a substantial number of molecules that take part in pathogenesis. Further, *S. aureus* possesses a battery of molecules responsible for diminishing the immune response; it also enables the immune evasion, which not only suppresses immunity but also undermines the majority of attempts to create effective vaccines. Third reason which should not be neglected is a large proportion of at-risk population which includes immune-compromised subjects (e.g., HIV, cancer and hemodialysis patients, patients with malignancy of hemopoietic cells and application of invasive therapy such as chemotherapy and immunomodulators, patients with metabolic disorders such as diabetes mellitus) and aging of the human population in developed countries (56).

Taking into account these considerations, strategy to develop a *S. aureus* vaccine could be the selection of antigens with different roles in pathogenesis, increasing the reliability and predictive value by using different mouse models and functional assays, and including an adjuvant that could elicit high antibody titers and potentiate vaccine efficacy (56). Perhaps the inhibition of binding to human host cells or vaccine against a common *S. aureus* antigens could lead to the resolution.

Ko et al. (2013) described a novel mechanism by which *S. aureus* can prevent uptake by phagocytic immune cells. Secreted *S. aureus* protein extracellular fibrinogen binding protein (Efb) generates a 'capsule'-like shield around the bacterial surface through a dual

interaction with the plasma proteins complement C3b and fibrinogen. The Efb-dependent fibrinogen shield masks important opsonic molecules like C3b and antibodies from binding to phagocyte receptors, since opsonizing antibodies may not function in the presence of this anti-phagocytic shield (57).

THERAPY

Therapy of *S. aureus* infections includes antibacterial drugs and surgical interventions. However, increasing resistance of *S. aureus* against recommended antibacterials, common isolation of MRSA in ICU, hospital environment and community diminish the effects of conservative approach. On the other hand, hidden location of infection, when finding efficient surgical approach, is a difficult task which may contribute to inefficient therapy. Therefore, including some immunomodulators can improve the outcome of systematic infection. It is observed that treatment with a combination of vasodilator prostaglandins, such as prostaglandin E1 (PGE1) and

prostaglandin E2 (PGE2), and antibiotics can lead to a rapid recovery from osteomyelitis in immunocompetent host, without the need for orthopedic surgery (53).

FUTURE PROSPECTS

Having in mind that *S. aureus* is widespread bacteria adapted to different and diverse life conditions, it is not difficult to assume that *S. aureus* will not easily leave its leading position among human bacterial pathogens. Humans will continue to search for the efficient antibiotic or vaccine or for the mechanisms to diminish the *S. aureus* pathogenicity. In response to aggressive attitude, bacteria will try to develop and to improve the mechanisms of pathogenicity gaining new factors, improving efficiency of existing ones and diminishing and ameliorating human immune response in order to survive the resistance mechanisms of macroorganisms.

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Staphylococcus aureus: imunopatogeneza i imunitet kod ljudi

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SAŽETAK

Brojni su faktori patogenosti koji omogućavaju visok stepen virulencije mikroorganizmu poput *Staphylococcus aureus* (*S. aureus*). Posebno je važno sagledati faktore sposobnosti stalne adaptacije na mehanizme imunskog odgovora domaćina, što bakteriji omogućava idealnu ekološku nišu za rast, razmnožavanje i širenje. Dosadašnji naponi da se dođe do vakcine koja bi omogućila efikasnu zaštitu od infekcija izazvanih *S. aureusom* ostali su bez uspeha. Razlozi za ovakvu situaciju se nalaze u izraženoj adaptaciji ovog mikroorganizma na gotovo sve uslove spoljašnje sredine, u postojanju velikog broja faktora virulencije čiji mehanizmi delovanja nisu dovoljno poznati, kao i nedovoljnog poznavanja imunskog odgovora na infekciju *S. aureus*. Svrha ovog rada je da se sa novijih aspekata sagleda navedena problematika i istaknu savremena saznanja o faktorima virulencije i imunskom odgovoru na *S. aureusu*.

Ključne reči: *Staphylococcus aureus*, faktori virulencije, imunitet