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# Update on molecular diversity and multipathogenicity of staphylococcal superantigen toxins

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## Abstract

Staphylococcal superantigen (SAg) toxins are the most notable virulence factors associated with *Staphylococcus aureus*, which is a pathogen associated with serious community and hospital acquired infections in humans and various diseases in animals. Recently, SAg toxins have become a superfamily with 29 types, including staphylococcal enterotoxins (SEs) with emetic activity, SE-like toxins (SEls) that do not induce emesis in primate models or have yet not been tested, and toxic shock syndrome toxin-1 (TSST-1). SEs and SEls can be subdivided into classical types (SEA to SEE) and novel types (SEG to SEIY, SE01, SE02, SEl26 and SEl27). The genes of SAg toxins are located in diverse accessory genetic elements and share certain structural and biological properties. SAg toxins are heat-stable proteins that exhibit pyrogenicity, superantigenicity and capacity to induce lethal hypersensitivity to endotoxin in humans and animals. They have multiple pathogenicities that can interfere with normal immune function of host, increase the chances of survival and transmission of pathogenic bacteria in host, consequently contribute to the occurrence and development of various infections, persistent infections or food poisoning. This review focuses on the following aspects of SAg toxins: (1) superfamily members of classic and novelty discovered staphylococcal SAgs; (2) diversity of gene locations and molecular structural characteristics; (3) biological characteristics and activities; (4) multi-pathogenicity of SAgs in animal and human diseases, including bovine mastitis, swine sepsis, abscesses and skin edema in pig, arthritis and septicemia in poultry, and nosocomial infections and food-borne diseases in humans.

**Keywords:** *Staphylococcus aureus*, Superantigen, Enterotoxin, Pathogenecity, Food poisoning, Infection

## Introduction

*Staphylococcus aureus* produces a variety of exotoxins and proteases that contribute to their ability to colonize and cause disease in humans and animals. Superantigen (SAg) toxins are important exotoxins of *S. aureus*, including staphylococcal enterotoxin A (SEA) to SEE, SEG to SET, staphylococcal enterotoxin-like toxins U (SElU) to SElY, SE01, SE02, SEl26, SEl27 and toxic shock syndrome toxin-1 (TSST-1) (Dinges et al. 2000; Hu and Nakane 2014; Ono et al. 2015; Suzuki et al. 2020; Zhang et al. 2018). SAg toxins are proteins composed of approximately 168–261 amino acids, with molecular size of 19–30 kDa (Table 1). The toxin genes are located in mobile genetic elements, such as υSa genome islands, pathogenic islands, phages, plasmids or near staphylococcal cassette chromosome (SCC), which are related to methicillin resistance (Hu and Nakane, 2014, Hu et al., 2018). SAg toxins share certain structural and biological properties (Kappler et al. 1989; Hu and Nakane 2014; Marrack and Kappler 1990). Unlike conventional antigen (Ag), SAg can bypass normal processing by antigen-presenting cells (APC) and induce a large proportion (5–30%) of T-cells to proliferate through co-ligation between major histocompatibility complex (MHC) class II molecules on APC and the variable portion of T-cell antigen receptor β

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**Table 1** Characteristic and pathogenicity of staphylococcal superantigen toxins

| Toxin | Genetic element | Molecular weight (kDa) | Super-antigen activity | Emetic activity (μg/animal) | | First reported year |
|---|---|---|---|---|---|---|
| | | | | Monkey[a] | Shrew[b] | |
| SEA | Prophage | 27.1 | + | 25 | 0.3 | 1963 |
| SEB | Chromosome, SaPI3, Plasmid (pZA10) | 28.3 | + | 100 | 10 | 1963 |
| SEC1 | SaPI | 27.5 | + | 5 | NE | 1965 |
| SEC2 | SaPI | 27.6 | + | NE | 1000 | 1965 |
| SEC3 | SaPI | 27.6 | + | < 50 | NE | 1965 |
| SED | Plasmid (pIB485) | 26.9 | + | NE | 40 | 1967 |
| SEE | Prophage (Hypothetical location) | 26.4 | + | NE | 10 | 1971 |
| SEG | egc1, egc2, egc3, egc4 | 27.0 | + | 160–320 | 200 | 1998 |
| SEH | Transposon (MGEmw2/mssa476seh/Δseo) | 25.1 | + | 30 | 1000 | 1994 |
| SEI | egc1, egc2, egc3 | 24.9 | + | 300–600 | 1 | 1998 |
| SEIJ | Plasmid (pIB485, pF5) | 28.6 | + | NE | NE | 1998 |
| SEK | Prophages, SaPI1, SaPI3, SaPI5, SaPIbov1 | 25.3 | + | 100 | 1000 | 1998 |
| SEL | SaPIn1, SaPIm1, SaPImw2, SaPIbov1 | 24.7 | + | 100[c] | 500 | 2001 |
| SEM | egc1, egc2, | 24.8 | + | 100[c] | 100 | 2001 |
| SEN | egc1, egc2, egc3, egc4 | 26.1 | + | 100[c] | 1000 | 2001 |
| SEO | egc1, egc2, egc3, egc4, Transposon | 26.8 | + | 100[c] | 500 | 2001 |
| SEP | Prophage (Sa3n) | 26.7 | + | 100[c] | 50 | 2001 |
| SEQ | SaPI1, SaPI3, SaPI5, Prophage | 25.2 | + | 100[c] | 4 | 2002 |
| SER | Plasmid (pIB485, pF5) | 27.0 | + | < 100 | < 1000 | 2003 |
| SES | Plasmid (pF5) | 26.2 | + | < 100 | 20 | 2008 |
| SET | Plasmid (pF5) | 22.6 | + | < 100 | 1000 | 2008 |
| SEIU | egc2, egc3 | 27.2 | + | NE | NE | 2003 |
| SEIV | egc4 | 26.7 | + | NE | NE | 2006 |
| SEIW | egc4 | 27.3 | + | NE | NE | 2006 |
| SEIX | Chromosome | 19.5 | + | NE | NE | 2011 |
| SEIY | Chromosome | 23.3 | +/− | 250[c] | 500 | 2015 |
| SEIZ | Chromosome | 27.4 | + | NE | NE | 2015 |
| SE01 | Plasmid | 26.4 | + | NE | NE | 2017 |
| SE02 | Chromosome | 27.2 | + | 250[c] | NE | 2020 |
| SEI26 | SaPI | 25.1 | + | NE | NE | 2018 |
| SEI27 | SaPI | 27.1 | + | NE | NE | 2018 |
| TSST-1 | SaPIs | 22.1 | + | – | – | 1981 |

Notes: +, Positive reaction; NE, not examined; [a)] oral administration, [b)] intraperitoneal administration, [c)] μg/kg body weight. *SE* staphylococcal enterotoxins; *TSST* toxic shock syndrome toxin; *SaPI S. aureus* pathogenicity islands

chain (TCR Vβ) or α chain (TCR Vα) (Kozono et al. 1995; Saline et al. 2010; Tiedemann and Fraser, 1996). SAg toxins activate APC/T-cells to release large amount of cytokines, exhibiting many immunomodulatory activities to T cells and/or B cells and enhancing endotoxic shock. They may undermine the immune response against bacterial infections (Choi et al. 1990; Deringer et al. 1997; Edwards et al. 2012), causing specific acute clinical syndromes such as toxic shock syndrome (TSS), staphylococcal scarlet fever (Bergdoll et al. 1981; Betley et al. 1992; Schlievert et al. 2000), atopic dermatidis (Schlievert et al. 2008), and Kawasaki-like illness (Hall et al. 1999) in humans, causing bovine mastitis (Ote et al., 2011; Veh et al. 2015), and arthritis (Hazariwala et al. 2002), edema dermatitis (Miwa et al. 2006; Van Gessel et al. 2004), and sepsis (Asgeirsson et al. 2018; Van Gessel et al. 2004) in animals. Furthermore, SEs are a major cause of food poisoning, which typically occur after ingestion of food contaminated with *S. aureus*. Symptoms of food poisoning rapid onset, include nausea and violent vomiting, with or without diarrhea (Bergdoll 1988; Hu et al. 1999, Hu et al., 2003a, b,

Hu et al., 2017; Suzuki et al. 2020). In addition, recent studies reported that SAg-modified vaccines showed therapeutic effects in melanoma-bearing mice and had a strong protective effect against wild-type melanoma challenge (Kato et al. 2011; Huang et al. 2004; Ma et al. 2004). These studies demonstrated that SAg-modified vaccines could induce a potent tumor-antigen-specific immune responses, which provided a novel approach for bridging specific and non-specific immunity for tumor therapy (Kato et al. 2011; Miller et al. 2020; Shimizu et al. 2003). In this review, we focus and discuss the highly important superfamily members of classsic and novelly identified SAg toxins produced by *S. aureus*, and presents new informations on biological characteristics, gene locations and molecular structures, and multiple pathogenesities of SAg toxins in human and animal diseases.

## Superfamily members of SAg toxins

*S. aureus* produces a large variety of T-cell superantigens, including TSST-1 that induce toxic shock syndrome (TSS), SEs that are important causive toxins of food poisoning, and SEls that are not emetic in primate models. It also produces B-cell superantigens, such as staphylococcal protein A (SpA), that capable of interacting with both antibody Fc and Fab regions of $VH3^+$ immunoglublins (Ig).

### SEs and SEls

Since Bergdoll and Casman characterized SEA, 5 SEs (SEA to SEE) have been identified due to the antigenic differences (Bergdoll et al. 1965; Bergdoll et al. 1971). Of them, SEC was further subdivided into 3 subtypes, SEC1, SEC2 and SEC3 (Bergdoll et al. 1973). Since the 1990s, many new types of SEs and SEls were discovered by our research group (Omoe et al. 2003; Ono et al. 2008, 2015; Suzuki et al. 2020) and other researchers (Aguilar et al. 2014; Letertre et al. 2003; Munson et al. 1998; Orwin et al. 2001, 2003; Su and Wong 1995; Thomas et al. 2006; Wilson et al. 2011; Zhang et al. 2018). The International Nomenclature Committee for Staphylococcal Superantigens (INCSS) proposed a standard nomenclature for newly discovered toxins to emphasize the emetic activity of toxins (Lina et al. 2004; Omoe et al. 2013). In order to name SE, the emetic activity must be demonstrated by oral administration to monkeys. If the emesis-inducing potential is not shown in vomiting experiments of the primate model, or vomiting experiments have not yet been carried out, the toxin should be named as "staphylococcal enterotoxin-like (SEl) toxin", even though the superantigen toxin is considered closely related to SE structure (Lina et al. 2004).

Omoe et al. (2013) used monkey feeding test to evaluate the emetic activity of some newly discovered SEls, including SElK, SElL to SElN, and SElO to SElQ. The results showed that all tested SEls induced emetic responses in monkeys at a dose of 100 μg/kg, indicating that these newly indentified SEls have emetic activity. Acording to the INCSS naming convention, these new SEls should be re-designated as SEK, SEL, SEM, SEN, SEO, SEP and SEQ, respectivily. A new staphylococcal emetic toxin, SElY, which showed strong emetic activity in a small emetic animal model but low superantigen activity, was reported by Ono et al. (2015). Later, Zhang et al. (2018) reported 2 novel SEls, SEl26 and SEl27, which present in *S. aureus, S. argenteus* and *S. schweitzeri*. More recently, Our research group reported a novel SE, SE02, that isolated from a food poisoning case in Japan (Suzuki et al. 2020). To date, SEs and SEls have become a superfamily with 29 types of toxins (Fig. 1).

### TSST-1

Todd et al. (1978) reported a toxin that induces TSS (toxic shock syndrome) caused by *S. aureus* infection, and named as SEF. However, SEF does not have emetic activity, later it was renamed TSST-1 (Bergdoll et al. 1981; Edwin and Kass 1989; Reiser et al. 1983). TSST-1 is a 22 kDa extracellular protein secreted by *S. aureus*. Its physical and chemical properties are very similar to those of SEs. TSST-1 is a T cell superantigen which stimulates polyclonal T-cell proliferation through co-ligation between MHC class II molecules on APC and T-cell receptor β (TCR Vβ) without prior antigen-present processing. It has unique primary amino acid sequence and contains only a low-affinity MHC II binding site in O/B folds that interacts with α-chains of MHC II molecules (Kozono et al. 1995; Saline et al. 2010). Toxin-activated APC/T-cells lead to the release of various cytokines and chemokines, enhance endotoxic shock, and cause T-cell and B-cell immunosuppression, fever, rash, vascular disorders, toxic shock syndrome, multiple organ failure, and lower blood pressure in humans and animals (Hu et al. 2003a; Krakauer, 2019; Schlievert et al. 2019).

### SpA protein

SpA produced by *S. aureus* is a B cell superantigen which capable of interacting with both antibody Fc and Fab regions of $VH3^+$ immunoglublins (Ig). Gene *spa* is encoded in the core genome of most clinical isolates. SpA proteins can be released from bacterial cell wall by hydrolase LytM (Becker et al. 2014; Shopsin et al. 1999). It has 2 distinct Ig-binding sites: one for IgG Fc domains, while another separate site binds an evolutionarily conserved surface on Fab encoded by VH3 clan related genes. SpA contains 4–5 highly conserved Ig binding domains and X hypervariable regions composed of sub-regions Xr and Xc (Guss et al. 1984; Kim et al. 2012). *S. aureus* isolates can be classified by the highly variable and repetitive octapeptides in Xr of SpA (Shopsin et al. 1999). Ig-binding domain on SpA molecule confers binding capacity

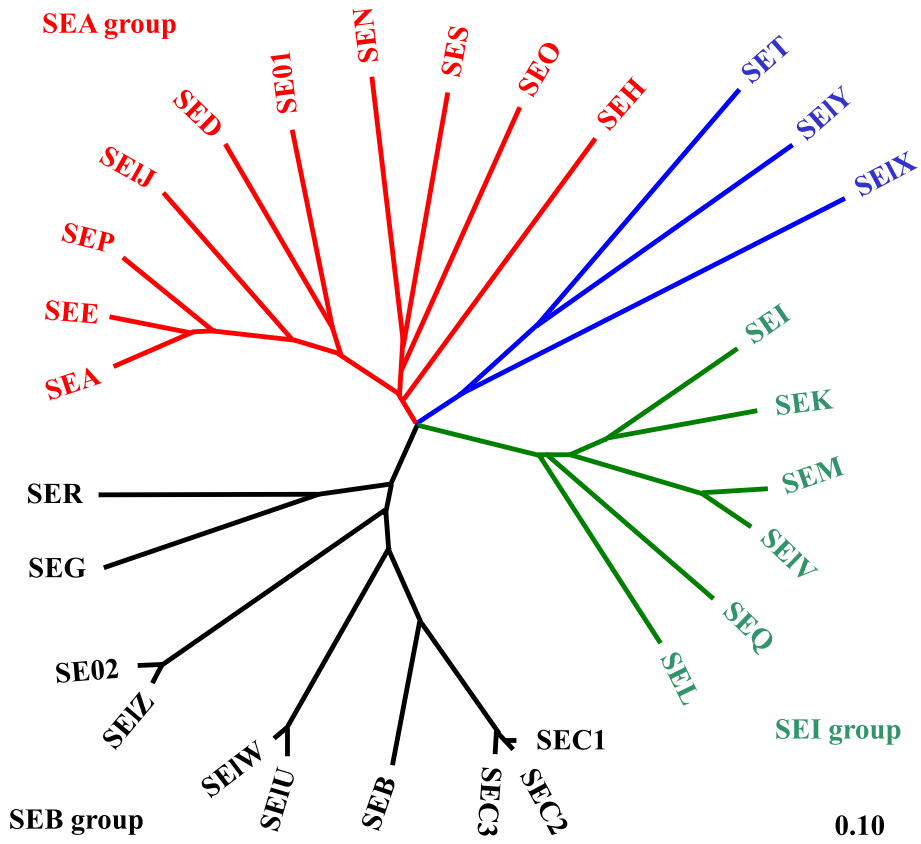


**Fig. 1** Superfamily members of SAg toxins and the grouping based on amino acid sequence comparison. SE, staphylococcal enterotoxins. SEA group are showed in red; SEB Group are showed in black; SEI Group are showed in green and the other toxins are showed in blue. This figure was prepared and modified from Hu et al. (2018) and Suzuki et al. (2020)

of SpA to Fcγ portion of Ig and prevents the opsonization of host cells (Becker et al. 2014). Ig-binding domains can also mediate the binding of SpA to B cells by cross-linking VH3-expressing B cell receptors and activate B cells. SpA exerts mitogenic activity by binding to the variable regions of heavy chain, rather than complementarity-determining regions required for common antigens, thereby bypassing the antigen specificity required for B cell activation (Graille et al. 2000; Silverman and Goodyear, 2006). It represents a paradigm relevant to other microbial toxins with unconventional V region targeted activity in *S. aureus* and other microbial pathogens (Keener et al. 2017; Pauli et al. 2014). As a B-cell superantigen, SpA may be very effective in destroying host defense and is necessary for the continued existence of *S. aureus* in nasopharynx (Sun et al. 2018).

## Diversity of gene location and molecular structure of SAg toxins

Genes of SAg toxins are encoded by diverse accessory genetic elements, and many of them are harbored by numerous mobile elements, including *S. aureus* pathogenicity islands (SaPIs), genomic islands (υSa), prophages and plasmids. Except SaPIbov2 (27 kb) and a highly degenerated SaPI (3.14 kb), SaPIs can be find in some sequenced genomes (Alibayov et al. 2014; Lindsay et al. 1998; Tallent et al. 2007). Some SaPIs carry genes encoding one or more SEs, such as, *sek* and *seq* are found together with *tst* in SaPI1; *sel* and *sec* are found in SaPIbov1; *seb, seq* and *sek* have been reported in SaPI3 (Alibayov et al. 2014; Novick and Subedi 2007; Sato'O et al., 2013, Sato'O et al., 2014). It has been found that strains carrying different SaPIs produce SAg toxins in significantly different ways (Sato'O et al., 2013, Sato'O et al., 2014). Gene islands υSaα and υSaβ contain gene clusters encoding virulence factors. υSaβ has an enterotoxin gene cluster (*egc*), which form an operon containing various number of *se* or *sel* genes. Enterotoxin gene cluster 1 (*egc*1) consists of 5 *se* genes (*seg, sei, sem, sen and seo*) (Monday and Bohach 2001; Hu et al. 2017). *egc*2 contains an additional *sel* gene (*selu*) (Letertre et al. 2003). The allelic variants of each *egc*2 gene forms *egc*3 cluster (Collery et al. 2009; Letertre et al. 2003), and *egc*4 consists of 2 new *sel* genes (*selv, selw*) (Thomas et al. 2006).

SEs genes can also be carried by prophages. Three *se/sel* genes (*sea, selk* and *selq*) are present together in ϕSa3ms and ϕSa3mw, while a single *se/sel* gene (*sea* or *sep*) is carried by ϕMu3A, ϕSa3a or other prophages

(Betley and Mekalanos 1985; Coleman et al. 1989; Zeaki et al. 2015). Two plasmids carrying *se*/*sel* genes have been identified. A 27.6 kb plasmid pIB485 encodes *sed*, *selj* and *ser* (Couch et al. 1988; Omoe et al. 2003; Ono et al. 2008), and another plasmid pF5 carries *selj*, *ser*, *ses* and *set* (Ono et al. 2008).

According to the homology of nucleotide and anino acid sequences, SAg toxins can be classified into several groups (Fig. 1). SEA group includes SEA, SED, SEE, SEH, SElJ, SEN, SEO, SEP, SES and SE01. Toxins of SEA group contain a cystine loop with 9 amino acids (Fitzgerald et al. 2003; Spaulding et al. 2013). These toxins have a low-affinity α-chain MHC II binding site and a high-affinity $Zn^{2+}$-dependent β-chain MHC II binding site (Fitzgerald et al. 2003; Petersson et al. 2002). The presence of $Zn^{2+}$-dependent high-affinity site makes them 10- to 100-fold more active overall in causing cytokine production from T cells and APCs than other SAg toxins. SEB group includes SEB, SEC, SEG, SER, SElU, SElW, SElZ and SE02. Toxins of this group contain a core superantigen structure plus a cystine loop that has a varying 10 to 19 amino acid sequence separating the cysteine residues (Fitzgerald et al. 2003; Hovde et al., 1994). SEI group includes SEI, SEK, SEL, SEM, SEQ and SElV, and the toxins of this group contain both low- and high-affinity MHC II binding sites, but lack the cystine loop (Günther et al. 2007; Orwin et al. 2001, 2002, 2003; Su and Wong 1995). These toxins contain one binding site with α-chain of MHC II, and the interaction between toxin and MHC II molecule does not depend on the antigenic peptide within MHC II peptide-binding groove (Jardetzky et al. 1994; Letertre et al. 2003).

Despite differences in amino acid sequence homology among SEs, SEls and TSST-1, these toxins share common phylogenetic relationships, secondary and tertiary structures, and biological activities (Fig. 2). The three-dimensional structures of SEs and SEls show very similar conformation that the canonical structure consists of 1 A domain and 1 B domain, and 1 α-helix that spans the center of the structure and connects A and B domains (Swaminathan et al. 1992, 1995). A set of α helices mark the interface between A and B domains. The helices form a shallow cavity on the top and a long groove on the back of the molecule (Hu et al. 2018; Swaminathan et al. 1995) (Fig. 2A).

## Biological characteristics and activities of SAg toxins

SAg toxins are single-chain proteins, which have significant resistance to heat-treatment and enzymatic degradation (Li et al. 2011; Maina et al. 2012; Suzuki et al. 2020). They are highly stable to most proteolytic enzymes to retain their toxic activity in the digestive tract after ingestion. Several studies have compared the respective integrity and toxicity of SEA and TSST-1 after treatment with heat, pepsin or trypsin in relation to the condition of food cooking or luminal location in stomach or intestine (Li et al. 2011; Suzuki et al. 2020). SEA retained significant superantigenic and emetic activities after treatment with heat or pepsin, indicating that cooked foods contaminated with the toxins may still cause food poisoning (Li et al. 2011).

SEs are the leading cause of foodborne bacterial intoxications worldwide (Genigeorgis, 1989; Hu et al., 2017; Mead et al. 1999; Tauxe 2002). Among them, SEA is the most frequently detected SEs from food poisoning outbreaks in many countries (Kitamoto et al. 2009; Suzuki et al. 2020; Veras et al. 2008; Wieneke et al. 1993). The typical clinical symptoms of staphylococcal food poisoning are vomiting, abdominal cramps, nausea and sometimes diarrhea within a few hours after ingesting contaminated foods (Bergdoll, 1988; Fisher et al. 2018; Hu et al. 1999). In contrast to the well-known clinical manifestations of food poisong, little is known about physiopathology of the symptoms and mechanisms of emetic activity of SEs. The reason of lacking progress in these research is partially attributed to the limited convenient and appropriate animal models. Monkeys are considered to be the primary animal model, but due to the high cost, availability of animals, and ethical considerations, the use in mechanism investigatingof SEs is severely restricted. Other animal models such as mouse, rat, rabbit, pig and cat are less susceptible to SEs or their responses to SEs are not specific (Bergdoll 1988; Normann et al. 1969; Hu et al. 1999; Stiles and Denniston 1971). Hu et al. reported that house musk shrew is a usefull small-scale emetic-inducing animal model for SEs. All tested SEs and SEls caused vomiting responses in house musk shrews (Hu et al. 1998, 1999, 2003b, Hu and Nakane, 2014; Omoe et al. 2013). Recent studies investigated the behavior of SEA in the gastrointestinal tract of house musk shrew and common marmoset, suggesting that submucosal mast cells in the gastrointestinal tract are one of the target cells of SEs. Histamin and serotonine (5-HT) released from submucosal mast cells play an important role in SE-induced emesis (Hirose et al. 2016; Hu et al. 2007; Ono et al. 2012, 2019). In addition, vagotomy prevented vomiting caused by SEA in the emetic-inducing animal model, indicating that 5-HT may bind to $5\text{-HT}_3$ receptors, expressed on the enteric nerves of the gastrointestinal tract, thereby causing these nerves to deprive polarization (Hu et al. 2007; Ono et al. 2017, 2019). SEA can also induce the increase of intracellular calcium ($[Ca^{2+}]$ i) in intestinal epithelial cells, due to the storage of intracellular calcium in cells (Hu et al. 2005b).

SAg toxins can cross-link MHC class II and T-cell receptors, stimulating large numbers of T cells activation, and sudden cytokines and chemokines storm which lead to the life-threatening condition such as toxic shock

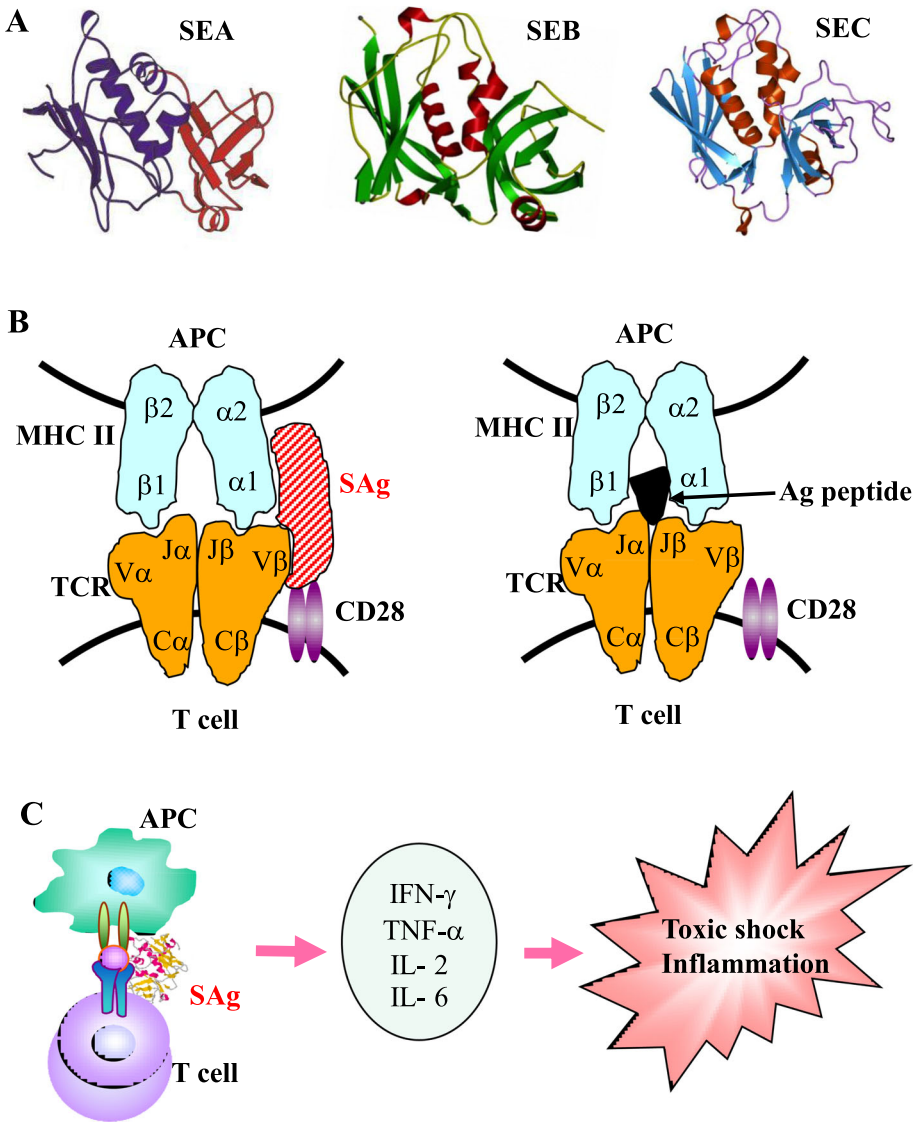


**Fig. 2** Characteristics and activities of SAg toxins. **A** Three-dimensional structures of SEA, SEB and SEC as representative of SAg toxins. **B** Diagram of superantigen (left) and normal antigen (right) bind to MHC class II of APC and T-cell receptor, CD28 molecules. **C** Superantigenic activities of SAg toxins, that induce massive cytokine production and subsequently cause inflammation and toxic shock in humans and animals. This figure was prepared and modified from Hu et al. (2014, 2018). SE, staphylococcal enterotoxins; APC, antigen-presenting cells; MHC, major histocompatibility comlex; TCR, T-cell antigen receptor

syndrome and various inflamations (Fig. 2B, C). Cytokines include interleukin-1 (IL-1), IL-2, interferon-γ (IFN-γ), tumor necrosis factora (TNF-α) and TNF-β, etc. (Jupin et al., 1988; McCormick et al., 2001; Trede et al. 1991). TNF-α and IL-1 are induced early and are direct mediators of fever, hypotension and shock (Jupin et al., 1988; Trede et al. 1991). IFN-γ produced by the activated T-cells acts synergistically with TNF-α and IL-1, enhancing host defense by establishing an inflammatory environment for T-cell activation and differentiation (Krakauer 2019; McCormick et al., 2001). It was found that IL-17A produced by SAg-activated CD4+ effector memory T cells was rapidly induced in human PBMC exposed to SEs (Szabo et al. 2017). IL-17 is known to have proinflammatory effects and induces tissue damage in various autoimmune diseases. Early induction of IL-17 likely contributes to mortality, hepatotoxicity and organ damage similar to IL-1 (Krakauer 2019; Narita et al. 2019; Szabo et al. 2017). SAg-activated host cells also produce other tissue-damaging molecules, such as matrix metalloproteinases (MMPs) and tissue factors, affecting both inflammatory and coagulation pathways. Neutrophils activated by SAg can produce reactive oxygen species

(ROS), thereby increasing vascular permeability and lung damage (Krakauer, 2019; McKay et al. 2000).

## Multi-pathogenicity of SAg in animal and human diseases

*S. aureus*, which produces SAg toxin, is an important pathogen related to serious community and hospital-acquired diseases, and has long been considered as a major problem of public health (Kérouanton et al. 2007; Martin et al. 2004; Mead et al. 1999; Normanno et al., 2005; Pesavento et al. 2007). SAg-producing MRSA (meticillin-resistant *S. aureus*) is currently important for nosocomial infections and food-borne diseases worldwide because of its global spreading and difficulty in therapy (Abdi et al. 2018; Hu et al. 2008, 2011; Omoe et al., 2005a, b). MRSA and MSSA (meticillin-susceptible *S. aureus*) isolates from different patients were comprehensively searched using multiplex PCR for toxin gene family. Both isolates carried a number of SAg genes, but MRSA isolates harboured more SAg genes than MSSA isolates. The most frequent genotypes of MRSA isolates were *sec*, *sel* and *tst-1* together with gene combination *seg*, *sei*, *sem*, *sen* and *seo* (Hu et al. 2008, 2011). Coexistence of SAg toxins and SCC genes in *S. aureus* may contribute to the biological fitness and pathogenicity of MRSA (Calderwood et al. 2014; Hu et al. 2011).

SAg-producing *S. aureus* is also an important etiological agent of animal diseases such as clinical and subclinical bovine mastitis, swine sepsis, abscesses and skin edema in pig, lethality in rabbits, arthritis and septicemia in poultry (Table 2). It is an exceptionally successful and adaptive animal pathogen that can cause epidemics of invasive diseases (Katsuda et al. 2005; Miwa et al. 2006; Veh et al. 2015). The most important virulence factor associated with this microorganism may be heat-stable and enzyme-resistant abilities (Krakauer 2019; Hu et al. 2008; Suzuki et al. 2020).

**Table 2** Multi-pathogenicity of SAg toxins in human and animal diseases and the application in vaccines

| Diseases or vaccines | Associated SAgs (SE, SEl or TSST-1) |
|---|---|
| **Animal diseases** | |
| Bovine mastitis | SEC, TSST-1, SEG, SEN, SEO |
| Swine sepsis | SEB, TSST-1 |
| Arthritis and septicemia in poultry | SEA, SEB, SEC, SEQ |
| **Human diseases** | |
| Staphylococcal food poisoning | SEA~SEE, SEH, SE02 etc. |
| Soft tissue infection associated | TSST-1, SEB, SEC |
| Post respiratory viral infection | TSST-1, SEB, SEC, SEIX |
| Purpura fulminans | TSST-1, SEB, SEC |
| Kawasaki-like diseases | TSST-1, SEB, SEC |
| Staphylococcal pneumonia | SEB, SEC, TSST-1, SEIX |
| Staphylococcal infective endocarditis | SEC, TSST-1 |
| Staphylococcal sepsis | SEA, SEC, TSST-1 |
| Chronic rhinosinusitis | SEA to SEE, SEG to SEO |
| Atopic dermatitis | SEs, TSST-1 |
| Staphylococcal nonmenstrual TSS | TSST-1, SEB, SEC |
| Inflammatory arthritis | SEA, SEB, SEC, TSST-1 |
| Autoimmune diseases | SEB, SEC, SED, TSST-1 |
| **Vaccines** | |
| Vaccine for *Saphylococcus* infection | Mutant SEC, mutant TSST-1 |
| Vaccine for food poisoning | Mutant SEA |

Notes: *SAg* staphylococcal superantigen; *SE* staphylococcal enterotoxins; *TSST* toxic shock syndrome toxin

### Bovine mastitis and endometritis

Bovine mastitis is a major disease of dairy cows, which has a great impact on the dairy industry and brings significant economic losses (Hata et al. 2010; Li et al. 2017; Wolf et al. 2011; Zaatout et al. 2020). *S. aureus* is the most frequently recovered pathogen from mastitis cases (Hata et al. 2010; Ote et al. 2011; Ren et al. 2020), and responsible for subclinical and persistent intramammary infections. Multiple studies reported the diversity of genotype and phenotype of *S. aureus* strains obtained from bovine mastitis (Haveri et al. 2005; Suleiman et al, 2018; Piccinini et al. 2012; Ronco et al. 2018; Veh et al. 2015). *sec* and *tst* or their combined presence in *S. aureus* isolated from bovine mastitis suggested that these strains contained pathogenicity island SaPIbov (Fitzgerald et al. 2001; Leuenberger et al. 2019). Some other studies showed that the presence of *seg* or *sen* and *sec* or *tst* could also occur alone (Haveri et al. 2007; Mitra et al. 2013; Wang et al. 2009; Wang et al. 2017). In genetic analysis of bovine *S. aureus* isolates from bovine mastitis cases by PCR, a total of 270 *S. aureus* strains presented genes encoding SEs, SEls and TSST-1. About 183 (67.8%) bovine isolates possessed either 1 or more SAg toxin genes and the most common pattern was *tst, sec, seg* and *sei*. Further, 161 isolates possessed at least 2 SAg genes (Katsuda et al. 2005; Hata et al. 2006). *S. aureus* strains isolated from bovine mastitic milk were separated into 60 patterns and 16 lineages by pulse field gel electrophoresis, and the most common combinations of toxin genes were *sec, seg, sei,* sel, and *tst*; or *seg* and *sei*; or *sec*, *seg, sei, sel, sen* and *tst* (Hata et al. 2010; Hoekstra et al. 2020; Li et al. 2017; Ren et al. 2020). The predominant isolate possessed SAg toxin genes supporting the theory that SAg toxins are important for udder pathogenesis of bovine mastitis. Furthermore, recent studies (Fang et al. 2019) demonstrated that SEC can directly cause inflammation, proinflammatory cytokine production and tissue damage in mammary glands, suggesting that SEC might play an

important role in the development of mastitis associated with *S. aureus* infection.

Clinical endometritis, which leads to decreased reproductive performance, is also an important disease in dairy cows (Jiang et al. 2019; Zhao et al. 2014). Zhao et al. investigated SAg gene distribution of staphylococcal isolates in uterus of cows with clinical endometritis. PCR analysis showed that most of isolates (63.0%) had at least 1 SAg gene. The most common SAg genes and genotypes were *selj* and *sec-selj-sen* (Zhao et al. 2014). These results indicated that *Staphylococci* recovered from cows with clinical endometritis contained extensive and complex SAg genes, suggesting that SAg may contribute to the pathogenicity of bacteria in bovine endometritis.

### Staphylococcal septicemia

Van Gessel et al. (2004) reported that clinical signs of piglets receiving intravenous SEB were biphasic, accompanied by fever, vomiting and diarrhea, followed by terminal hypotension and shock. Lymphoid lesions were identified with severe lymphadenopathy, splenomegaly and obvious Peyer's patches. Extensive edema was found in animals, most notably in mesenteric and retroperitoneal connective tissue. Additional histologic changes included perivascular aggregates of large lymphocytes variably present in lung and brain, circulating lymphoblasts, and lymphocytic portal hepatitis. Preliminary molecular studies using gene arrays found changes in several gene profiles that may have an impact on pathophysiology that leads to irreversible shock. Five genes were selected for further studies, all of which showed increased mRNA levels after SEB exposure. Miwa et al. (2006) evaluated blood adsorption effect of SAg (TSST-1) adsorption equipment in septic pigs, and proposed the potential application of superantigen adsorption equipment in the treatment of SAg-induced respiratory dysfunction and sepsis.

Activities of SAg toxins have many systemic effects on people and animals. A large number of patients and animals develop sepsis after staphylococcal pneumonia and infective endocarditis or following surgery. Studies showed that certain SAgs, especially SEA, SEC and TSST-1 are overepresented in sepsis cases compared with non-sepsis animals or patients (Dauwalder et al. 2006; Ferry et al. 2005). SAg toxins are likely to be produced in infected lesions protected by hemoglobin peptides and then secreted into the bloodstream (Schlievert et al. 2007; Asgeirsson et al. 2018).

### Staphylococcal pneumonia

Previous tudies showed that *S. aureus* necrotizing pneumonia in children was associated with the emergent CA-MRSA USA400 clonal group, which produced SEB and SEC (Fey et al. 2003; Spaulding et al. 2013). Subsequent studies showed that these 2 SEs were almost always present in CA-MRSA USA400 strains. When purified SEB and SEC were installed intrapulmonarily, they induced hemorrhagic lung lesions, respiratory distress, and lethal TSS in rabbit model (Strandberg et al. 2010). TSST-1 stimulates human bronchial epithelial cells to express high levels of proinflammatory molecules, TNF-α and IL-8 (Aubert et al. 2000). The newly discovered SElX (Wilson et al. 2011) appears to be critical for the development of necrotizing pneumonia and lethal TSS in rabbits. Furthermore, vaccination against TSST-1, SEB or SEC provide protection against highly lethal doses of *S. aureus* strains that producing respective SAgs (Strandberg et al. 2010).

### Staphylococcal infective endocarditis

Staphylococcal infective endocarditis occurs most often in areas of pre-existing heart damage, usually involving valves. Research showed that, as many as 90% infective endocarditis isolates of *S. aureus* produce TSST-1 (Nienaber et al. 2011; Wang et al. 2018). TSST-1 is critical for development of infective endocarditis as tested in rabbits using isogenic strains (Pragman et al. 2004). Staphylococci initially colonize damaged endothelial cells to initiate infective endocarditis (Asgeirsson et al. 2018). TSST-1 and SEC then interact with host cells to affect endothelial wound healing by directly acting on endothelial cells (Lee et al. 1991). TSST-1 is toxic to porcine aortic endothelial cells. SAg toxins can also cause mild or severe capillary leakage and change blood flow in the initially damaged part of heart, thereby enhancing vegetation formation (Asgeirsson et al. 2018). The use of passive neutralization of SEC in CA-MRSA USA400 strain MW2 and administration of Vβ-TCRs specific for SEC can prevent the development of cardiac vegetations (Mattis et al. 2013).

### Staphylococcal food poisoning (SFP)

SFP resulted from the ingestion of one or more SEs produced in foods by *S. aureus*. The first well-documented report which clearly identified SEs as the cause of food poisoning outbreaks was done by Rosenau and Mccoy (1931). They isolated the pathogenic bacterium *S. aureus* from Christmas cake that caused food poisoning outbreak, and proved that the sterile filtrate obtained from the microbial growth broth could cause the same disease when ingested by human volunteers (Rosenau and Mccoy 1931; Bergdoll et al. 1965). Initially, SEA to SEE types were identified and reported in the literature (Bergdoll et al. 1965; Casman et al. 1967). Since the 1990s, a lot of new types of SAg toxins have been identified and designated in *S. aureus* strains isolated from food poisoning cases (Lina et al. 2004; Ono et al. 2015; Suzuki et al. 2020; Wang et al. 2018). All SEs, but not SEls, cause emesis when administered orally to primates.

SEA was the most common SE recovered from food poisoning outbreaks in many countries (Kirk et al. 2014; Kitamoto et al. 2009; Veras et al. 2008; Wieneke et al. 1993). Symptoms of SFP are vomiting, abdominal cramps, nausea, and sometimes followed by diarrhea after a short period of incubation (Bergdoll 1988; Hu et al. 1999, Hu et al., 2003a, b; Ono et al. 2019). Although SEs do not show cytotoxic activity on intestinal epithelial cells in morphological characteristics (Buxser and Bonventre, 1981), they can pass through the intestinal epithelium in an immunologically intact form, and participate in the initiation, exaggeration and reactivation of intestinal inflammatory diseases (McKay and Singh 1997; McKay et al. 2000).

### Toxic shock syndrome (TSS)

TSS is caused by the activation of a large number of T cells induced by SAg, resulting in a cytokine storm (Krakauer 2019; McCormick et al., 2001). It is a capillary leak syndrome, in which patients have fever, rash, hypotension, multiorgan involvement and convalescent desquamation (Gossack-Keenan and Kam 2020; McCormick et al. 2001). SAg TSST-1 was related to menstrual form of TSS in 1981 (Bergdoll et al. 1981; Schlievert et al. 1981), while other SAgs, primarily SEB and SEC, could cause non-menstrual TSS forms (Bohach et al. 1990; McCormick et al. 2001). Literatures showed that 50% nonmenstrual TSS cases were caused by USA200 and related strains produced TSST-1, and the remaining 50% strains nearly always produced SEB or SEC (Gossack-Keenan and Kam 2020; Schlievert and Kim 1991, Schlievert et al. 2004). Immunization with mutant SEC and TSST-1 can provide protection against *S. aureus* infection and toxic shock in mouse models (Hu et al. 2003a, 2005a; Narita et al. 2019).

### Kawasaki disease

Kawasaki disease was first described by Tomisaku Kawasaki in 1967 and has now become the main cause of acquired heart disease in children in developed countries (van Crombruggen et al., 2011; Yeung 2010). It is an acute self-limiting vasculitis that usually affects the coronary arteries and is thought to be triggered by infectious agents in genetically susceptible people. There is convincing evidence that bacterial SAgs are involved and may be related to host genetic factors (Matsubara and Fukaya 2007; Nagata 2019). SAgs toxins also present in Kawasaki-like syndrome, and mainly occur in adults with severe immunosuppression including HIV/AIDS (Stankovic et al. 2007).

### Chronic rhinosinusitis

Chronic rhinosinusitis can occur with or without nasal polyps, and accumulated evidence is now convincing that SAgs form *S. aureus* can cause chronic rhinosinusitis with nasal polyposis (Cheng et al. 2017; Dobretsov et al. 2019; Poddighe and Vangelista, 2020; Van Zele et al. 2004; Wagner Mackenzie et al. 2019). It is believed that SAgs can tilt the response of cytokines to the T helper 2 phenotype, thereby inducing eosinophilia and polyclonal IgE production, which may be further related to asthma (Bachert et al. 2010; Delemarre et al. 2020; Flora et al. 2019; Stow et al, 2010; Van Zele et al. 2008).

### Staphylococcal arthritis

*S. aureus* also causes invasive diseases such as arthritis and septicemia in poultry. SAg-producing *S. aureus* can be isolated from chickens suffering from dermatitis and septicemia, pneumonia, arthritis and tenosynovitis (Terzolo and Shimizu, 1979). SEs have also been associated with other *S. aureus* illnesses in domestic poultry and other avian species. Many studies reported that *sea*, *seb* and *sec* genes were found in *S. aureus* isolates associated with invasive disease in poultry (Hazariwala et al. 2002, Mojahed Asl et al. 2019).

### Atopic dermatitis

Atopic dermatitis is a chronic recurrent highly itchy inflammatory skin disease and a prelude to the development of food allergies, asthma or allergic rhinitis. Skin infections caused by *S. aureus* exacerbate skin diseases in patients with atopic dermatitis and change host response to environmental allergens and viral pathogens, which may be due to both the damaged skin barrier and impaired host immune responses (Aziz et al. 2020; Kawakami et al. 2009; Kim et al. 2019). Significant evidences indicated that SAg plays an important role in exacerbating the disease (Aziz et al. 2020; Schlievert et al. 2010). It is known that SAgs induced skin homing receptor cutaneous lymphocyte-associated antigen on T cells, thereby recruited these cells to the skin (Leung et al. 1995; Seiti Yamada Yoshikawa et al. 2019). Recent evidence suggested that phenotypic Treg ($CD4^+$ $FoxP3^+$) cells homing from a patient's skin might actually show type 2 T helper cells that respond to SEB stimulation (Lin et al. 2011; Suwarsa et al., 2017a, b). Patients may also develop anti-SAg IgE antibodies which can further worsen the condition (Bunikowski et al. 1999).

## Conclusion

The large family of SAg toxins continues to grow. The most interesting question in this field remains why *S. aureus* possesses such a large, genetically and antigenically distinct, extremely effective, and seemingly redundant group of toxins. Although many studies have investigated the existence of a large number of SAg toxins in *S. aureus*, and analyzed the correlation of specific SAg genes with specific clinical syndromes, the existence of genes are not equivalent to the actual expression and function of toxins. SAgs act as both superantigen toxin and potent gastrointestinal toxin.

Although the evolutionary function in *S. aureus* life cycle remains unclear, these prominent SAg toxins obviously represent highly unique and well adaptable virulence factors. An open question remains if these separate functions of SAg are related. It is still unclear how these toxins enter body *via* intestine, induce emetic responses in human and animals, and what is the receptor of target cells in intestine and/or nervous system for SE-induced emesis. Understanding the complex biology and relationship of different functions of SAg toxins will undoubtedly answer many of these important questions. Continued efforts into understanding the mechanisms of subversion immune response by *S. aureus* will not only lead to new insights into the pathophysiology of infections and antimicrobial strategies, but also help to improve the prediction of invasive diseases and propose new targets for therapeutic intervention.

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