



Review

Staphylococcus aureus strategies to evade the host acquired immune response

Oliver Goldmann*, Eva Medina*

Infection Immunology Research Group, Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany

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ABSTRACT

Staphylococcus aureus poses a significant public-health problem. Infection caused by *S. aureus* can manifest as acute or long-lasting persistent diseases that are often refractory to antibiotic and are associated with significant morbidity and mortality. To develop more effective strategies for preventing or treating these infections, it is crucial to understand why the immune response is incapable to eradicate the bacterium. When *S. aureus* first infect the host, there is a robust activation of the host innate immune responses. Generally, *S. aureus* can survive this initial interaction due to the expression of a wide array of virulence factors that interfere with the host innate immune defenses. After this initial interaction the acquired immune response is the arm of the host defenses that will try to clear the pathogen. However, *S. aureus* is capable of maintaining infection in the host even in the presence of a robust antigen-specific immune response. Thus, understanding the mechanisms underlying the ability of *S. aureus* to escape immune surveillance by the acquired immune response will help uncover potentially important targets for the development of immune-based adjunctive therapies and more efficient vaccines. There are several lines of evidence that lead us to believe that *S. aureus* can directly or indirectly disable the acquired immune response. This review will discuss the different immune evasion strategies used by *S. aureus* to modulate the different components of the acquired immune defenses.

1. *Staphylococcus aureus*: a tenacious pathogen

Staphylococcus aureus is one of the most common pathogens causing infections in humans that can be life-threatening, especially in individuals with serious underlying health conditions (Tong et al., 2015). *S. aureus* colonizes > 20% of the population in an asymptomatic manner, but it can become symptomatic upon breaching the epithelial barriers (Lowy, 1998). The extraordinary capacity of *S. aureus* to acquire antibiotic resistance is a cause of great concern (Chambers and Deleo, 2009). Furthermore, *S. aureus* is capable of producing slow growing natural sub-populations designated as small colony variants (SCVs), which are often associated with chronic antibiotic exposure (Proctor et al., 2006). SCVs represent a serious clinical problem because they exhibit increased resistance to aminoglycosides and to cell wall-active antibiotics and therefore they can persist for long periods in patients despite antibiotic treatment (Garcia et al., 2013; Kahl et al., 2016). For these reasons, an efficacious vaccine that can prevent *S. aureus* infections is eagerly wanted. Although several *S. aureus* vaccines based on active or passive immunizations have been developed, none of them has shown significant efficacy in clinical trials (Giersing et al., 2016). A major problem for the development of an efficient vaccine to prevent *S. aureus* infection is the capacity of this pathogen to establish productive infection in the host even in the presence of a robust

antigen-specific immune response. This is illustrated by the high frequency of recurrent and chronic infections that implies that prior infection with *S. aureus* often does not result in protective immunity to subsequent infections (Miller et al., 2015; Montgomery et al., 2015). Furthermore, a large *S. aureus*-specific T-memory cell pool that recognizes extracellular staphylococcal antigens is commonly present in healthy adults (Kolata et al., 2015). This indicates that an immune memory response is indeed generated against *S. aureus* antigens that is not protecting against re-infection. Experimental data obtained in animal models after repeatedly challenges with *S. aureus* further support the failure of the antigen-specific immune response to confer protection (Kim et al., 2012). Likewise, evidence has been provided that induction of pathogen-specific T and B cells by vaccination of mice with heat-killed bacteria failed to eradicate a subsequent *S. aureus* challenge (Schmalzer et al., 2011). Together, these observations indicate that *S. aureus* has developed sophisticated mechanisms to dampen the host adaptive immune defenses, enabling the pathogen to establish productive infection in the face of a robust antigen-specific immune response.

2. *S. aureus* manipulation of humoral immune responses

Antigen-specific antibodies against *S. aureus* have been shown to

* Corresponding author.

E-mail addresses: oliver.goldmann@helmholtz-hzi.de (O. Goldmann), eva.medina@helmholtz-hzi.de (E. Medina).<http://dx.doi.org/10.1016/j.ijmm.2017.09.013>Received 3 July 2017; Received in revised form 1 September 2017; Accepted 13 September 2017
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confer only partial protection against ensuing infections. Thus, despite of the fact that increased antibody levels against *S. aureus* can be detected in convalescent patients, the rate of recurrent staphylococcal infections in those patients is high (Huang et al., 2008; Huang and Platt, 2003). Furthermore, high levels of circulating antibodies against *S. aureus* antigens are present in *S. aureus*-colonized individuals that are not protecting them from acquire *S. aureus* infections (Verkaik et al., 2009; Verkaik et al., 2010). Along the same line, it has been reported that cystic fibrosis patients persistently colonized with *S. aureus* produce high antibodies titers against numerous staphylococcal virulence factors that are not conferring protection against chronic airway infection (Junge et al., 2016). This clearly indicates that *S. aureus* possesses strategies that enable the bacterium to circumvent the humoral immune response and establish infection in the presence of high levels of antigen-specific antibodies.

One important mechanism used by *S. aureus* to interfere with the elicitation of protective humoral immune responses is through the polyclonal activation of B cells by staphylococcal protein A (SpA). SpA is a 45-kD surface-bound and secreted protein that is expressed by most clinical isolates and can bind immunoglobulins (Becker et al., 2014). SpA contains five immunoglobulin-binding domains and is capable of binding both the Fc γ domain as well as the Fab portion of Variable Heavy 3 (VH3) clan of immunoglobine G (IgG) and immunoglobulin M (IgM) (Romagnani et al., 1982; Silverman and Goodyear, 2006) (Fig. 1). The site of SpA binding the Fc γ domain is different than that binding the Fab domain (Graille et al., 2000) (Fig. 1). Whereas binding the Fc γ domain by SpA prevents opsonophagocytic killing of *S. aureus* (Forsgren, 1970; Peterson et al., 1977), Fab binding leads to the activation and clonal expansion of B cells (Goodyear and Silverman, 2003). Since the VH3-family of immunoglobulin idiotypes represents the largest portion of VH genes in B cell populations in humans (Cook and Tomlinson, 1995), Fab binding is responsible for SpA superantigenic effect on B cells, inducing a robust polyclonal activation of up to 30% of B cells in humans and approximately 10% in mice (Palmqvist et al., 2005; Pauli et al., 2014). This contrasts to the 0.01% of B cells targeted by specific antigens. Crystallographic analyses have revealed that SpA forms a complex with human Fab via a conformational surface on B-cell antigen receptor (BCR) that involves side chains from four β strands present in framework subdomains of the clan III gene-encoded VH region in a similar way as T cell superantigens bind the T cell receptor complex on T cells (Graille et al., 2000). It has been reported that, as a

result of this interaction, *S. aureus* induces VH3-biased plasmablasts responses against SpA, limiting host responses to other *S. aureus* virulence factors (Pauli et al., 2014). The VH3-biased response repertoire have been also observed during experimental infections in mice (Falugi et al., 2013). Furthermore, it has been show that SpA binding to murine B cells results in down-regulation of B cell receptors and the co-receptors CD19 and CD21 as well as in limiting rounds of proliferation leading to apoptotic cell death (Goodyear and Silverman, 2003). These observations suggest that SpA enables *S. aureus* to interfere with the elicitation of protective humoral immune responses and with the generation of sufficient memory to prevent future infections.

Based on the critical role of SpA in the modulation of B cell responses, Kim et al. constructed a non-toxicogenic SpA variant, designed SpAKKAA by substituting twenty amino acid residues essential for its association with Ig Fc γ and Fab (Kim et al., 2010). Immunization of rabbits and mice with SpAKKAA but not with the wild-type SpA, elicited anti-SpA neutralizing antibodies (Kim et al., 2010). These antibodies not only suppressed the B cell superantigenic activity of SpA but also promoted humoral immune responses to other staphylococcal antigens and elicited protective immunity against *S. aureus* challenge (Kim et al., 2010).

3. *S. aureus* manipulation of T cell responses

Several studies have provided evidence that T cell-mediated immune responses play an important role in the containment of *S. aureus* infection. This is illustrated by the increasing incidence of *S. aureus* infections in HIV-infected patients with functional defects on CD4+ T cell responses (Shadyab and Crum-Cianflone, 2012; Utay et al., 2016). In addition, several groups have demonstrated that mice with deficiencies in the T cell compartment were significantly more susceptible to lethal challenge with *S. aureus* than wild-type animals (Spellberg et al., 2008; Ziegler et al., 2011). Among the different T cell subsets, IL-17-producing T cells seem to be the most prominent conferring protection against *S. aureus* infection. Thus, it has been reported that IL-17-producing epidermal $\gamma\delta$ T cells play a key role in protection against *S. aureus* cutaneous infection (Cho et al., 2010). Protection after vaccination with IsdB (Joshi et al., 2012) and ClfA (Narita et al., 2010) has been also shown to be mediated by Th17/IL-17. Furthermore, patients with defects in Th17/IL-7 axis have a greater incidence of *S. aureus* infections than individuals with a normal Th17/IL-17 compartment (Ishigame et al., 2009; Minegishi et al., 2009). The protective role of IL-17 seems to be associated with its involvement in the recruitment of neutrophils to sites of pathogen invasion and therefore in bacterial clearance (Iwakura et al., 2008). In mice, Th1 cells have also been reported to confer protection against *S. aureus* by promoting the activation of macrophages involved in bacterial elimination (Brown et al., 2015). However, the fact that protection conferred by these T cell populations is incomplete indicates that *S. aureus* have developed strategies to interfere with the development and function of effector T cells.

3.1. Manipulation of T cell responses by staphylococcal superantigens

Antigen-presenting cells (APC) such as macrophages and dendritic cells can phagocyte and process bacteria or antigenic material and present the resulting fragments loaded into the to peptide binding groove of the major histocompatibility complex (MHC) molecules to antigen-specific T lymphocytes (Mantegazza et al., 2013) (Fig. 2). Antigenic peptide loading onto MHC-II molecules generally occurs in compartments of the endocytic pathway (Mantegazza et al., 2013). In the process of antigen-specific presentation, only a very small fraction of the T cell repertoire (< 0.01%) will be initially activated. Superantigens, on the other hand, bind directly to the MHC class II molecule and to the T cell receptor extracellularly, without been processed (Dellabona et al., 1990; Li et al., 1999) (Fig. 2). Superantigens are able to bypass the mechanisms of conventional, MHC-restricted, antigen

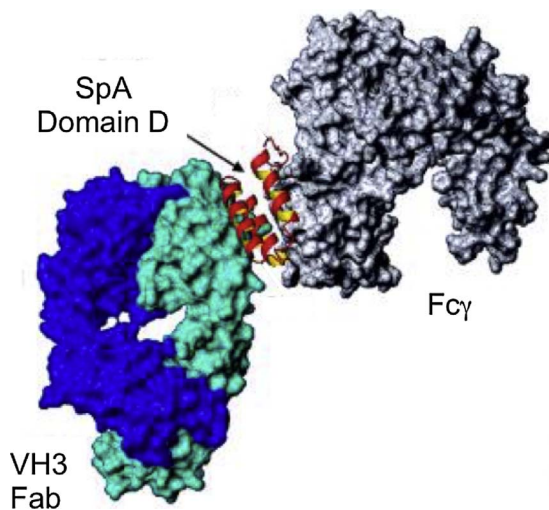


Fig. 1. Ternary model of a complex between Fab (cyan area), SpA domain (red ribbon) and Fc γ molecule (gray area). The Fab and Fc γ form a sandwich about opposite faces of the helix II of SpA illustrating how the SpA domain can simultaneously display both Fab and Fc γ binding activities. Adapted from Graille et al., Proc Natl Acad Sci U S A. 2000; 97(10): 5399–5404 (Graille et al., 2000).

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