Staphylococcus aureus and Host Immunity in Recurrent Furunculosis

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Abstract

Staphylococcus aureus is one of the severest and most persistent bacterial pathogens. The most frequent *S. aureus* infections include impetigo, folliculitis, furuncles, furunculosis, abscesses, hidradenitis suppurativa, and mastitis. *S. aureus* produces a great variety of cellular and extracellular factors responsible for its invasiveness and ability to cause pathological lesions. Their expression depends on the growth phase, environmental factors, and location of the infection. Susceptibility to staphylococcal infections is rooted in multiple mechanisms of host immune responses and reactions to bacterial colonization. Immunological and inflammatory processes of chronic furunculosis are based on the pathogenicity of *S. aureus* as well as innate and acquired immunity. In-depth knowledge about them may help to discover the whole pathomechanism of the disease and to develop effective therapeutic options. In this review, we focus on the *S. aureus*-host immune interactions in the pathogenesis of recurrent furunculosis according to the most recent experimental and clinical findings.

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Introduction

Staphylococcus aureus is one of the severest and most persistent bacterial pathogens. Infections caused by *S. aureus* may have local or generalized character (invasive infections). Additionally, they may be accompanied by specific diseases caused by staphylococcal toxins. Among the severest invasive infections associated with high mortality are sepsis and endocarditis related to natural heart valves or associated with the presence of vascular or cardiac prostheses as well as various types of vascular catheters [1, 2]. Local infections encompass most of all infections of the skin and subcutaneous tissue which are characterized by purulent secretion. The most frequent infections include impetigo, folliculitis, furuncles, furunculosis, abscesses, hidradenitis suppurativa, and mastitis [3, 4].

S. aureus possesses a great variety of cellular and extracellular factors responsible for its invasiveness and ability to cause pathological lesions. Figure 1 shows immune reactions activated in response to pathogens and their virulence factors. Their expression depends on the growth phase, environmental factors, and location of the infection [5]. Correlations between the presence and expression of selected virulence factors and location of infection

Fig. 1. Immune reactions in the skin in response to pathogen invasion. TNF, tumor necrosis factor; INF-γ, interferon-γ; pDC, plasmacytoid dendritic cell.

was observed. At the initial stage of infection, superficial proteins responsible for adhesion of the pathogen to host tissues are particularly important. They are commonly known as microbial surface components recognizing adhesive matrix molecules. Those proteins may bind fibronectin, fibrinogen, collagen, thrombospondin, laminin, sialoprotein, and vitronectin. Thanks to these proteins, colonization is possible in areas where skin continuity is interrupted. Those areas become quickly coated by serum proteins or extracellular matrix [6–8]. Clumping factors A and B are important surface proteins and serve as adhesins. They bind to fibrinogen promoting plasma clotting via nonenzymatic activation, which is used for the routine diagnostics of *S. aureus*. The polysaccharide capsule plays an important role in the process of coloniza-

tion. Out of 11 determined types of capsular polysaccharide, types 5 and 8 are a common cause of severe staphylococemia. The capsule is antiphagocytic, similarly to protein A present in the cell wall. Protein A can bind to the Fc receptor of immunoglobulin (Ig), especially IgG, but IgA and IgM as well. This binding is responsible for blocking complement activation via the classical pathway and inhibits phagocytosis [9, 10].

S. aureus produces a wide range of cytolytic toxins (e.g., hemolysins and leukocidins) and enzymes (e.g., coagulase and proteinases) which facilitate spreading of this microorganism within the infected body and cause tissue damage [2]. Superantigens are a particular group of toxins. They are responsible for specific diseases commonly associated with the separation of the epidermis. They in-

clude exfoliantines or epidermolysins (ETA, ETB, and ETD), toxic shock syndrome toxin and enterotoxins. Over 70% of the isolated *S. aureus* are exotoxin-producing strains which can secrete various exotoxins such as staphylococcal enterotoxins A, B, and C as well as toxic shock syndrome toxin-1. Enterotoxins can act as superantigens penetrating the epidermal barrier and exacerbating the inflammatory process. In the studies from the literature, the dependency between colonization by *S. aureus* and the severity of atopic dermatitis is highlighted [11, 12]. The ability of *S. aureus* to develop biofilms is an important mechanism of its pathogenicity. It is particularly essential in *Staphylococcus epidermidis* [13]. It was shown in a recent study that lipases secreted by *S. aureus* are one of the main factors promoting biofilm development [14]. *Staphylococcus hyicus* is the second microorganism whose lipases are the most known and studied. The majority of *S. aureus* strains contain two lipase genes. The first gene (geh) encodes a 682-aa lipase, and according to the new nomenclature, it is named SAL1 encoded by gehA. The activity of SAL1 is Ca^{2+} -independent and primarily reacts with short-chain glycerides such as tributylglycerol or *p*-nitrophenyl octanoate and does hydrolyze Tween 20 or 80 [15]. The second lipase gene SAL2 is encoded by gehB. SAL2 hydrolyzes both short- and long-chain triglycerides [16]. Both SAL1 and SAL2 show a high degree of similarity particularly in the mature lipase part and are organized as pre-pro-enzymes.

Pathogenicity factors are regulated by various systems, the best known of which is agr. In *S. aureus*, the genetic polymorphism of agrB, agrC, and agrD is determined by 4 allelic groups (from I to IV). Some of the virulence factors are located on the so-called *S. aureus* pathogenicity islands, which are mobile elements and give staphylococcal cells enormous plasticity and variability [17].

The factors that predispose to the development of staphylococcal infections are complex mechanisms of innate immune responses and those which appear as a reaction to bacterial colonization. The infection can be particularly fulminant in people infected with human immunodeficiency virus, suffering from diabetes, and in patients undergoing immunosuppressive treatment. Also, in patients with an impaired structure and skin functioning as a barrier which is common in patients with atopic dermatitis, recurrent and severe furuncles are observed [18–20]. Nevertheless, in immunocompetent patients without any history of atopy and metabolic diseases, factors that determine predisposition to the development and recurrence of furuncles are understudied and not fully explained [21]. In the study by Du-

rupt et al. [22] carried out on a large group of patients, nasal carriage of *S. aureus* was found in 37 out of 64 (58%) patients with culture-confirmed staphylococcal infection of the skin. A significant difference ($p < 0.007$) in the rate of nasal carriage was observed between patients with simple furuncles (2 of 7, 29%) and patients with chronic furunculosis (14 of 16, 88%). The difference in nasal carriage rate between patients with bullous (40%; 4/10) and nonbullous impetigo (62%; 13/21) was insignificant. Also, the difference in nasal carriage rate between patients with Panton-Valentine leukocidin (PVL)-positive furuncles (46%; 6/13) and patients with PVL-negative furuncles (72%; 13/18) was insignificant [22–24]. Nasal cavity colonization by *S. aureus* is considered a risk factor for recurrent and chronic furunculosis. Emonts et al. [25] found polymorphisms in interleukin (IL)-4, complement factor H, and C-reactive protein in subjects with the presence of *S. aureus* in the vestibule of the nose and skin furuncles. They also discovered that those polymorphisms are associated with the decrease in or the total lack of functioning of the respective factors. Thus, there is a justification for tracing the factors responsible for immunity in this disease [25, 26].

In the treatment of staphylococcal infections, one of the most important problems seems to be methicillin resistance which was first reported in 1961. Methicillin-resistant *S. aureus* are resistant to all β -lactam antibiotics. Their resistance is determined by receptors encoded by mecA gene located on the bacterial chromosome which is an element of staphylococcal cassette chromosome mec. Acquiring resistance by *S. aureus* strains is associated with spreading of staphylococcal cassette chromosome mec included in the so-called genomic islands [27].

S. aureus is the main pathogen that causes recurrent furuncles. On one hand, this condition depends on the pathogenicity of this bacterium but on the other, on the ability of the macroorganism to defend itself against it. The interaction between *S. aureus* and the host may last for many years; however, when the immune system is weakened, furuncles may develop, and symptoms of infection may appear.

Host immunity is a complex and still poorly understood biological mechanism which depends on humoral and cellular factors. There are some components of host immunity which create the first-line defense activated regardless of the type of pathogen. They include humoral and cellular innate immunity and the adaptive immunity activated by previous exposure to antigen – also humoral and cellular.

Skin Immune System

The skin constitutes an important physical and immunological barrier. The epidermis with all its layers – especially the stratum corneum – serves as a physical barrier. Keratinocytes predominantly located in the epidermis produce antimicrobial peptides, proinflammatory mediators, complement components, and chemotactic factors [28, 29]. Keratinocytes recognize the presence of *S. aureus* using pattern recognition receptors. Toll-like receptor 2 (TLR-2) on keratinocytes recognizes pathogen-associated molecular patterns (PAMPs) including peptidoglycan and lipopeptides [30]. Abu-Humaidan et al. [31] have recently found that persistent intracellular *S. aureus* surviving in epidermal keratinocytes promoted complement activation on the cell surface; this complement activation, in turn, initiated cellular responses that subsequently reduced the intracellular bacterial burden by an extracellular signal-regulated kinase-dependent mechanism. The intracellular reservoir is suggested to contribute to dissemination, recurrence, and antibiotic resistance [31–33]. Moreover, Mohanty et al. [34] found that saliva (as a model of wound licking) reduced the number of intracellular *S. aureus* in keratinocytes, paralleled with an expression of antimicrobial peptides, especially human β -defensin-3.

Other cells that participate in the immune response against *S. aureus* include skin-resident macrophages and Langerhans cells, myeloid and plasmacytoid dendritic cells, mast cells, T and B lymphocytes, plasma cells, and natural killer (NK) cells as well as neutrophils and other cells recruited from the circulation during infection [35].

Macrophages play a key role in host defense by recognizing, engulfing, and killing microorganisms [36]. However, the survival of *S. aureus* within polymorphonuclear leukocytes might lead to prevention of macrophage efferocytosis and induce programmed necrosis [37]. Moreover, the intracellular persistence also provides *S. aureus* with an ideal strategy to escape professional phagocytes and promote recrudescence infection [38]. While IL-1 produced by phagocytes is an important cytokine orchestrating host defense against *S. aureus*, IL-1 β is an important proinflammatory cytokine that activates monocytes, macrophages, and neutrophils [39–42]. *S. aureus* from atopic dermatitis skin can alter cytokine production triggered by monocyte-derived Langerhans cells [43].

Dendritic cells, professional antigen-presenting cells, are very important for the recognition of invading pathogens. Armbruster et al. [44] showed that the virulence factor phenol-soluble modulin produced by community-as-

sociated methicillin-resistant *S. aureus* strains induces tolerogenic dendritic cells upon TLR-2 activation via the p38-CREB-IL-10 pathway.

Mast cells also play an important protective role against various microbial infections, like *S. aureus*, by phagocytosis and by releasing mediators (e. g. tumor necrosis factor- α and histamine) [45]. However, it was proven that in the *S. aureus*-infected mice, severe infiltration of inflammatory cells in the dermis was observed, and mast cells were markedly accumulated in the skins. Besides, tryptase, the marker for mast cell activation, has a positive correlation with mast cell activity. The mast cells identified in the tissues were likely to be activated since they were associated with cell degranulation and the presence of tryptase; so, it was suggested that mast cells and their mediator tryptase contribute to the inflammation of skin abscesses induced by *S. aureus* infection [46].

S. aureus has the ability to modulate and evade neutrophil bactericidal mechanisms including priming, activation, chemotaxis, and production of reactive oxygen species; it also uses sensory/regulatory systems to tailor the production of virulence factors specifically to the triggering signal, e.g. neutrophils and defensins [47].

Innate Immunity

Innate immunity is a synergistic process between humoral and cellular response which is assisted and coordinated by the inflammatory response with the subsequent elimination of the pathogen via the most effective route. Early events in innate immunity in recognition of microbial pathogens in the body lead to increased microbicidal activity, cellular recruitment, a boost of hematopoiesis, fever, and production of acute-phase proteins [48–50]. Natural antibodies secreted by B1 lymphocytes – mainly IgM class and complement are the humoral components of this immunity. Antibodies alone cannot prevent the occurrence of an infection. In case of bacteria (including *S. aureus*), there are 3 ways of activation of the complement cascade: the classical pathway triggered by activation by the C1q molecule; the alternative pathway via C3, and the mannose-binding lectin mechanism, which all contribute to the lysis of bacterial cells and enable their phagocytosis by peripheral blood cells. In the case of *S. aureus*, activation of the complement is possible thanks to binding of C-reactive protein to protein A which leads to opsonization of bacteria [51]. Activation of the complement is controlled by genes located within the regulator of complement acti-

vation gene cluster on human chromosome 1q32. Complement factor H, which is encoded by regulator of complement activation as well, regulates complement activation and limits the action of the complement to activating surfaces [52]. Familial mannose-binding lectin deficiency was found to be frequently associated with furunculosis in subjects with a decreased level of functional mannose-binding lectin [53, 54].

Cellular components of innate immunity include neutrophils, monocytes, macrophages, and NK cells. They have specific receptors on their surface, so-called pattern recognition receptors (PRRs) which can recognize bacteria [55]. PRRs detect molecular structures located on the surface of bacteria – PAMPs and internal components released during lysis of bacterial cells such as fragments of DNA or heat shock proteins – damage-associated molecular patterns [4, 56]. NK cells belong to the fastest responding cells to infection among blood cells. They induce bacterial lysis via secretion of porphyrins and granzymes. Our previous study revealed a significant increase in both the absolute number and percentage of NK and NKT-like cells in patients with recurrent furunculosis in comparison with healthy subjects [57]. This shows their significant, though maybe substitute role in this disease during host defense.

Phagocytic cells like neutrophils, monocytes, and macrophages migrate to the focus of inflammation in response to various types of chemoattractants such as chemokines and cytokines as well as complement component C5a – an anaphylatoxin. Neutrophils engulf bacteria in a complement- and antibody-dependent phagocytosis process and then kill them by producing reactive oxygen species and hypochlorous acid. The phagosome also contains antibacterial peptides (e.g., cathelicidins, lysozyme, azurocidin and α -defensins) and numerous proteinases (e.g., elastase, gelatinase, proteinase 3, hydrolases) which are helpful in the degradation of bacterial components [58, 59]. Figure 2 shows mechanisms of killing bacteria by phagocytic cells. After phagocytosis, neutrophils undergo apoptotic cell death. During infection, some bacteria may survive in host cells in case of delayed apoptosis or disseminate in case of cell lysis due to inflammation or tissue damage [60]. Neutrophil chemotaxis depends on many factors that have been known for long [61, 62]. Keszei and Westerberg [63] presented causes of congenital disorders of neutrophil dynamics.

Studies on leukocyte function in patients with recurrent furunculosis encompass several topics. Demirçay et al. [64] demonstrated that phagocytosis and oxidative burst by neutrophils in patients with recurrent furuncu-

losis are impaired only in those with hypoferremia. Gilad et al. [65] compared superoxide production (basal and after stimulation), phagocytosis, and chemotaxis between recurrent furunculosis ($n = 10$) and nonrecurrent furunculosis patients ($n = 13$). They revealed that impaired chemotaxis appears only in patients with recurrent furunculosis and can serve as an independent risk factor for recurrent furunculosis. Hamaliaka and Novikova [66] demonstrated depression of nitric oxide formation at stimulation and a decrease in the production of reactive oxygen species in 58 patients suffering from recurrent furunculosis.

Monocytes from peripheral blood are recruited to the site of infection and undergo phenotypic conversion to become tissue-resident macrophages. They do not always die in the process of phagocytosis. *S. aureus* may survive in vacuoles due to the presence of pathogenic factors such as global regulatory locus *agr* and alternative sigma factor which may cause macrophage lysis with subsequent proliferation of bacteria thanks to pleiotropic properties of *sarA* [67]. Such a mechanism of spreading the infection is also possible in recurrent furunculosis [67]. Human α -defensins and β -defensins are produced by macrophages, neutrophils, and NK cells. They are collected in cell granules and secreted to the site of bacterial infection. Harder et al. [68] demonstrated that human β -defensin-3 plays a role in the defense against *S. aureus*.

Mastocytes are involved mainly in the phagocytosis of parasitic pathogens, but they play a role in case of bacterial pathogens as well. Mast cell degranulation contributes to the increase in phagocytosis by mononuclear cells. Additionally, an antibacterial effect which reduces their anti-inflammatory properties in tissues is exerted by antimicrobial peptides such as peptidoglycan from peptidoglycan recognition proteins. Under their influence, the bacterial wall is hydrolyzed with a subsequent reduction in proinflammatory activity. They are present in neutrophils and secreted by the skin and digestive tract as well. Their presence can also be detected in tears. They play a very important role in the defense against pathogenic bacteria such as *S. aureus*. It was demonstrated that the activation of the TLR signaling pathway responsible for internalization and maturation of phagosomes is induced by bacterial PAMPs [68–70].

Another important finding for innate immunity was the discovery of TLRs in humans as they participate in the recognition and elimination of pathogens. TLRs belong to PRRs. They are present in numerous cells of the body such as monocytes, macrophages, dendritic cells, keratinocytes, fibroblasts, epithelial cells, B lymphocytes, and some

Fig. 2. Phagocytic cell – neutrophil and the mechanisms of bacterial killing. CR1, complement receptor type 1; C3b, complement component 3b; FcR, Fc receptor; IgG, immunoglobulin G; ROC, reactive oxygen species.

T lymphocytes. The TLR family includes the following subfamilies: TLR-1, TLR-2, and TLR-6 which can recognize lipids; TLR-7, TLR-8, and TLR-9 which can recognize nucleic acids; and TLR-4 which can recognize lipopolysaccharides present on the surface of pathogens and classified as PAMPs. TLR-2 is mainly responsible for the recognition of gram-positive bacteria via detection of lipoteichoic acid, lipoproteins, and peptidoglycan of their cell wall, while TLR-1 and TLR-6 recognize them via detection of the lipid portion of lipoproteins. The recognition of the pathogen inside the cell is possible thanks to various cytosolic PRRs which include proteins that contain a nucleotide-binding oligomerization domain (NOD) and leucine-rich repeats as well as helicase proteins that contain caspase activation and recruitment domains. NOD and leucine-rich domains include NOD1 and NOD2 which can detect γ -D-glutamyl-meso-diaminopimelic acid and muramyl dipeptide present in the bacterial peptidoglycan leading to the activation of NK- κ B and production of pro-inflammatory cytokines [71–74].

It was also shown that internalization of *S. aureus* by monocytes and macrophages is possible via activation of TLR-2/6 by the COOH-terminal cytoplasmic portion of CD36. Macrophages with a lack of functional CD36 signaling showed a reduced level of phagocytosis of *S. aureus* in vitro and a defect in the production of tumor necrosis factor- α and IL-12. Additionally, CD36-deficient mice presented with severe bacteremia after infection with *S. aureus* [75].

Adaptive Immunity

During infection as well as after repeated contact with the pathogen, previously created mechanisms of the adaptive immune system become activated. They encompass involvement of antibodies produced by B lymphocytes and cell-mediated immune responses which are controlled by T lymphocytes [76–78]. B lymphocytes bind to the ligand for CD40 on the surface of T lympho-

cytes which initiate signals for antibody production thanks to the recognition of the complex of a peptide processed from a bacterial antigen and the major histocompatibility complex II (MHC II) via the T-cell receptor on the surface of antigen-presenting cells. The resulting signal activates B lymphocytes. Next, thanks to cytidine deaminase, activated B cells undergo antibody class switching that changes a B cell's production of the isotype IgM to the immunoglobulin isotypes. Cooperation between B lymphocytes and Th1 results in a production of IgG which is present mainly in the blood and IgA which is produced in association with mucosal membranes. IgE requires antibodies produced as a result of cooperation with Th2 lymphocytes [65, 79]. Produced antibodies are helpful in the opsonization of bacteria and their engulfment in the phagocytosis process. Antibodies against antigens produced by *S. aureus* (e.g., α -toxin and PVL) are used to fight this pathogen and can stop the activity of those toxins [22, 80]. In a murine model, treatment of experimental infection by a methicillin-resistant *S. aureus* strain with anti-PVL antibodies resulted in bacterial inocula and formation of abscesses in the skin [81]. Another animal study showed that vaccination against a combination of 7 virulent factors of superantigens secreted by *S. aureus* protected rabbits against life-threatening pneumonia but promoted infective endocarditis probably due to antibody-mediated bacterial aggregation [82]. In humans, the protective effect against infections by *S. aureus* in patients undergoing cardiothoracic surgery after vaccination with vaccine candidate V710 against *S. aureus* was not observed [83]. It was determined however that a low level of antibodies against *S. aureus* is associated with a high risk of sepsis [84]. Antibodies against *S. aureus* are not essential for protection against infections by *S. aureus* but may play a role in modulating susceptibility to infections, which will be the subject of future studies [77].

The cellular response relates to T lymphocytes. Subsets of T cells include Th1, Th2, and Th17 as well as, less frequently, $\gamma\delta$ T cells and regulatory T cells (Tregs). The cellular response was studied mainly experimentally in various *S. aureus* infections in animal models and in selected diseases in humans [23, 85]. T cells do not directly kill bacteria, but via cytokines, such as interferon- γ and IL-17, they can orchestrate many downstream effects on phagocytes that enhance their microbial activity [86, 87].

MHC II is an essential molecule for adaptive immunity. Its expression is modulated both by host's mechanisms and microbial factors. It was experimentally determined that *S. aureus* inhibits antigen presentation and may increase susceptibility to infection. *S. aureus* has the

ability to downregulate the expression of the MHC II antigen HLA-DR. It also induces the upregulation of CD40, CD80, CD83, together with a slight increase in CCR7 which can be a potential result of TLR signaling and feedback responses to secreted inflammatory cytokines. A partial induction of antigen-presenting cell markers and chemokine receptors results in an impaired T-cell activation and anergy. *S. aureus* suppresses the T-cell IL-2 response to alloantigen via downregulation of HLA-DR and CD86 in an IL-10 dependent manner and increases the expression of programmed cell death 1 (PD-1) ligand 1 (PD-L1). Those mechanisms suggest that T-cell IL-2 is affected by *S. aureus* through modulation of monocyte/macrophage antigen-presenting cell function [88, 89].

Activity via T-Cell Receptor in Chronic Infections

Functioning of individual components of adaptive immunity has not been studied in patients with recurrent furunculosis. In our studies, we found a significant decrease in the number and percentage of Treg, CD3+, and CD4+ cells in comparison with healthy subjects as well as a significant increase in the number and percentage of CD3+CD25+ and CD19+CD25+ cells. Those differences indicate impaired activation by IL-2, pronounced reduction of FOXP3 generation, decreased production of Tregs, and increased number of Th17+. Additionally, a statistically insignificant increase in the number of B lymphocytes that determines the production of antibodies against *S. aureus* was also demonstrated. It should be assumed that these types of disorders affect the pathomechanism of the development of chronic furunculosis [90–92 and data not published]. In septic conditions caused by *S. aureus*, opposite changes are observed. An increase in Tregs was noted, especially in post-traumatic sepsis; it is possible that a higher level of Treg cells is associated with increased mortality which seems to have enormous clinical significance. Mechanisms responsible for a reduction in the number and percentage of Treg cells in chronic furunculosis have not been fully elucidated, but authors suggest that they may be one of the mechanisms contributing to the pathogenesis of this disease [84, 93].

Tregs develop from naïve CD4 T cells. They differentiate either in the thymus as induced Tregs or peripherally – outside the thymus from naïve CD4 T cells (in vivo or in vitro) – as peripherally induced Tregs. Their functioning depends on the concentration of IL-2; however, they do not produce this interleukin themselves

[94]. We found that in patients with chronic furunculosis, the concentration of proinflammatory cytokines, tumor necrosis factor- α , IL-2, and anti-inflammatory IL-10 is significantly higher in comparison with healthy subjects. Other proinflammatory cytokines such as IL-17, interferon- γ , and anti-inflammatory IL-4 showed a tendency to increased concentrations in patients with furunculosis. It is interesting that there is a statistically significant reduction in other anti-inflammatory cytokines – IL-13 occurred in patients with furuncles in comparison with healthy controls [57]. The concentration of IL-13 in contrast to IL-10 and IL-4 does not increase in this disease which may affect the course of the inflammatory process. Previous studies demonstrated only the fact that this cytokine is released from mast cells undergoing degranulation due to parasitic infection [95].

The interaction between adaptive and innate immunity against staphylococcal infections is possible thanks to cytokines produced by cells of both immune types. Identification and characterization of individual cytokines during the performance of various functions seems to be crucial for the near future. One of the best known cytokines is IL-10 which exerts multiple, pleiotropic effects in immunoregulation. IL-10 plays a key role in differentiation and functioning of a newly appreciated type of T cells and Tregs, which may figure prominently in the control of immune responses and tolerance in vivo. Uniquely among hemopoietic cytokines, IL-10 has closely related homologs in several virus genomes, which testify to its crucial role in regulating immune and inflammatory responses. IL-10 is a regulatory cytokine that diminishes the development of proinflammatory immune responses, including responses mediated by both innate and adaptive immune cells [96].

S. aureus is a potent immune activator as superantigenic staphylococcal enterotoxins are able to engage large numbers of conventional T cells via MHC-mediated binding to the variable domains of the T-cell receptor [97–99]. It thereby efficiently avoids immune clearance by inducing T-cell exhaustion and anergy [100]. PD-1 as the major immune checkpoint displays an important inhibitory function in the maintenance of peripheral tolerance. Expression of PD-1 and its ligand PD-L1 may contribute to continuous T-cell activation and the development of inflammation and injury of the tissue. Patil et al. [101] using an animal model of burn injury demonstrated that the increase in myeloid cell PD-L1 expression was associated with a reduction in the number of T cells in the

spleen and wound draining lymph nodes as well as with impairment in T-cell functioning. Anti-PD-L1 treatment of systemic infection with *S. aureus* was effective in terms of reduction in bacterial burden in major organs and improvement in 7-day survival [101]. Our recent study indicates that the PD-1/PD-L1 axis may contribute to the pathogenesis of furunculosis, as patients with recurrent disease are characterized by higher frequencies of PD-1-positive T and B cells than healthy subjects. We observed a significantly increased percentage of lymphocytes with PD-1 receptors and PD-L1 on their surface which inhibits effector functions of T lymphocytes; hence, in patients with furunculosis, a decrease in the percentage of Treg lymphocytes may increase inflammatory responses. The impaired proportions of lymphocyte subpopulations translate into relations between clinical presentation and the PD-1/PD-L1 pathway. An inverse correlation between the percentage of CD19+/PD-1 B lymphocytes and the age at the onset of the first symptoms suggests that the predominance of this type of cells may predict the early start of the disease. An inverse correlation between the number of furuncles per year and the percentage of CD4/PD-L1 cells suggests that a reduction in the number of CD4/PD-L1 cells is associated with the severe clinical course. The expression of PD-1 and PD-L1 on the surface of CD4+, CD8+ T lymphocytes and CD19+ B lymphocytes was significantly higher in patients with recurrent furunculosis than in healthy subjects (data not published).

Conclusion

Immunological and inflammatory processes occurring in chronic furunculosis constitute a complex mechanism based on the pathogenicity of *S. aureus* and innate and acquired immunity. It seems that in-depth knowledge about those processes can be the key to getting to know the whole pathomechanism of the disease and translate into increased therapeutic options.

Key Message

Immunological and inflammatory responses to *S. aureus* pathogenicity factors contribute to chronic furunculosis.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.N. – conception or design of the work; acquisition, analysis, and interpretation of data for the work; writing and revising the work critically for important intellectual content; final approval of the version to be published. E.G. – conception or design of the work; acquisition, analysis, and interpretation of data for the work; writing and revising the work critically for important intellectual content; final approval of the version to be published.

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