All That Glisters Is Not Gold – *Staphylococcus aureus* and Innate Immunity

In this issue of *Journal of Innate Immunity*, Dai et al. [1] discuss myeloid-derived suppressor cells (MDSCs) in an interesting review. MDSCs are a heterogeneous population of immature suppressor cells that are generated due to aberrant myelopoiesis under pathological conditions. These cells have immunosuppressive properties and may contribute to immune homeostasis. However, their expansion may impair pathogen elimination and thus may lead to disease persistence [1]. Recently, Shime et al. [2] showed that MDSCs are a target of poly I:C to prime NK cells, which exert antitumor activity to NK-sensitive tumor cells.

*Staphylococcus aureus* is a major human pathogen that was first identified in 1880 by the British surgeon Sir Alexander Ogston in pus from a knee joint abscess [3]. Notably, the mortality of patients with *S. aureus* bacteremia in the preantibiotic era exceeded 80%, but the introduction of penicillin in the early 1940s dramatically improved the prognosis. However, by the late 1960s, more than 80% of both community- and hospital-acquired staphylococcal isolates were resistant to penicillin. *S. aureus* cause a diverse array of infections, ranging from less harmful to life threatening. While effective antibiotics against this important pathogen still exist, their number is becoming increasingly limited. Thus, novel approaches to therapy and prevention will become more and more important [4]. In the light of this, novel understanding of innate immune mechanisms can provide templates for novel antimicrobial pharmaceuticals.

Recently, several virulence strategies of *S. aureus* have been elucidated. The *S. aureus* α-toxin is a pore-forming toxin that utilizes the receptor ADAM10 to injure cells of the host. Utilizing myeloid lineage-specific Adam10 knockout mice, Becker et al. [5] have shown that α-toxin causes tissue-specific effects on innate immunity. The effects correlated with a defect in toxin-induced IL-1β production. The *S. aureus* α-toxin also plays other roles in corrupting innate immunity. After phagocytosis by macrophages, *S. aureus* evades killing in an α-toxin-dependent manner, and then prevents the apoptosis of infected cells by upregulating expression of antiapoptotic genes. Using purified α-toxin, Koziel et al. [6] have shown that α-toxin is critical for the induction of MCL-1 expression and the cytoprotection of infected macrophages.

Recognition and signaling through Toll-like receptors are crucial molecules in the induction of host defense responses. This requires adaptor proteins that contain a Toll/interleukin-1 receptor (TIR) domain. *S. aureus* produces several innate immune-evasion molecules that interfere with the host’s innate immune response. Askarian et al. [7] found a homologue of the human TIR domain in *S. aureus*. **Abstract**
that was named staphylococcal TIR domain protein (TirS). Interestingly, TirS was found to interfere with signaling through TLR2, including MyD88 and TIRAP, NF-κB and/or mitogen-activated protein kinase pathways. The ability of \textit{S. aureus} to infect tissues is dependent on the precise control of virulence through gene-regulatory systems. The Saer/S two-component system is a major regulator of \textit{S. aureus} virulence, but the importance of the host environment on Saer/S-regulated genes (saer/S targets) was until recently less well defined. Using transcriptional assays, Zurek et al. [8] examined the expression of genes with the Saer binder site in the \textit{S. aureus} strain USA300 upon exposure to neutrophils and host-derived peptides. They found that only some of the saer/S targets, as opposed to the entire Saer/S virulon, were activated during the early phase upon encounter with neutrophils as well as α-defensins. Thus, Saer/S is the major regulator of virulence factors, while Agr, a quorum-sensing two-component system, has moderate influence on the transcription of the saer/S targets.

Neutrophils constitute key cells in innate immunity and are an important player in the defense against staphylococcal infections. Specific growth factors sequentially activate distinct genes in myeloid progenitors of the bone marrow, resulting in the distinct phenotype with cytoplasmic granules having a content of antimicrobial proteins and enzymes. Granulocyte colony-stimulating factor is a key factor, but several other molecular mechanisms are involved in regulating the flow of neutrophils emigrating from the bone marrow, being transported in the blood and finally recruited to sites of inflammation by chemotactic factors [9–12]. The importance of neutrophil adherence for phagocytosis and killing of \textit{S. aureus} by neutrophils has recently been demonstrated [13]. In addition to antimicrobial proteins and enzymes, reactive oxygen species and the release of DNA (i.e. NETs) play important roles in killing pathogens [14, 15]. Eventually, the resolution of inflammation is important to avoid excessive damage [16].

Interestingly, neutrophils can interact with the complement system through the release of the granule protein myeloperoxidase (MPO). The alternative pathway (AP) of complement consists of C3, factor B, factor D and properdin, which amplifies AP activation. AP has been implicated in many neutrophil-mediated diseases, such as antineutrophil cytoplasmic antibody-associated vasculitis. In a recent study, O’Flynn et al. [17] showed that MPO could induce C3 activation. Furthermore, they could demonstrate that MPO binds properdin directly, demonstrating an activation of the AP that is dependent on properdin.

\textit{S. aureus} release potent proteolytic activity. Jusko et al. [18] showed that the four major extracellular proteases of \textit{S. aureus}, the cysteine proteases staphopain A and staphopain B, the serine protease V8 and the metalloprotease aureolysin, all drastically decreased the hemolytic activity of serum. These four proteases were found to inhibit all pathways of complement due to the efficient degradation of several key components. In another study, the same group showed that proteases of \textit{S. aureus} can degrade pulmonary surfactant protein A, a major surfactant component with innate immune functions [19].

\textit{S. aureus} is an increasing threat to human health and one of our major guards against this pathogen is the neutrophil. Hopefully, novel therapeutic concepts can be inspired from the strategies used by the innate immune system.

\textit{Heiko Herwald, Lund}

\textit{Arne Egesten, Lund}

\section*{References}


