Infections with *Streptococcus pyogenes*, a major human pathogen, are typically of a mild and superficial nature. However, under rare and unfortunate conditions, patients can experience severe and life-threatening complications, such as necrotizing fasciitis and streptococcal toxic shock syndrome [1]. Notably, invasive streptococcal disease can occur in previously healthy individuals with no obvious preceding superficial infection. This has led to the hypothesis that streptococci have to cause a transient bacteremia that facilitates their dissemination within the host’s body. In this issue of the *Journal of Innate Immunity*, Ochel et al. [2] show that *S. pyogenes* of the M1 serotype can invade endothelial cells. The study focuses on the tissue-invasive serotype M1 of *S. pyogenes*, demonstrating that the pathogen can enter the endothelial cells of blood vessels, thereby escaping host defense, and can survive in the cytoplasm of these cells. At a later stage, the bacteria may then spread further, causing systemic and severe infections.

*S. pyogenes* is extremely virulent in the bloodstream, not least via the M-proteins, both surface-associated and released, that may trigger a cytokine storm and other pathologic conditions as is often seen in patients with severe sepsis. A better understanding of these reactions may lead to the discovery of novel diagnostic tools and antimicrobial therapies. One example is TREM-1 (trigging receptor expressed on myeloid cells), a surface molecule expressed on neutrophils and macrophages. Recent findings in an animal model showed that TREM-1 was upregulated during sepsis caused by *S. pyogenes* and that administration of the TREM-1 decoy receptor rTREM-1/Fc attenuated the proinflammatory cytokine response, improving the outcome [3].

*S. pyogenes* also produces several proteases and two of these have distinct activities against immunoglobulins (IgGs). The classical cysteine proteinase of *S. pyogenes* is SpeB, having broad proteolytic activities including IgG degradation [4]. In addition, *S. pyogenes* secretes one of the best-described bacterial enzymes with glycoside hydrolase activity specific for human IgG. The glycan of IgG is crucial for the stability and conformation of the Fc portion, and deglycosylation of IgG can result in the loss of activation of the complement and a failure to bind to Fc receptors. The activity of EndoS on opsonizing IgG has been shown to lead to a significant reduction in the killing of *S. pyogenes* in blood compared to untreated IgG [5]. In addition to SpeB and EndoS, *S. pyogenes* has evolved an IgG-specific endopeptidase, IdeS, which is highly specific for the lower hinge region of IgG [6].

*S. pyogenes* can also manipulate the innate immune response, as described in the following three examples: complement activation, phagocytosis and neutrophil extracellular traps (NETs). Complement fragments, such as C3a and C5a, are important in host defense because both peptides serve as anaphylatoxins and, similarly to IL-8/CXCL8, they can recruit neutrophils to sites of infection [7]. There are two specific proteases released from *S. pyogenes* that can target these chemotactic factors, i.e. C5a peptidase-degrading C5a and SpyCEP-processing IL-8/CXCL8, respectively [8, 9], which, in both
cases, have been shown to promote resistance to neutrophil killing.

Upon internalization in endothelial cells, the M1 protein of *Streptococcus pyogenes* serotype is incorporated into phagosomes that traffic via the endosomal/lysosomal pathway [2]. Intracellular killing in nonprofessional phagocytes may also include other mechanisms, for example perforin-like molecules, as seen in fibroblasts [10]. However, in endothelial cells, some of the streptococci successfully evade this innate killing process and escape into the cytoplasm of the host cell [2]. In macrophages, the intracellular pattern-recognition receptor TLR9 (Toll-like receptor 9) promotes macrophage hypoxia-inducible factor-1α levels, oxidative burst and nitric oxide production in response to group A *Streptococcus*. TLR9 contributes to group A *Streptococcus* clearance in vivo in both localized cutaneous and systemic infection models [11].

Neutrophils are an important part of the host defense against *S. pyogenes*. These bacteria are likely to corrupt phagocytic killing, and it has been suggested that both resistance to phagocytosis and maturation of the phagosome are escape mechanisms [12, 13]. Another more recently described way for neutrophils to counteract bacterial dissemination is through the release of nuclear DNA resulting in the formation of NETs [14]. *S. pyogenes*, like many other bacterial species, can escape entrapment in NETs through the release of extracellular DNase [15, 16]. However, it may be that the extracellular DNA neutralizes the bactericidal activity of antimicrobial proteins as exemplified by hBD-3 (human β-defensin 3) [17]. In line with this, it has been suggested that NETs trap bacteria but may not necessarily exert bactericidal activities [18].

After escape from their intracellular repositories, the bacteria encounter other host defense mechanisms and barriers. It was recently demonstrated that in deep tissues, matrix molecules (in particular collagen VI) counteract streptococcal invasion [19]. These few examples underline the complexity of host-parasite interactions and they illustrate that the bacteria are very rapidly able to adjust to their environment by modulating and countering the host’s immune responses in a spatial and temporal manner.

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References