EDITORIAL

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Staphylococcus epidermidis: a major player in bacterial sepsis?

“... *Staphylococcus epidermidis* is among the most frequent bacterial sources underlying bacteremia and sepsis.”

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Blood infection (sepsis) causes millions of deaths worldwide and is the most frequent cause of death in hospitalized patients. Sepsis is most commonly due to bacteria [1]. In addition to symptoms related to the specific bacterial infection, symptoms of sepsis include fever, tachycardia and tachypnea. The definition of sepsis is clinical, with the sepsis-related organ failure assessment score, a combination of scores for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological conditions, giving an understanding of the severity of sepsis in terms of the prediction for a fatal outcome.

Sepsis develops from bacteria being present in the blood (bacteremia) when the immune system launches an overwhelming responsive defense [1]. While sepsis is well defined clinically, the molecular immunological mechanisms that underlie the development of sepsis are poorly understood. Long believed to be predominantly due to Gram-negative bacteria, during the second half of the 20th century, Gram-positive bacteria, in particular *Staphylococcus aureus*, have become leading causes of sepsis and sepsis-related deaths [2]. Coagulase-negative staphylococci (CNS), with the major species *S. epidermidis*, are also often reported as frequent causes of sepsis, particularly among neonates [3,4].

However, the fact that they are ubiquitous commensals on the human skin makes the microbiological diagnosis of a true CNS blood infection difficult, as the detection of CNS in blood samples is often due to contamination rather than a true infection. The precise percentage of how many positive blood cultures are due to contamination varies considerably among the many studies that have attempted to estimate that number. Nevertheless, there is agreement that *S. epidermidis* is among the most frequent bacterial sources underlying bacteremia and sepsis [4].

In theory, bacterial factors can influence the development of sepsis in at least two different ways. First, the reaction of the immune system differs depending on the bacterial triggers or pathogen-associated molecular patterns. In Gram-negative bacteria, the most important proinflammatory trigger is lipopolysaccharide. Structural modifications of this surface structure, which is ubiquitous in Gram-negative bacteria, can have a significant impact on the strength of the immune reaction. In Gram-positive bacteria, lipoteichoic acid is often stated to play a similar role. In addition to those invariant structures on the Gram-negative or Gram-positive cell envelope, some particularly aggressive

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bacteria such as *S. aureus* produce toxins that may further significantly exacerbate the immune reaction. Many *S. aureus* toxins, such as the bi-component leukotoxins or the phenol-soluble modulins (PSMs), have been reported to have proinflammatory activity [5,6]. Furthermore, several *S. aureus* and *Streptococcus pyogenes* strains produce superantigens, whose activity is linked to very severe forms of sepsis termed as septic shock [7].

Second, bacteria can produce factors that interfere with the ability of the immune system to eradicate the bacterial invaders. Some of those factors decrease the ability of the immune system to recognize the bacteria, such as bacterial proteins interfering with human immune receptor activation. Such mechanisms may be more important for bacterial infections other than sepsis, as during sepsis, the immune system is already over-reacting to the presence of the bacteria. However, bacterial protein toxins that kill important immune cells, such as leukotoxins or PSMs, may significantly decrease the resolution of sepsis [5,8].

Sepsis often arises from the constant seeding of bacteria from contaminated indwelling medical devices. For CNS, this is by far the most common cause of bacteremia. CNS are among the most frequent causes of bloodstream infection originating from indwelling medical device contamination [4]. The most frequent types of such device-associated infections are central line-associated bloodstream infection and catheter-related bloodstream infection. Their severity is ultimately dependent on the extent of bacterial colonization. Thus, the most important bacterial factors underlying the pathogenesis of such infections have always been considered those that increase the propensity of the bacteria to form biofilms on the devices, which significantly decreases the capacity of phagocytic cells and other innate immune mechanisms to remove the bacteria. For *S. epidermidis*, these factors include the biofilm exopolysaccharide polysaccharide intercellular adhesin (PIA), in addition to a series of proteins and other matrix components such as teichoic acids [9].

In contrast to *S. aureus*, *S. epidermidis* as well as other CNS have not been known to produce aggressive proinflammatory or even cytolytic toxins [10]. Reports that claim that α -toxin or superantigenic toxins are widespread in *S. epidermidis* or other CNS have to be regarded as incorrect due to the failure to appropriately

identify isolates. The notion that CNS do not produce toxins, however, had to be corrected when it was found that *S. epidermidis* produces PSMs. PSMs are amphipathic, α -helical peptides with surfactant character [6]. Many PSMs have strong proinflammatory and broadly cytolytic properties. At nanomolar concentrations, in predominantly formyl peptide receptor-2 mediated fashion [11], they elicit leukocyte chemotaxis, activation and cytokine release. In contrast, their cytolytic properties, which are observed at micromolar concentrations and have been described for neutrophils, monocytes, erythrocytes and osteoblasts are receptor-independent. Notably, PSMs are produced in high amounts in a quorum-sensing controlled fashion [12], with stationary phase bacterial cultures reaching far more than the concentrations needed for cytotoxicity. In *S. aureus*, PSMs have been shown to contribute significantly to pathogenesis [8].

PSMs have been grouped according to length. The α -type PSMs are 20–25 and the β -type PSMs are approximately 44–45 amino acids long. All PSMs are secreted by a dedicated transporter without a signal peptide and thus have an N-terminal formyl-methionine [13]. While virtually every staphylococcal species produces PSMs, the pattern is different and characteristic for every species. After the initial description of three PSMs in *S. epidermidis* (PSM α , PSM β and PSM γ , which is equal to δ -toxin), the entire *S. epidermidis* PSM pattern was determined. One particular *S. epidermidis* PSM, PSM δ , has astounding cytolytic character at the level of the most strongly cytolytic *S. aureus* PSM (PSM α 3) [14]. Overall lower cytolytic capacity of *S. epidermidis* as opposed to *S. aureus* strains is due to a relatively low production level of PSM δ in comparison [14].

In addition to the species characteristic presence of PSMs, which are normally genome-encoded, the methicillin-resistant elements of types II, III and VIII, which are present in many staphylococcal species, contain a gene encoding the α -type PSM, PSM-mec [15,16]. Many clinical *S. epidermidis* strains are methicillin-resistant, contain this element and thus produce PSM-mec, often in very high amounts. In recent research, Qin *et al.* showed that PSM-mec has a considerable role in *S. epidermidis* sepsis as shown by cellular assays and a mouse sepsis model [17]. The important message of that finding is that in contrast to previous notions, CNS can produce toxins that significantly impact the

development of sepsis and thus represent possible targets for target-oriented drug development against acute disease caused by those bacteria. While not yet shown by isogenic mutants, it is likely that other *S. epidermidis* PSMs, and possibly also PSMs in other CNS, have a similar impact on sepsis. To analyze this, the relatively difficult production of isogenic mutants, in particular a sequential mutant that has all *psm* loci deleted will be necessary.

In conclusion, the bacterial mechanisms in *S. epidermidis* that promote sepsis not only include its ability to form biofilms on indwelling medical devices, but also toxin production. It is important to note that the surfactant PSMs are also involved in detaching the bacteria from biofilms, thus enabling their dissemination into the bloodstream [18]. Mechanistically, whether the main role that PSMs play in sepsis is to function as biofilm detachment factors, major pro-inflammatory, diffusible pathogen-associated molecular patterns or to directly

kill immune cells via their cytolytic properties, remains to be elucidated. All these mechanisms may be important and future research with PSMs in *S. epidermidis* should also shed more light on the yet incompletely understood host response to *S. epidermidis* acute infection [19]. Finally, the notion that PSMs contribute to CNS-mediated disease suggests that they may be valuable targets for antivirulence drug development [20].

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