Review Article

Pathogenicity and virulence factors in *Staphylococcus aureus*.

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Abstract: *Staphylococcus aureus* is a pathogen that resides in the skin and nasal membranes and can cause a broad spectrum of hospital-acquired infections. These diseases are becoming more common, and treating them has become much more complicated. The pathogen's capacity to secret a variety of host-damaging virulence factors contributes to its pathogenicity. *S. aureus* destroys and supersedes immune cells throughout infection via toxins and virulence proteins, yielding non-neutralizing infective antibodies which already impede adaptive immunity. *S. aureus* has different biofilm-forming mechanisms on devices, necrotic bone tissue, bone marrow, and finally within the osteocyte lacuno-canicular networks of living bone (OLCN).This review focuses on gaining a better understanding of *S. aureus* toxin-based pathogenesis and its effects on infectious diseases.

Keyword: *Staphylococcus aureus*, Virulence factors, enzymes, toxins, adhesion proteins.

1. Introduction

As a commensal and a human pathogen, *Staphylococcus aureus*, *S. aureus* colonized by around 30% of the human population [1]. Around the same time, bacterial endocarditis (IE), osteoarticular, muscle and, soft tissue infections, pleuropulmonary, and device-related infections are leading causes [2,3]. Clinical *S. aureus* infections are expected to remain both frequent and serious, not only have waves of increased antimicrobial tolerance existed, but the clinical disease continuum still tends to change[4].

1.1 Pathogenicity in *S. aureus*

S. aureus causes several forms of human infections and syndromes, especially infections of the skin and soft tissue [5].*S. aureus* nasal carriage in children is considerably larger, varying from 45 percent to 70 percent[1], although colonization is not normally dangerous to the host, *S aureus* may get through the host's natural defences and into underlying tissue, resulting in a variety of topical and invasive infectious agent [6]. *S. aureus* often causes minor skin and soft tissue infections such as impetigo, folliculitis, and cutaneous abscesses in healthy people in

the community, more uncommon but serious community infections include pyomyositis [4], necrotizing fasciitis [4], and necrotizing pneumonia [7,8]. In nosocomial conditions, *S. aureus* can lead to infection at implant site or by inserted surgical devices such as artificial heart valves, catheters, prosthetic joints, and orthopedic implants [9,10]. Throughout sepsis, *S. aureus* circulates in the bloodstream and can propagate internal organs[11], endocarditis, osteomyelitis, and developing UTI are examples of distributed illnesses[1]. With the pathogen's ability to live in a variety of skin-related hosting niche areas [12], to abiotic devices [13], it is impossible to remove deep-seated tissues, resulting in recurrent infections [6].

1.2. Pathogenicity and Effects on Response to Treatment

S. aureus infection and multidrug-resistant strains are becoming more common, rendering therapeutic anti-infective care more complex[14]. A decline in membrane permeability causes *S. aureus* tolerance to aminoglycosides, which contributes to a depletion in drug consumption[15]. Antibiotic tolerance in S. aureus is caused by a variety of mechanisms, including pharmaceutical outflow upregulation, and modification of specific proteins, this has compelled the use of novel treatment strategies, which has required the use of revolutionary approaches. [16]. Several investigations have centered on developing innovative therapeutic methods to combat-proven *S. aureus* biofilm-associated infections, resulting in the creation of phytochemicals, enzymes, sulfhydryl compounds nanoparticles, phage combinations, antibodies, and metal chelators. In addition to standard approaches, the medicinal effects of ultrasound, shock waves, and photodynamic treatment for treating *S. aureus* biofilms are being researched[17].

1.3. Virulence Factors Secreted By *S. aureus*

For pathogenesis, the bacteria can be retained in the host by a peptidoglycan layer that inhibits complement opsonization and thereby escapes phagocytosis [18]. Cytolytic toxins, tissue-cleaving enzymes can also be secreted [19], *S. aureus* could exhibit a variety of adherence agents which facilitate host cell and extracellular matrix (ECM) interfaces, making colonization more efficient[20]. *S. aureus* has evolved mechanisms to combat antimicrobial peptides, the complement system, and phagocyte recruiting efforts and behaviour. [21], Most of these are counter-measures to the host's natural immune system[22].

Enzymes, toxins, adherence proteins, cell surface proteins, influences which really help

bacteria avoid an innate immune system, and drug tolerance all lead to S. aureus' capacity to cause infection[23], a group of membrane-damaging toxic substances incapable of generating gaps in the cell membranes of host cells, resulting in lysis [24]. These virulence factors include: 1) “panton valentine leukocidin” (PVL) is a cytotoxin which attach to the complementary receptors “C5aR and C5L2” on neutrophils surface and had formed pore [25]. PVL-positive *S. aureus* is often linked to chronic infections, delayed diagnoses, and ultimately an elevated risk of spread, resulting in clusters of infected patients living in close areas[26].

2) “Bi-component leukocidins” form an octameric assembly of overlapping S and F subunits which really form a pore surrounding the host cytoplasmic membrane's lipid bi-layer, resulting in transfection[27]. Human neutrophils are vulnerable to PVL's cytolytic action [28]. While distilled “LukED”, “LukAD”, and PVL induce inflammation, “LukAB” and “LukED” had identified different host cell receptors than PVL[29,30].

In the same manner as leukocidins, 3) the heptameric β-barrel forming alpha-toxin (Hla), attaches to target sites and forms a heptamer to coat the -barrel pore with a lipid bi-layer, Hla is involved many types of host cells[31]. “Disintegrin” and “metalloprotease10” are both Hla receptors [32], many cells possess this protein on leukocytes, but it is also found in the liver, heart, kidney, lung, and lymphoid tissue[33]. When Hla-ADAM10 interacts, host cell membranes become destroyed, which leads to epidermal cells and dermal layer necrosis throughout skin diseases[34].

4) PSMs (phenol-soluble modulins) are thin, amphipathic, alpha-helical peptides that are divided into two categories: alpha-type PSMs with 20-25 a.a. and -type PSMs with only about 44 amino acids[35]. In contrast to -barrel-forming toxins, their capability to denature cells is assumed to have been non-specific and receptor-independent[36]. PSMs therefore had high propensity for lysing human neutrophils, with PSM lysis occurring after *S. aureus* had already been phagocytosed[37,38]. Human neutrophils can be easily lysed and the stability of the neutrophil plasma membrane has been weakened after just 5 minutes of exposure to PSM alpha [39]. During skin infection, the primary function of PSMs is to kill leukocytes and thereby promote the escape of *S. aureus* from host immune defense systems, unlike *S. aureus*, which is nearly exclusively induced by extracted toxins through SSTIs, dermonecrosis causes extreme inflammation, that might also escalate to ever more skin damage[24]. Besides that, certain secretory proteins' cytolytic role on leukocytes acts as an immune easy escape for *S. aureus*, facilitating infection persistence[40].

5) "Clumping Factor A" is a large fibrinogen-binding protein found in *S. aureus* that links to the fibrinogen gamma-chain's C-terminal region[41], which cause platelet accumulation or bacteria clustering in the blood, "ClfA" is a major *S. aureus* virulence factor and has been shown to lead to pathogenesis, including endocarditis, arthritis, and sepsis [42], 6) By forming greater connections with the keratinized envelope ClfB, clumping factor B encourages respiratory settlement in individuals[43]. ClfB link with plasma fibrinogen[44], "cytokeratin10"[45] (the most prevalent protein in the cornified squamous membrane), and "loricrin" (widely available protein in the squamous cell interior). [43].

7) *S. aureus* can attach to and penetrate a specific cells, including epithelial, endothelial, fibroblast, and osteoblast cells, according to the A and B fibronectin-binding proteins (FnBPs)[46]. Incursion is assisted by the host cell's fibronectin receptor, integrin alpha5 beta1[47].

8) SpA is a multi - functional membrane protein that has been preserved in S. aureus. The N-terminus comprises five triple-helical bond residues which are essential for connecting to IgG and other receptors including TNF receptor 1 and von Willebrand factor[20]. The SpA seems to have a number of immunoregulatory properties and has become one of *S. aureus'* another very effective immune avoidance processes, SpA connects to the Fc portion of IgG, causing the bacteria to become covered in IgG in the wrong orientation, leading to a reduction identification by neutrophils and, as a consequence, phagocytosis elusion[48]. It is indeed a B cell superantigen that binds to Heavy chain' immunoglobulins on the BCR, inducing clonal proliferation and programmed cell death[49].

9) Comparison for enzymatic function impact as a host virulence factor, i) catalase expels H_2O_2, which would also be needed for nasal colonization [50], ii) coagulase connects to prothrombin while becoming enzymatically effective, facilitating the transformation of fibrinogen to fibrin and trapping bacteria into fibrin, rendering them prone to opsonins and phagocytes[51], in connective tissue, iii) hyaluronidase diminishes hyaluronic acid and metabolised the tissue's intra-cellular matrices with mucopolysaccharide acids, encouraging pathogens to spread to nearby tissue sites and converting localized tissue into vital nutrition supporting bacterial development[52], iv) Nuclease activity aids in the escape of extra-cellular neutrophil tricks, which could also transform host tissue into nutritional requirements for bacterial development. [53], v) protease destroy human fibronectin, fibrinogen, and kininogen offenders of human alpha-1, and elastin can lead to *S. aureus'* tendency to propagate in host helps in tissue penetration [54], vi) more than 67 percent of S. aureus strains

have the staphylokinase gene, which forms an alpha-defensin structure to repel the bactericidal activity, can cleave complement factor C3 regulates fibrinolysis, bacteria take advantage of plasmin's proteolytic activity to degrade ECM components, as well as fibrinogen components [55,23].

10) Exfoliative toxins glutamate-specific serine proteases digesting desmoglein1, ETs are keratinocyte ligand binding molecules that function as "molecular scissors," facilitating bacterial skin aggression, The two main isoforms linked to staphylococcal bullous impetigo and staphylococcal scalded skin syndrome are ETA and ETB, whereas staphylococcal bullous impetigo is not linked to ETC, ETD is involved in super Ags activity[56,57,23].

11) Cytolytic action of hemolysin pore-forming toxin on RBCs and monocytes, neutrophil and monocyte binding (δ-hemolysin), hemolytic alpha-toxin has pro-inflammatory properties on host hemolysins [21,23].

12) Gastroenteric toxicity of staphylococcal enterotoxins; food intoxication had been induced by immunomodulation by sAgs action. At least 20 serologically distinguished staphylococcal sAgs have been identified[58,23].

13) Superantigen function is regulated by the toxic shock syndrome toxin (TSST), which is toxic to the endothelium and has been regulated by cytokines, toxicity causes the rare condition toxic shock syndrome (TSS). A rapid occurrence of elevated fever, rash, vomiting, diarrhea, and multiorgan deficiency characterizes such infections [21,23,59].

2. Conclusion

S. aureus is a human pathogen with techniques for evading host cell antimicrobial defenses following internalization. It could survive by gaining the hidden feature of small-colony variants, secreting membrane-active toxins that free bacteria from their phagosomal envelope, or allowing bacteria to expand within phagosomes. Intracellular *S. aureus* leads to cell and tissue degradation by inducing host cell death, while intracellular persistence can lead to infection spread across the host or chronicity. Many S. aureus strains have high pathogenicity and antibiotic resistance, which is wreaking havoc on health-care programs around the world.

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