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MODERN APPROACHES TO ANTIVIRULENT THERAPY OF DISEASES ASSOCIATED WITH STAPHYLOCOCCUS AUREUS

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Staphylococcus aureus – це універсальний бактеріальний патоген, який здатний швидко розвивати резистентність до нових антибіотиків, перш за все за рахунок великого арсеналу факторів вірулентності, основна роль яких зводиться до поширення захворювання шляхом подолання імунних факторів захисту господаря. Широке поширення в стаціонарах, а також поява клінічних ізолятів Staphylococcus aureus, стійких до метициліну у позалікарняному середовищі, залишає лікарів без ефективних засобів контролю над цією інфекцією. Метою нашої роботи став аналіз основних факторів вірулентності S.aureus і шляхів впливу на них з позиції етіопатогенетичної терапії. Складність лікування бактеріальних інфекцій визначає актуальність впровадження в медичну практику альтернативних, більш ефективних засобів профілактики і лікування захворювань, до яких бактерії не здатні так легко і швидко розвивати резистентність. Поряд із загальними механізмами, які формують стійкість до антибіотиків, S.aureus продукує безліч індивідуальних факторів вірулентності, які моделюють імунну відповідь, впливаючи на виживання макроорганізму. Фактори вірулентності, що виробляються S. aureus різноманітні і мають здатність не тільки викликати лізис клітин, але і стимулювати відторгнення і руйнування тканин. Важливо відзначити, що більшість з них здатність специфічно видозмінювати як вроджені, так і адаптивні імунні реакції, включаючи пригнічення активації комплементу, нейтралізацію нейтрофілів і порушення функції фагоцитів. Стратегії пригнічення факторів вірулентності можуть варіювати від використання невеликих молекул-інгібіторів або повноцінних антитіл, до створення анатоксинів та білків вірулентності. Особливий інтерес представляють ті інгібітори, які, володіють перехресною реактивністю по відношенню до множинних факторів вірулентності, а також інгібітори, головна мета яких представляє собою глобальний регулятор з багатоцільовою активністю, наприклад agr оперон. Активні дослідження з вивчення конкретних альтернативних антивірулентних методів лікування тяжких форм захворювань, викликаних S.aureus потенційно можуть зупинити величезний потік проблем і труднощів, з якими ми стикаємося в постантибіотичну еру.

Ключові слова: *Staphylococcus aureus*, фактори вірулентності, бактеріальні інфекції

Staphylococcus aureus is a universal bacterial pathogen, which is able to develop the resistance to new antibiotics, by means of virulence factors, whose main function is the spread of diseases by inhibiting the immune factors of host defense. Its wide spread at in-patient departments and also the presence of clinical probationary wards Staphylococcus aureus, resistant to methicillin at out-patient departments, deprive the doctors of effective means for control of the infection. Complications caused by MRSA lead to hospitalization and indices of lethality. The aim of the paper is to analyze the main factors of S. aureus virulence and ways the of its interaction as a result of etiological and pathogenetic treatment. Complexity of treatment of bacterial infections is determined by alternative ways of prevention and treatment of diseases to which bacteria are not able to develop resistance. Along with general mechanisms that form antibiotic resistance, S. aureus produces many individual virulence factors that model the immune response, affecting the survival of the microorganism. The virulence factors produced by S. aureus are diverse and have the ability not only to cause cell lysis, but also to stimulate tissue rejection and destruction. It is important to determine that many specific factors of virulence caused by S. aureus, have ability to change both congenital and adaptive immune reactions including inhibition of complement activation, neutrophils neutralization, phagocytes inhibition. Strategies for inhibiting virulence factors can

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range from using small inhibitor molecules or full-fledged antibodies to creating toxoids and virulence proteins. Great interest is focused upon those inhibitors that have cross-reactivity with respect to multiple virulence factors, as well as inhibitors, the main target of which is a global regulator with multi-purpose activity, for example, agr operon. Active research into the specific alternative antivirulent treatments for severe diseases caused by S. aureus can potentially settle a number of problems and difficulties of post-antibiotic era.

Key words: *Staphylococcus aureus,* virulence factors, bacterial infections

Staphylococcus aureus is a universal bacterial pathogen, which is able to develop the resistance to new antibiotics, by means of virulence factors, whose main function is the spread of diseases by inhibiting the immune factors of host defense. Its wide spread at in–patient departments and also the presence of clinical probationary wards *Staphylococcus aureus*, resistant to methicillin (*methicillin-resistant Staphylococcus aureus, MRSA*) at out-patient department deprive the doctors of effective means for control of the infection. Complications caused by *MRSA* lead to hospitalization and indices of lethality. Complexity of treatment of bacterial infections is determined by alternative ways of prevention and treatment of diseases to which bacteria are not able to develop resistance.

Along with general mechanisms that form antibiotic resistance, *S. aureus* produces many individual virulence factors that model the immune response, affecting the survival of the microorganism [1]. The virulence factors produced by *S. aureus* are diverse and have the ability not only to cause cell lysis, but also to stimulate tissue rejection and destruction. It is important to take into account that many specific factors of virulence caused by *S. aureus* have the ability to change both congenital and adaptive immune reactions including inhibition of complement activation, neutrophils neutralization, phagocytes inhibition [2].

The aim of the paper is to analyze the main factors of *S. aureus* virulence and the ways of its interaction as a result of etiological and pathogenetic treatment.

Nowadays, alternative ways of staphylococci resistance were studied and the obtained results were analyzed [3] (Figure 1).

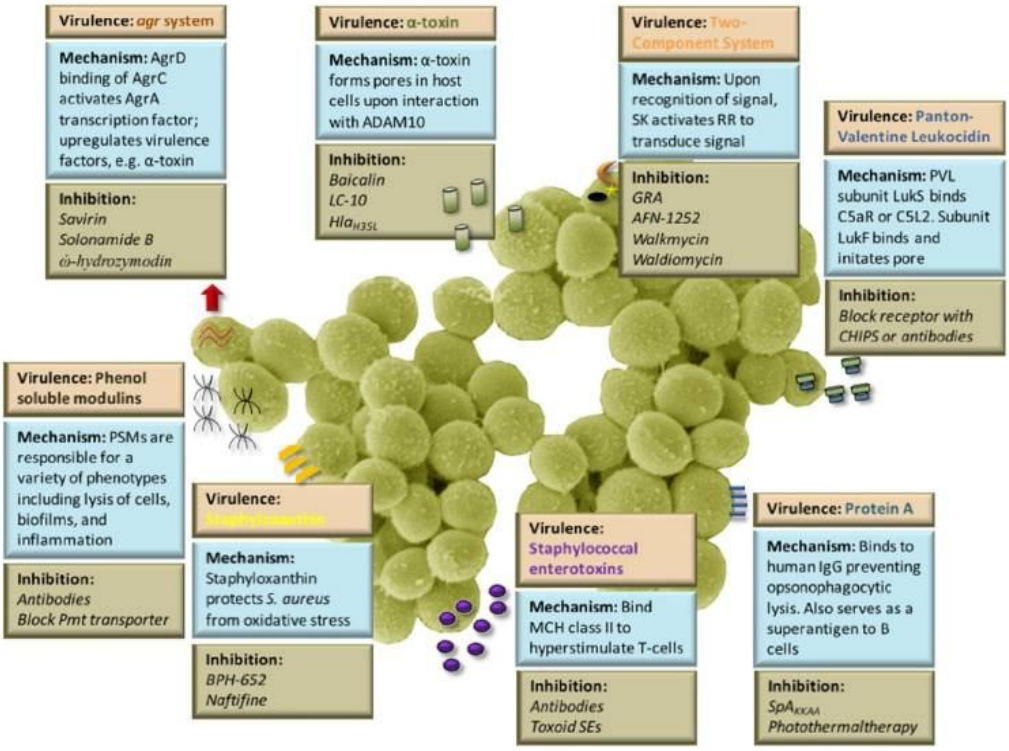

Figure 1. Factors of virulence, their functions and ways of inhibition [3].

One of the most significant pathogenesis of staphylococcal infections is the additional gene regulator (accessory gene regulator (*agr*)) of the operon system (a structural unit consisting of related genes that regulates other genes responsible for protein synthesis) was first discovered in the late 80s years of the last century. A therapeutic strategy focused on the *agr* system can be very effective, since by acting on it, it is possible to destroy many of the virulence factors associated with it, rather than oppressing each separately [4]. Determining the specific role of *agr* in the course of infection is complicated by different models of the course of diseases, the existence of different patient populations. When modeling acute infections in mice, there is clear evidence that *agr* is an important virulence factor [5]. In humans, a strong association has been found between the colonization of *S. aureus* in nosocomial infections with *agr* dysfunction [6]. In other studies, association was not found between *agr* deficiency and negative clinical outcomes. To establish a clear link between the *agr* operon and specific pathogenetic processes, further studies are needed because current research has led to various conclusions that may be associated with strain-specific differences. Considering well known factors of virulence, which regulate *agr*, strategy of interaction can be a target of antivirulent approaches to the treatment. During experiment on mice it has been established the influence of *agr* demonstrates the decrease of virulence of *S. aureus* associated pneu-

monia and dermonecrosis. Recently researches *Sully et al.*, were published where authors can define the small molecule of inhibitor AgrA affecting *agr* operon and it is called savirin (*S. aureus* virulence inhibitor). Using a model of infection of the skin and soft tissues in mice, the authors were able to define a reduction in tissue damage and a reduction in the bacterial load in the treatment of infections with savirin. Savirin blocks the binding of AgrA to its promoter sites, which further contributes to a change in the expression of most secreted virulence factors. Treatment by savirin does not inhibit "quorum sensing" with *Staphylococcus epidermidis*, and it indicates the specificity of the given inhibitor to *S. aureus* [7]. Inhibiting action on *agr* also has natural received from *Photobacterium halotolerans* cyclodepsipeptides called Solonamide B (Solonamide B) [8]. Additional inhibitor cluster of *agr*-genes was described by foreign scientists in 2015 [9]. They defined that ω-hydroxyemodin (OHM), small connection selected from *Penicillium restrictum* inhibits the function of quorum sensing *agr* operon by binding with promoter protein and by preventing the interaction of DNA. In the course of the experiment, the treatment of *S. aureus* infections in mice with OHM helped to reduce the size of the lesion, as well as the reduction of colony forming units (CFU colony forming unit) of bacteria.

The virulence factors also include α-toxin, which is a secreted protein capable of lysing cells, forming pores on their membrane [10]. In a study using the α-toxin antibody LC10 on a pneumonia model in mice, it was shown that LC10 in combination with vancomycin or linezolid improves the survival of mice compared to monotherapy. Kennedy *et al.* demonstrated that immunization to α-toxin using antiserum or a non-toxic form of α-toxin (Hla_{H35L}) results in a reduction of skin lesions and dermonocrosis in mice with *S. aureus* infection by reducing α-toxin oligomerization [11]. Nagy developed cross-reactive antibody which is able to bind conformative epitopes of α-toxin, γ-hemolysine and Panton-Valentine leukocidin. Using the strain MRSA USA300, they were able to increase the survival rate of mice by injecting this antibody both intranasally and intravenously [12]. α-toxin is an extremely important virulence factor for S. *aureus,* and recent studies have shown that inhibition of this toxin may lead to improved results in the treatment of bacterial infections. It has been proved that over-expression of α-toxin correlates with increased virulence of the strain CA-MRSA ST93 [13]. Treatment using a single antibody aimed simultaneously on most virulence factors may be quite effective and promising in the future. Currently, in a second phase of clinical trials, Astra Zeneca is testing a compound that acts on α-toxin called MEDI4893.

Phenol-soluble modulins (phenol-soluble modulin (PSMs)) include a family of amphipathic alpha-helical peptides (PSMα, PSMβ and S. aureus δ-toxin associated with PSMα) that perform various functions in the pathogenesis of staphylococcal diseases [14]. Unlike many virulence factors produced by *S. aureus*, which are encoded by mobile genetic elements, PSM are encoded in the main genome and therefore are present in almost all strains of *S. aureus* [13]. The presence of PSMα and PSMβ in strains of S. aureus is clinically important, which makes them potential targets for antivirulent therapy. It should also be emphasized that phenol-soluble modulins play different roles both in the pathogenesis of *S. aureus*-associated diseases and in the initial colonization of human epithelial tissues. PSMα peptides are cytolytic, with the ability to lyse various human cells, including white blood cells and red blood cells. PSMβ peptides are involved in the distribution of biofilms, but have less cytolytic activity [15]. In a model of cutaneous *S. aureus* infection, researchers and Kahlenberg determined that a strain with impaired synthesis of PSMα and PSMβ did not lead to any significant damage [16]. In animals treated with anti-PSMβ, researchers found a decrease in the spread of infection to organs, including the liver, spleen and lymph nodes associated with a biofilm on a catheter [17]. However, immunization against the PSMα-type, which has more aggressive cytolytic properties, requires further study. The second treatment strategy involves blocking the export of PSM through a phenol-soluble modulin transporter (phenol-soluble modulin transporter, or Pmt, ABC transporter). This approach is justified for the purpose of broad inhibition of PSM, since Pmt is a specialized transporter for all types of PSM and is encoded in the main genome [18]. In conclusion, the phenol-soluble modulins encoded by the genome play an important role in the pathogenesis of *S. aureus*-associated infections, including lysis of host cells, the formation of biofilms, the initiation of inflammatory reactions. Inhibition of these proteins can help increase the survival rate of MRSA infections. There are several promising ways to influence PSM: directly through the use of antibodies and indirectly by targeting export and regulatory pathways, and given their complex and diverse structure, successful inhibition of PSM virulence is likely to occur through a multifaceted approach.

Protein A (SpA) presents a protein, which is released during bacteria growth and is coded as *spa*-gene. Many factors of virulence *S. aureus*, protein A is regulated by system *agr*, and expression of protein A specifically is inhibited by RNAIII [19]. Protein A contains two areas with clear structural and functional differences: area X and binding immunoglobulin's domain. X area is responsible for joining to cellular wall of protein A; N-terminal protein area A contains 5 immunoglobulin-binding domains (E, D, A, B, C). That's why, protein A presents protein, which is fixed by cellular wall using antibodies aimed at protein A and contains gold nanoparticles, scientists (Zanjani) could affect *S. aureus* by photothermal therapy [20].

An antibody aimed at a bacterial cell, followed by irradiation with a gold nanoparticle, induces heating, transfers energy and causes physical damage to the bacterial cell. This approach to exposure to bacteria using conjugated antibodies to specific factors is very specific, since protein A and gold nanoparticles in mammalian systems have a low level of toxicity [21]. The proposed method can be used in combination or completely replace antibiotic therapy of bacterial infections. Over time, resistance of various mutations to the antibody's binding site is likely to form, and the combination of photothermal therapy and standard antibiotic treatment can be an innovative and new approach to the treatment of bacterial infections. Synthesis of antibodies to α-toxin, as one of the methods for neutralizing the *S. aureus* virulence factors, has reached the second phase of clinical trials, so we hope to succeed in studying SpA antibodies in the future.

The virulence factor leukocidin Panton-Valentine (PVL), produced by *S. aureus*, is a toxin that destroys leukocytes and is associated with severe skin infections, necrotic pneumonia. Most of the diseases caused by PVL-positive strains are sporadic, in particular, small outbreaks of necrotizing staphylococcal infections of the skin

and soft tissues are recorded, but more and more severe pneumonia with high mortality occurs, which mainly affect healthy young people. Clinical studies have determined that only PVL-positive strains of *S. aureus* can complicate the course of influenza in healthy young patients with rapid progression up to severe necrotizing pneumonia. In contrast, PVL-negative strains usually cause nonspecific *S. aureus* pneumonia in the elderly, where the risk of fulminant outcome is much lower (aged ≥60 years). Despite the close correlation between the severity of the disease and the presence of PVL genes, the definition of the role that PVL plays during infection remains controversial. Some studies have emphasized the importance of PVL in the pathogenesis of the disease, while others refute this hypothesis [22]. Interesting results presented by Otto and others determined that expression of PVL and other virulence factors such as SpA can be inhibited using sublethal concentrations of antibiotics [23]. Assuming that PVL does play a significant role in human infection, blocking its activity with a receptor inhibitor can provide important protection during infection [24]. The disadvantage of using PVL inhibitors is that most strains of HA-MRSA do not have this gene, and they will simply be ineffective against many strains of HA-MRSA. In addition, there are also virulent strains of CA-MRSA, which lack PVL genes [25]. Therefore, strain-typing before treatment can be one of the approaches of selective antivirulent therapy.

A unique group of virulence factors are staphylococcal enterotoxins (SE), which, due to their ability to bind to human T-cells and induce hyperstimulation, are called "superantigens" [26]. Staphylococcal enterotoxins (SE) are very resistant to heat and proteolysis and are the main cause of food poisoning [27]. It has been identified twenty-one staphylococcal enterotoxin (SE-A - SE-U) [28]. They belong to category B substances according to the CDC classification, since a small amount of protein it is necessary for the onset of symptoms and their rapid spread [28]. Different strains of *S. aureus* produce different amounts of SE-toxin ranging from 1 μg / ml to 10 ng / ml.

The work of *Bavari et al.* demonstrates that immunization of mice with antibodies to one SE causes cross-resistance to other SE-toxins [29]. Mice were injected with recombinant antibodies against one specific SE and, further, they formed partial immunity to other SE isoforms. The use of the SE-B mutated subunit as a vaccine approach also leads to increased immunity against the toxicity of SE-B. In piglets vaccinated with the non-toxic form of SE-B, IgG and IgA production increased, which cross-reacted with wild-type SE-B, which indicates the possibility of using this method as an immunization strategy [30]. Recently *Reddy et al.* able to create a recombinant peptide consisting of parts of SE-A and toxic shock toxin 1, which is able to generate an immune response against these toxins [31]. Preventive immunization of mice led to an increase in their survival by 50-80% with the introduction of a lethal dose of SE-A.

Considering promising results regarding the formation of immunity against staphylococcal enterotoxins using antibodies, aptamers or mutated forms of the SE protein itself as vaccines, they can provide significant potential in the treatment of severe forms of diseases associated with *S. aureus*.

Bacterial two-component systems (*Bacterial two-component systems* - TCS) are among the basic means of vital activity of bacteria that are able to interact with the environment [26, 31]. As the name suggests, TCS consists of two proteins: sensory kinase, which responds to a signal and a response regulator that binds to DNA. In *S. aureus*, two-component systems may affect the virulence of the bacteria. The *agr* system is one of the important regulators of virulence and its structure is also represented by a two-component protein, i.e. TCS consisting of an AgrA reaction regulator and AgrC kinase. TCS saeR / S by reducing reactive oxygen species protects the bacterium from host proteins, thereby masking it from the innate immune response, reducing the expression of IL-8 and increasing the expression of leukocidins [32].

Using a natural substance isolated from *Glycyrrhiza,* called 18β-glycyrrhetinic acid (GRA), researchers were able to determine that at high concentrations the compound is able to destroy *S. aureus*, and in sublethal concentrations to inhibit virulence genes, including *saeR* [33]. The authors determined that during the treatment of the infection with the GRA, the number of CFUs did not change significantly, while the size of the damage in the mice was significantly reduced, which indicates not only the antibiotic effect, but also the suppression of virulence.

Using a small molecular inhibitor of the synthesis of fatty acids of staphylococcus of the second type called AFN-1252, *Parsons et al.* could show that it significantly reduces the expression of *sae* genes [34]. With the introduction of repeated doses of AFN-1252, the concentration of microorganisms decreased by almost five orders of magnitude. The authors noted that the treatment also had a significant effect on the level of transcription of the *sae* gene, since the cells that were actively growing had a much more stable decrease in *sae* compared to when bacteria were processed in the stationary phase [34]. This work once again confirmed the possibility of influencing component systems, thereby exerting a positive influence on the course of infection, however, and the dynamics of bacterial growth can significantly affect the effectiveness of treatment.

It has been determined that inhibitor TCS causes bactericidal effects [35, 36]. In particular, such influence on two-component system WalK/WalR (YycG/YycF), which is necessary for cells in *S. aureus,* leads to bacteria death. *Okada et al.* determined natural component in *Streptomyces* sp. MK632-100F11 and called it Walkmycin B, which caused antibacterial activity against *B. Subtilis* [35]. Connection also demonstrates antibacterial peculiarities to both strains MRSA and MSSA. It has been indicated that in result of medicinal drug action by decrease of auto-phosphorylation vancomycin inhibits components of the protein WalK TCS. This interaction between vancomycin B and protein TCS was approved by superficial plasmonic resonance with using *B. Subtilis* [35]. Analogue research was also done by *Igarashi et al.* authors could determine new type of *Streptomyces,* so called MK844-mF10, which is able to produce active substance to correlation to WalK *B. Subtilis* and called it waldiomycin [36]. Waldiomycin, has structural similarity with diozamycin an also inhibits the activity of some strains of *S. aureus,* including two different strains of MRSA with minimal inhibition concentration (MIC) 16 mkg/ml. It has been indicated that waldiomycin prevents auto-phosphorylation WalK both for released protein *B. subtilis* and for *S. aureus*. Two-component systems remain relevant and encouraging field of research in the area of *S. aureus* virulence both in terms of studying the degree of inhibition of SaeR and SaeS and as a target of antibiotic therapy.

S. aureus has a golden or yellow color due to pigments from the group of carotinoids, the main of which is Staphyloxanthin - β-D-glucopyranosyl-1-O- (4,4'-diaponeurosporen-4-octa) -6-O- (12 –methyltetradecanoate) [37]. Staphyloxanthin can be a critical factor in the virulence of infections caused by S. aureus because of its ability to neutralize antiseptic substrates of various chemical groups, such as superoxide, hydrogen peroxide, hypochlorous acid, aldehyde-containing drugs. Staphyloxanthin can be critical factor of virulence caused by *S. aureus* to neutralize antiseptic substrates of chemical groups such as superoxide, hydrogen peroxide, hypochlorus acid, aldehyde containing drugs. Staphyloxanthin allows bacteria to detoxify reactive forms of oxygen, generated mainly by neutrophils. Mutant colonies of the strain *S. aureus* in the absence of staphyloxanthin quickly die under the influence of neutrophils. Synthesis of this pigment is regulated by the rsbUVWsigB system. When a mutation occurs in one of the genes of the system, the synthesis of staphyloxanthin is reduced or completely inhibited. Therefore, the study of factors affecting the synthesis of carotinoids in *S. aureus* is very important for understanding the conditions of variability of microorganisms of this species.

The search for staphyloxanthin inhibitors can be carried out by treating S. aureus with a compound that reduces its golden color. Recently, Chen and his colleagues used this approach to screen 412 drugs in order to find substances that inhibit staphyloxanthin biosynthesis [17]. They were able to select only three compounds that led to the loss of pigment in S. aureus: ibandronate, terbinafine and naftifine, the last of which inhibited the production of staphyloxanthin most clearly. Bacteria processed by naftifine determined increased sensitivity to hydrogen peroxide and possibility of survival in blood of person decreased in 20 times. 70 % of mice received treatment by naftifine survived during 12 days, as against control group where all mice died in 24 hours. Using methods of expression *E.coli*, authors could determine that naftifine also was able to inhibit activity of enzyme CrtN. Despite promising results, the authors note that not all strains of S. aureus produce staphyloxanthin, and, therefore, treatment is limited to individual strains [17]. Yet in cases where it is present in bacteria, the use of inhibitory molecules may be a very promising direction in the future. Taken together, these data show that inhibition of the synthesis of staphyloxanthin can be a vital strategy, because the effect on virulence, especially with the selection of different models of computer inhibition, will help identify various modifications in the synthesis of already existing compounds.

Conclusions

Given the prevalence of MRSA and, accordingly, certain limitations in the creation of new antibiotics, the strategy of creating drugs as an alternative treatment for diseases aimed at specific inhibition of the activity of S. aureus virulence factors remains an active and promising direction. Mechanistic studies explaining the structural and functional properties of these factors open up new possibilities for studying ways to inhibit or inactivate them and, ultimately, improve pathogenetic treatment. Strategies for inhibiting virulence factors can range from using small inhibitor molecules or full-fledged antibodies to creating toxoids and virulence proteins. Great interest is considered to those inhibitors that have cross-reactivity with respect to multiple virulence factors, as well as inhibitors, the main target of which is a global regulator with multi-purpose activity, for example, *agr* operon. Active research into the study of specific alternative antivirulent treatments for severe diseases caused by S. aureus can potentially stop huge stream of problems and difficulties of post-antibiotic era.

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