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REVIEW

Pathogenesis of *Staphylococcus aureus* Abscesses

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Staphylococcus aureus causes many types of human infections and syndromes—most notably skin and soft tissue infections. Abscesses are a frequent manifestation of *S. aureus* skin and soft tissue infections and are formed, in part, to contain the nidus of infection. Polymorphonuclear leukocytes (neutrophils) are the primary cellular host defense against *S. aureus* infections and a major component of *S. aureus* abscesses. These host cells contain and produce many antimicrobial agents that are effective at killing bacteria, but can also cause non-specific damage to host tissues and contribute to the formation of abscesses. By comparison, *S. aureus* produces several molecules that also contribute to the formation of abscesses. Such molecules include those that recruit neutrophils, cause host cell lysis, and are involved in the formation of the fibrin capsule surrounding the abscess. Herein, we review our current knowledge of the mechanisms and processes underlying the formation of *S. aureus* abscesses, including the involvement of polymorphonuclear leukocytes, and provide a brief overview of therapeutic approaches. *(Am J Pathol 2015, 185: 1518–1527; http://dx.doi.org/10.1016/j.ajpath.2014.11.030)*

Staphylococcus aureus is a widespread commensal bacterium and pathogen. Approximately 50% to 60% of individuals are intermittently or permanently colonized with *S. aureus* and, thus, there is relatively high potential for infections.[1,2] Indeed, *S. aureus* is among the most prominent causes of bacterial infections in the United States and other industrialized countries.[3,4] For example, *S. aureus* was the most frequently recovered bacterium from inpatients among 300 clinical microbiology laboratories in the United States from 1998 to 2005.[5] *Staphylococcus aureus* ranked second (after *Escherichia coli*) among bacterial isolates recovered from bacteremias in Europe in 2008, and the prevalence of *S. aureus* bacteremias increased from 2002 to 2008.[4] Recently, *S. aureus* has been reported to be second only to *Clostridium difficile* as a cause of health care–associated infections in the United States.[6]

In addition to its high prevalence, *S. aureus* is well known for its ability to acquire resistance to antibiotics. Notably, antibiotic resistance in *S. aureus* has occurred in epidemic waves.[7] Penicillin-resistant *S. aureus* emerged in the late 1940s, and by the mid-1950s, penicillin resistance was so prevalent that the antibiotic was no longer effective for treatment of infections. Methicillin-resistant *S. aureus* (MRSA) was reported in the early 1960s and then ultimately spread worldwide over the next several decades. MRSA is now endemic in health care facilities in virtually all industrialized countries, although recent data indicate a decrease in the number of invasive MRSA infections in US health care facilities.[8] Community-associated MRSA (CA-MRSA) appeared inexplicably in the 1990s and is currently a major problem in many countries worldwide, including the United States.[8,9] Unlike health care–associated MRSA infections, which occur in individuals with predisposing risk factors, CA-MRSA typically causes disease in otherwise healthy individuals. Although resistance to β-lactam antibiotics is arguably the greatest problem for treatment of *S. aureus* infections, the pathogen can develop resistance to multiple antibiotics beyond β-lactams, including vancomycin, an important therapeutic agent for severe MRSA infections.[9] Taking these attributes collectively, it is not surprising that there is a high prevalence of *S. aureus* infections globally or

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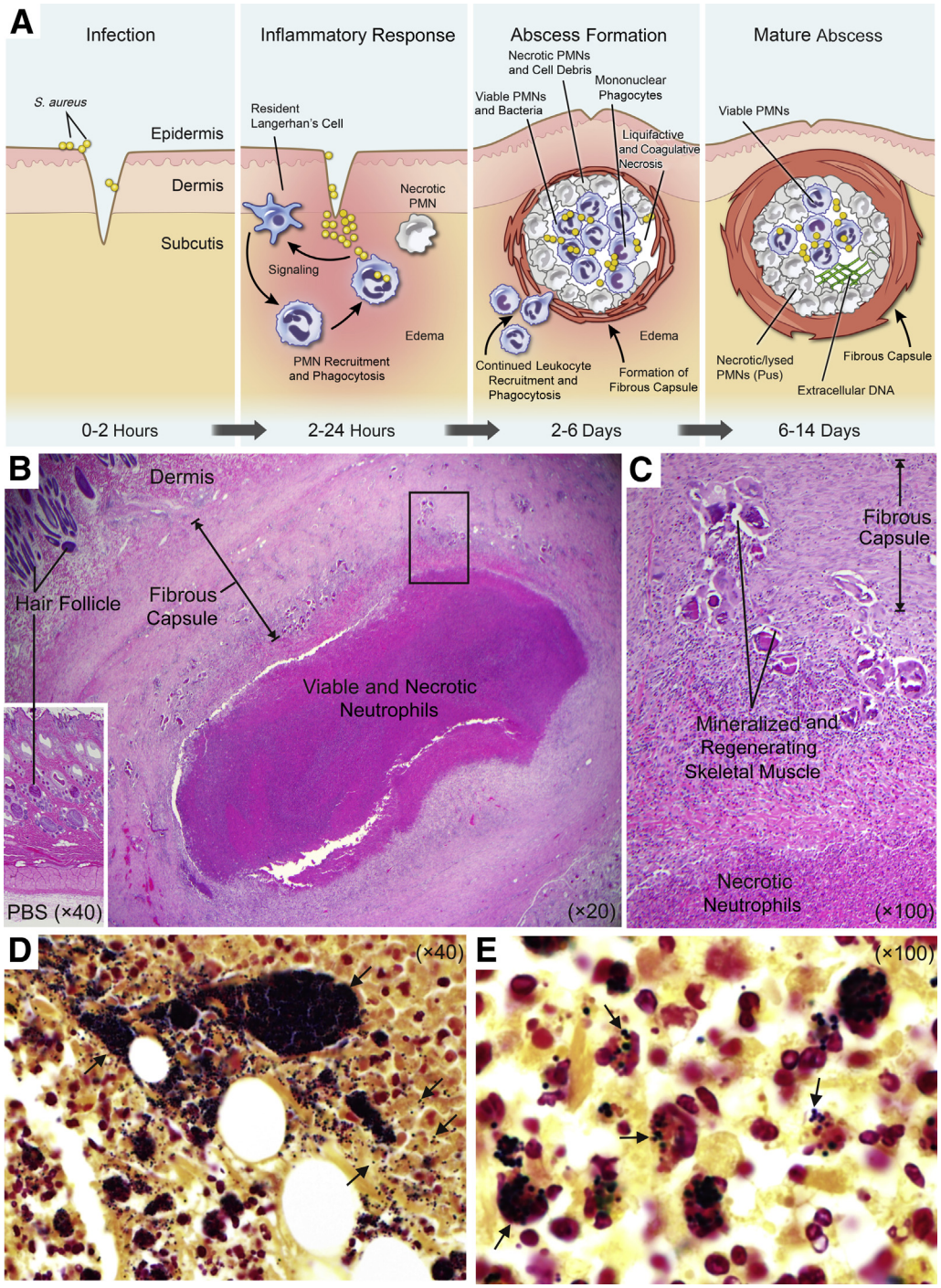

Figure 1 *Staphylococcus aureus* skin abscesses. **A:** Formation of a *S. aureus* skin abscess. **B:** Representative histopathological section of a typical rabbit skin abscess at day 14 after infection. **C:** Increased magnification of the **boxed area** shown in **B**. **D** and **E:** Gram stains of histological sections of a rabbit abscess. **Arrows** in **D** indicate *S. aureus*. The dark area is a colony of *S. aureus*. **Arrows** in **E** indicate *S. aureus* associated with leukocytes within the abscess. These studies conformed to the guidelines set forth by the NIH and were approved by the Institutional Animal Care and Use Committee at Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases (Hamilton, Montana). PBS, phosphate-buffered saline; PMN, polymorphonuclear leukocyte.

that it remains a leading cause of pathogen-associated morbidity and mortality in the United States.[6,8,10,11]

Although *S. aureus* causes a wide range of diseases and syndromes, including bacteremia, pneumonia, cellulitis, and osteomyelitis, most community-associated infections in the United States are those that affect skin and soft tissues.[9,11,12] Of all military personnel, 4% to 6% ultimately acquire a skin and soft tissue infection (SSTI), and 91% of these infections are caused by *S. aureus* (70% are MRSA).[10] A CA-MRSA strain known as pulsed-field type USA300 (referred

to herein as USA300) was the most frequently recovered bacterial isolate from community-associated SSTIs in the early-to-mid 2000s.[3,13] This particular *S. aureus* strain gained additional notoriety after it caused skin abscesses in several US professional football players.[14] USA300 has remained the most frequent organism recovered from individuals reporting to hospital emergency departments for purulent SSTIs,[11] with infections classified as abscesses in 85% of these cases.[11] Many SSTIs are relatively minor and self-limiting, but complicated SSTIs can be life threatening. There are several defining features or clinical manifestations of complicated *S. aureus* SSTIs, and these often include formation of large abscesses.[15]

Herein, we review our current knowledge of the pathogenesis of *S. aureus* abscesses, with emphasis on the involvement of polymorphonuclear leukocytes (PMNs; or neutrophils) and selected bacterial molecules.

S. aureus SSTIs

The skin is an essential first line of defense against invading bacterial pathogens, including those present in the external environment and opportunistic skin microbes. At the most basic level, the skin serves as a physical barrier to prevent entry of bacteria into deeper layers of tissue and/or dissemination to internal organ systems. Keratinocytes form this important physical barrier. Traumatic breech of the skin enables entry of pathogenic microorganisms into the underlying tissue and initiates a complex cellular response that includes mobilization of immune cells to the site of infection (Figure 1A). The clinical presentation of bacterial SSTIs can vary from superficial to highly invasive and/or disseminated disease. The importance of *S. aureus* in SSTIs has long been appreciated since Alexander Ogston first unveiled the role of the pathogen in the etiology of the pyogenic abscess in the late 19th century.[16] Although a diversity of bacteria are currently implicated in SSTIs, *S. aureus* is overwhelmingly the most prominent cause of infection (eg, a recent study of a large US health care delivery system found approximately 80% of SSTIs to be associated with *S. aureus*),[17] with the most common clinical presentation being abscess and cellulitis (63%).

In addition to SSTIs, pyogenic bacterial abscesses can form in deeper tissues, such as underlying muscle, and bacteria can disseminate to form abscesses at distal sites and affect virtually any internal organ system. The overall structure of *S. aureus* abscesses is consistent regardless of anatomical location, based, at least in part, on lesion histopathology from experimental animal models of infection (eg, rabbit SSTIs[18] and murine skin,[19] kidney,[20] and brain).[21] Similarities aside, it is unclear if there are variations in organ-specific immune response and/or bacterial response that may govern the process of abscess formation, depending on anatomical location. *Staphylococcus aureus* kidney abscesses in mice have features not found in *S. aureus* skin abscesses in rabbits. For example, Cheng et al[20] found a large mass of replicating *S. aureus* at the center of the kidney abscess that was surrounded by an eosinophilic pseudocapsule—a feature not observed in rabbit skin abscesses.[18] Inasmuch as *S. aureus* can produce molecules that promote abscess formation (see below), it is possible there is species and tissue specificity conferred by these molecules.

The pyogenic abscess begins as a localized host acute inflammatory response to bacterial infection. In addition to serving as a physical barrier to protect against microbes, keratinocytes possess pattern recognition receptors that detect invading microbes and, in turn, signal the proinflammatory response.[22] These host cells also produce antimicrobial peptides that have direct activity against *S. aureus*.[23,24] As an abscess forms, it acquires several characteristic features. The center of the abscess contains an acute inflammatory exudate composed of many viable and necrotic PMNs, tissue debris, fibrin, and live bacteria (Figure 1).[25] Maturation of the abscess is accompanied by fibroblastic proliferation and tissue repair at the abscess margin and formation of a fibrous capsule at the periphery (Figure 1). SSTIs that present as bacterial abscesses form in the dermis, epidermis, or subcutaneous tissue and are often accompanied by cellulitis. Abscess formation is a mechanism used by the host to contain and ultimately eliminate the pathogen. Indeed, some SSTIs resolve spontaneously in the absence of treatment. Notably, PMNs play a prominent role in the formation and resolution of abscesses.

Circulating PMNs are elicited from the vasculature to the infection site in response to tissue damage,[26] host proinflammatory molecules, and signals imparted directly by bacteria.[27] For example, *S. aureus* induces expression of many host proinflammatory factors *in vitro* or during experimental infection in mice, including IL-1α,[28] IL-1β,[29] IL-6,[30] IL-8,[31] IL-17,[32] leukotriene B4,[31] tumor necrosis factor-α,[33] CXCL1,[34] and CXCL2.[34] These factors are known to promote PMN extravasation and recruitment to infected tissues. Keratinocytes,[35] T cells,[34] PMNs,[32] and macrophages[36] produce chemotactic factors that contribute to the large influx of neutrophils that occurs in response to *S. aureus* SSTIs. In addition, experimental animal models provide evidence that *S. aureus* SSTIs result in increased numbers of PMNs in circulation,[37] and myeloid progenitor cells are recruited to infection sites where they undergo granulopoiesis.[37,38] The accumulation and persistence of PMNs, followed by necrotic cell lysis, contribute to the overall pathology of *S. aureus* SSTIs.

Innate Host Defense against *S. aureus* Infections—the Role of PMNs

PMNs are arguably the most important cellular defense against invading bacteria, such as *S. aureus*. Indeed, genetic disorders that negatively affect PMN function

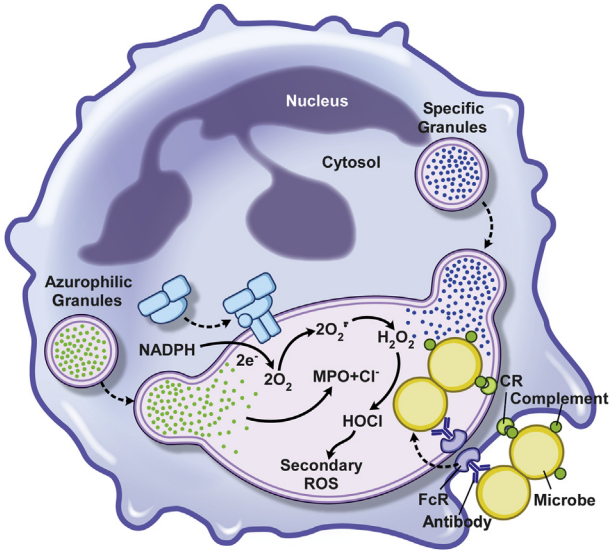

Figure 2 Polymorphonuclear leukocyte phagocytosis and microbicidal processes. Surface receptors for host opsonins, such as complement and antibody, promote ingestion of *S. aureus*, which, in turn, activates the microbicidal processes that operate in a bacteria-containing phagosome (the cytoplasmic vacuole containing bacteria). The enzyme complex responsible for generation of superoxide—NADPH oxidase—is depicted by the blue cluster of shapes on the phagosome membrane. CR, complement receptor; HOCl, hypochlorous acid; MPO, myeloperoxidase; ROS, reactive oxygen species.

typically predispose individuals to severe (and frequent) bacterial and fungal infections. For example, individuals with chronic granulomatous disease, a genetic disorder characterized by the inability of PMNs and other phagocytes to produce superoxide, often acquire severe and recurrent *S. aureus* infections. These infections often manifest as abscesses that can ultimately transform into granulomas, which obstruct organ function and must be surgically removed. Inasmuch as PMNs play a central role in *S. aureus* abscess formation and the resolution of infection, it is important to understand basic functions of these prominent host cells.

Phagocytosis of Bacteria

Neutrophils are recruited rapidly to the site of infection and remove invading microorganisms through a process known as phagocytosis (Figure 2). Bacteria express a litany of molecules on their surface, such as lipopolysaccharide, lipoprotein, and lipoteichoic acid, and these pathogen-associated molecular patterns interact with receptors on the surface of neutrophils. In general, ligation of the neutrophil pattern recognition receptors (eg, Toll-like receptors and CD14) activates signal transduction pathways that ultimately contribute to bactericidal activity. PMN phagocytosis is most efficiently promoted by opsonization of bacteria with antibody and complement. Specific antibody binds to epitopes on the surface of bacteria and enables the deposition of complement. Antibodies bound to the bacterial surface are recognized by neutrophil receptors specific for the Fc region, including CD64 (FcγRI, IgG receptor), CD32 (FcγRIIa, low-affinity IgG receptor), CD16 (FcγRIIIb, low-affinity IgG receptor), CD89 (FcαR, IgA receptor), and CD23 (FcεRI, IgE receptor). Bacteria opsonized with complement are recognized by PMN surface receptors, including ClqR, CD35, CD11b/CD18 (CR3), and CD11c/CD18 (CR4). Ingested bacteria are sequestered within membrane-bound vacuoles called phagosomes (Figure 2).

Killing of Bacteria

PMN phagocytosis is followed by the execution of bactericidal mechanisms, including the production of superoxide radicals and other reactive oxygen species (ROS), and enrichment of antimicrobial peptides, proteins, and degradative enzymes in the phagosome (Figure 2). ROS are generated by a multicomponent membrane-bound complex known as the NADPH-dependent oxidase,[39] which is defective in individuals with chronic granulomatous disease. In resting neutrophils, components of the NADPH oxidase are either cytosolic ($p40^{phox}$, $p47^{phox}$, $p67^{phox}$, and the GTPase Rac2) or located in membranes (flavocytochrome b_{558}). NADPH oxidase assembly involves translocation of the cytosolic protein components to the plasma or phagosome membrane and their subsequent association with flavocytochrome b_{558}, a transmembrane heterodimer that serves as the nidus of the assembling enzyme complex. After activation of the NADPH oxidase, electrons are transported from cytosolic NADPH to molecular oxygen, thereby generating superoxide anion.[39] Multiple oxygen metabolites, including hydrogen peroxide, superoxide anion, and hypochlorous acid, contribute to neutrophil bactericidal activity.[40]

In addition to activation of PMN oxygen-dependent bactericidal mechanisms, phagocytosis triggers degranulation, which involves fusion of cytoplasmic granules with the phagosome membrane (Figure 2).[41,42] Peroxidase-negative granules, including secretory vesicles, gelatinase granules, and specific granules, are a reservoir of functionally important membrane proteins, such as CR3, formyl peptide receptor, flavocytochrome b_{558}, and β2-integrins.[40,43] Peroxidase-positive granules (primary/azurophilic granules) contain the bulk of oxygen-independent antimicrobial agents of neutrophils, including α-defensins, cathepsins, proteinase-3, elastase, azurocidin, lysozyme, and bactericidal permeability–increasing protein.[43] Thus, fusion of azurophilic granules with phagosomes enriches these microbe-containing vacuoles with a relatively large repertoire of antimicrobial agents. PMN antimicrobial activity, composed of ROS and a broad range of antimicrobial peptides and enzymes, is sufficient to kill most invading bacteria. Notwithstanding, bacterial pathogens, such as *S. aureus*, have the ability to evade the host innate immune response to promote disease. Indeed, there are numerous *S. aureus* molecules that can contribute to

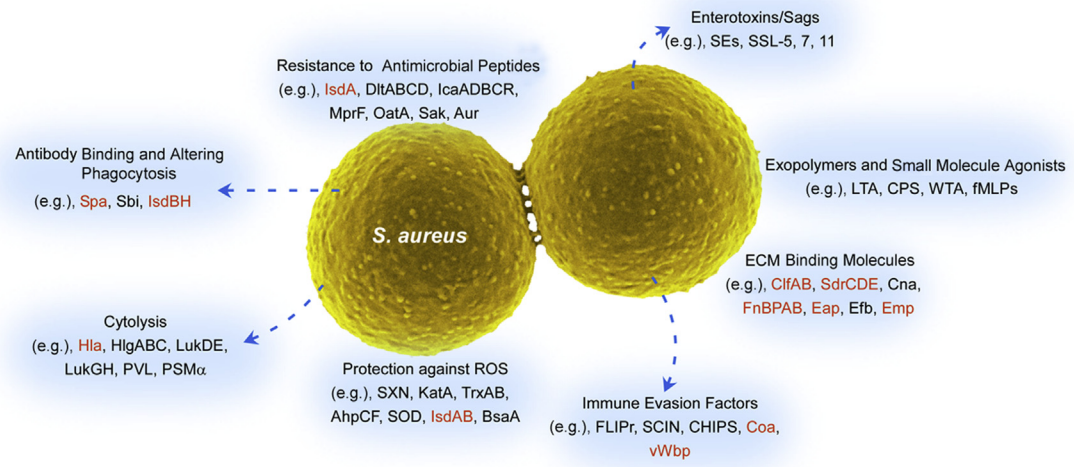

Figure 3 *Staphylococcus aureus* virulence molecules. *Staphylococcus aureus* can produce multiple types of molecules that contribute to virulence and pathogenesis. Many of these molecules have been linked to the pathogenesis of abscesses (red text). AhpCF, alkyl hydroperoxide reductase subunits C and F; Aur, aureolysin; BsaA, glutathione peroxidase; CHIPS, chemotaxis inhibitory protein of staphylococcus; Clf, clumping factor; Cna, collagen adhesin; Coa, coagulase; CPS, capsule; Eap, extracellular adherence protein; Efb, extracellular fibrinogen binding protein; FLIPr, formyl peptide receptor-like 1 inhibitory protein; fMLP, *N*-formyl-methionyl-leucyl-phenylalanine; FnBPAB, fibronectin binding protein A and B; Hla, α-hemolysin; HlgABC, gamma-hemolysin subunits A, B, and C; IcaADBCR, intercellular adhesin subunits A, D, B, C, and R; Isd, iron-regulated surface determinant; KatA, catalase; LTA, lipoteichoic acid; Luk, leukocidin; MprF, multiple peptide resistance factor; OatA, O-acetyltransferase A; PSM, phenol-soluble modulin; PVL, Panton-Valentine leukocidin; ROS, reactive oxygen species; Sak, staphylokinase; Sbi, staphylococcal IgG-binding protein; SCIN, staphylococcal complement inhibitor; SdrCDE, Ser-Asp rich fibrinogen/bone sialoprotein-binding protein subunits C, D, and E; SE, staphylococcal enterotoxin; SOD, superoxide dismutase; Spa, staphylococcal protein A; SSL, staphylococcal superantigen-like protein; SXN, staphyloxanthin; TrxAB, thioredoxin (TrxA) and thioredoxin reductase (TrxB); vWbp, von Willebrand factor binding protein; WTA, wall techoic acid.

destruction of PMNs, and these molecules are discussed below in more detail.

Molecules Produced by *S. aureus* that Affect/Alter PMN Function and Viability

S. aureus Immune Evasion Molecules

Staphylococcus aureus produces an array of potential virulence factors that play an important role on every level of host-pathogen interactions, including immune evasion molecules that allow bacteria to circumvent host innate and adaptive immunity. A multitude of these virulence factors protects *S. aureus* from bactericidal activity of PMNs or directly alters neutrophil function.[44] These molecules can be categorized according to their functions, and include those that do the following: i) affect PMN recruitment, ii) moderate the effects of phagocyte microbicides, iii) alter phagocytosis, and iv) cause host cell lysis (cytolytic toxins) (Figure 3).

As an example, *S. aureus* secretes short N-formylated peptides, which are produced during protein biosynthesis or released during bacterial cytolysis. These peptides generate a chemotactic gradient for PMNs.[45] N-formylated peptides, along with other bacteria-derived molecules, also signal resident host cells to produce proinflammatory molecules (chemoattractants) that signal PMN recruitment. The battle between *S. aureus* and PMNs begins early during infection, during which time, for example, secreted staphylococcal superantigen-like protein-5 and protein-11 obstruct interaction of PSGL-1 on the PMN surface and P-selectin on the endothelial lining, thereby blocking PMN rolling in the vessel.[46,47] Extracellular adherence protein hinders association of Mac-1 and intercellular adhesion molecule-1 or binding of lymphocyte function-associated antigen-1 to intercellular adhesion molecule-1, which negatively affects PMN adhesion and diapedesis through the endothelium of the blood vessel.[48] After extravasation, PMNs migrate toward infection sites on the basis of an increasing gradient of chemoattractants, which involve, in part, the formyl peptide receptor, C5a receptor, and formyl peptide receptor like-1. To counter this process, the chemotaxis inhibitory protein of staphylococcus and staphylococcal complement inhibitor are directed to inhibit chemotaxis dependent on C5a and formyl peptide receptor, and formyl peptide receptor-like 1 inhibitory protein impedes formyl peptide receptor like-1–dependent migration of PMNs.[49–52] At the site of *S. aureus* infection, PMNs encounter secreted cytolytic toxins that can permeabilize host cell plasma membranes and/or cause rapid cytolysis and must overcome the effects of molecules that potentially inhibit bacterial uptake. Among these antiphagocytic molecules are protein A, which binds the Fc region of IgG (thereby blocking opsonization with specific antibody), clumping factor A, and extracellular fibrinogen binding protein, which blocks phagocytosis by depositing fibrinogen on the bacterial

surface.[53–55] Despite these obstacles, *S. aureus* is readily engulfed by PMNs—especially by those that are adherent.

Bacterial pathogens have also evolved mechanisms to protect against oxygen-dependent and oxygen-independent killing by human PMNs (Figure 3). For example, *S. aureus* uses alkyl hydroperoxide reductase, catalase, and superoxide dismutase to protect against ROS.[56] Moreover, staphylococcal golden pigment or staphyloxanthin functions as an antioxidant and is additional protection against ROS.[57] *Staphylococcus aureus* has multiple, redundant molecules/systems that promote resistance to antimicrobial peptides, and such resistance typically involves modification of the cell wall.[44]

Thus, given the prominent role played by PMNs in host defense against *S. aureus* infections, and considering the pathogen has many molecules that can potentially contribute to evasion of neutrophil function, it is not surprising that PMNs play a major role in the formation of abscesses.

Lysis of PMNs and the Role of *S. aureus* Secreted Toxins

To maintain proper homeostasis, the host immune system is subject to constant turnover of cells, including neutrophils. Typically, aging PMNs undergo apoptosis and are removed by macrophages in a process known as efferocytosis.[58] However, bacteria such as *S. aureus* have the ability to alter and/or circumvent this process and cause PMN lysis.[59] Because PMNs contain numerous cytotoxic and proinflammatory molecules, uncontrolled lysis can have pivotal consequences to host health and additionally can promote dissemination of bacteria previously contained within phagosomes. Recent studies revealed that after PMN engulfment, *S. aureus* is able to divert PMNs from conventional apoptotic pathways and cause subsequent lysis of these host cells by means of a process termed programmed necrosis.[60] *In vitro* studies have shown that within 3 to 4 hours after phagocytosis of *S. aureus*, neutrophils initiate morphological changes, such as blebbing, increase exposure of phosphatidylserine on the surface of the cell, and nuclear condensation, which are hallmarks of PMN apoptosis. Although the initial steps of programmed necrosis are similar to apoptosis, *S. aureus*–induced programmed necrosis is a receptor-interacting protein 1–dependent process that does not result in activation of caspases 2, 3, 8, and 9.[60] Moreover, PMN phagocytosis of *S. aureus* is accompanied by increased expression of CD47 (a don't eat me signal), a molecule that has been shown to prevent efferocytosis of apoptotic PMNs by macrophages.[60] Notably, bacterial burden plays an essential role in directing PMNs toward programmed necrosis. Inasmuch as a relatively high bacteria/PMN ratio (10:1) is sufficient to induce the process, a low bacterial burden (1:1) requires additional caspase inhibition. Furthermore, engulfment of *S. aureus* by PMNs alters macrophage production of cytokines, such as IL-6, IL-8, or tumor necrosis factor-α, and lowers secretion of IL-1β, which is an essential cytokine in subcutaneous infections.[29,60,61]

In addition to triggering programmed necrosis, *S. aureus* secretes virulence factors that promote direct lysis of neutrophils (Figure 3). Among them are leukotoxins, such as Panton-Valentine leukocidin, leukocidin GH, or leukocidin DE, and α-type phenol-soluble modulins, γ-hemolysin, and δ-toxin.[62–72] Permeabilization of the cell membrane by Panton-Valentine leukocidin or leukocidin GH can cause neutrophil lysis that results in the formation of structures called neutrophil extracellular traps, which are web-like structures of nuclear DNA to which histones and other cationic molecules are bound non-specifically.[73–75] Whether these structures play a direct role in the formation of abscesses is not clear, although there is no question that abscesses contain a bolus of lysed PMNs and PMN debris, which includes extracellular DNA.

Hla and Dermonecrosis

α-Hemolysin (Hla; α-toxin) is one of the earliest studied staphylococcal virulence factors.[76,77] This pore-forming cytotoxin is freely secreted by *S. aureus* as a water-soluble monomer, and then binds the surface of target cells, forming a heptameric transmembrane pore.[78] Formation of functional pores generates ion imbalance, including efflux of potassium cations and ATP or influx of calcium ions, and ultimately leads to cell death. Hla targets many different cell types, including epithelial and endothelial cells, blood cells, and platelets.[79]

Hla plays a crucial role in the pathogenesis of *S. aureus* SSTIs and, in particular, promotes dermonecrosis in animal infection models. Functional inactivation of the gene encoding Hla by mutagenesis or deletion, or passive or active immunization against this toxin, significantly reduces size of abscesses and virtually eliminates dermonecrosis in animal infection models.[18,19,80–82] The relatively recent discovery of an Hla receptor—a disintegrin and metalloprotease 10—was a major advance for our understanding of the role played by Hla during SSTIs.[83] By activating a disintegrin and metalloprotease 10, Hla contributes to proteolysis of E-cadherin, which leads to the disruption of the adherens junction in the epithelial layer, thereby prompting potential remodeling of the epithelial layer and consequently pathogen dissemination.[83,84] In a similar manner, Hla contributes to the breach of blood vessel endothelium integrity by causing proteolysis of the extracellular domain of vascular endothelial cadherin.[85] The toxin also promotes a vigorous host inflammatory response, and this response has been linked to increased morbidity and mortality in animal infection models (eg, in *S. aureus* pneumonia).[86] Hla also acts directly or indirectly with intracellular host sensor molecules, notably, members of the nucleotide-binding domain leucine-rich repeat containing (NLR) family, such as NLRC2 and NLRP3.[87–89] Activation of the NLRP3 inflammasome by Hla and costimulation of NLRC2 by Hla and muramyl dipeptide trigger downstream activation of caspase 1, which subsequently leads to activation of the potent proinflammatory cytokine IL-1β that largely contributes to PMN influx to the site of infection.[87,88]

The ability of Hla to cause host cell cytolysis (and thus destabilize the dermis) and elicit neutrophil recruitment

likely plays a central role in the pathogenesis of SSTIs. More notably, Hla can promote dermonecrosis in animal skin infection models, a more severe manifestation of SSTIs. Whether this virulence attribute of Hla is recapitulated in human SSTIs remains unknown, but the toxin is potentially a target for therapeutics designed to moderate the severity of disease. Key features of mature abscesses in experimental animal models and those of humans have many similar attributes, and thus the experimental abscesses in animals seem to be a reasonable approximation of *S. aureus* skin abscesses in humans. However, there are clear differences between experimental *S. aureus* abscesses in animals and human *S. aureus* abscesses. These differences include those in the innate immune systems of experimental animals and humans; for example, there are known differences in the ability of leukocidins, such as Panton-Valentine leukocidin, to cause cytolysis of rodent and human PMNs.[90]

Coagulases

Although the contribution of Hla to *S. aureus* SSTIs is clear in animal infection models, there is little known about the contribution of additional staphylococcal factors to abscess formation and development. Notwithstanding, several recent studies provide evidence that *S. aureus* coagulase (Coa) and von Willebrand factor binding protein (vWbp) facilitate abscess formation in a mouse model of disseminated infection.[91–93] Coa and vWbp are perhaps best known for their ability to alter host defense by promoting coagulation and altering normal hemostasis, and thus contribute to *S. aureus* pathogenesis.[91,94] Both Coa and vWbp activate prothrombin in a non-proteolytic manner, which diverts prothrombin activation away from host regulation.[95,96] Furthermore, the C-terminal domain of Coa binds fibrinogen and subsequently enables proteolytic conversion of fibrinogen to fibrin, and the deposition of fibrin. Coagulase and high levels of vWbp accumulate at the abscess peripheries, and these molecules likely contribute to abscess development via formation of a pseudocapsule (also called fibrous capsule) and microcolony-associated meshwork.[97] These structures generate a mechanical barrier that hinders the recognition and phagocytosis of bacteria by host neutrophils and other immune cells.[98] Single Coa or vWbp deletion mutants alter bacterial survival and/or decrease abscess formation, but the greatest decrease in abscess formation occurs with *coa/vwbp* double deletion mutant strains in animal infection models. This phenomenon is likely correlated with functional redundancy of Coa and vWbp during prothrombin activation and fibrin deposition.[93,97]

The importance of Coa and vWbp in the formation of *S. aureus* abscesses is best illustrated by recent vaccine studies, in which active and passive immunization with antibodies against Coa and vWbp significantly reduced number of lesions in a murine kidney abscess model.[93,97] Whether such an approach would be successful in treatment or prevention of severe/complicated SSTIs remains unclear.

Treatment and Future Perspective

Staphylococcus aureus is a human commensal microbe and has been a cause of infections throughout recorded history. There is no question that it will continue to be a significant cause of human infections. Many of the infections caused by *S. aureus* are nonsevere SSTIs that are self-limiting or resolve without therapeutic intervention. However, severe or complicated SSTIs require some type of therapy or treatment. Indeed, skin infections often led to invasive disease or death before the antibiotic era.[65]

The Infectious Diseases Society of America has set forth specific guidelines for treatment of *S. aureus* SSTIs.[99] Incision and drainage alone is the recommended treatment for cutaneous abscesses, whereas antibiotics are recommended only for abscesses associated with severe and/or disseminated disease or those that fail to respond to incision and drainage.[100] That said, outpatients with minor abscesses can be treated with empirical antibiotic therapy that is effective against CA-MRSA.[100] Such antibiotics include trimethoprim-sulfamethoxazole, clindamycin, and doxycycline or minocycline.[99,100] By comparison, vancomycin, linezolid, daptomycin, televancin, and clindamycin are among the antibiotics recommended for hospitalized patients with complicated SSTIs, which include major abscesses.[99]

Given the ability of *S. aureus* to develop resistance to antibiotics rapidly, it is worthwhile to consider alternative therapies for—or prophylactic measures to prevent—severe *S. aureus* disease. A potential therapeutic and/or prophylactic approach is the use of active or passive vaccination against *S. aureus* molecules known to promote severe SSTIs. There has been significant effort put forth in recent years to develop a vaccine designed to protect against *S. aureus* infection, but these vaccines have failed in human clinical trials.[101] One confounding issue is our lack of knowledge about the factors (both host and microbe) that contribute to protective immunity against *S. aureus* infections. Recently, Fritz et al[102] reported that anti-Hla antibody titers correlate with protection against subsequent *S. aureus* infection, albeit SSTIs elicit a limited protective immune response. Consistent with those findings, work in mouse infection models has demonstrated that antibodies directed against Hla, Coa, and vWbp protect against severe *S. aureus* skin disease.[19,93] Sampedro et al[103] took these models one step further by testing the ability of anti-Hla approaches, which include direct toxin neutralization or receptor blocking, to moderate or prevent recurrent *S. aureus* SSTIs in a mouse model.

Collectively, these studies suggest that it should be possible to use a vaccine or similar (eg, receptor blocking) approach for treatment, moderation, or prevention of severe SSTIs. Although significant progress has been made (eg, use of incision and drainage as a treatment approach), more work is needed in this general area to develop therapies that are not dependent on antibiotics.

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