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Basis of Virulence in Enterotoxin-Mediated Staphylococcal Food Poisoning

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The *Staphylococcus aureus* enterotoxins are a superfamily of secreted virulence factors that share structural and functional similarities and possess potent superantigenic activity causing disruptions in adaptive immunity. The enterotoxins can be separated into two groups; the classical (SEA-SEE) and the newer (SEG-SE*Y* and counting) enterotoxin groups. Many members from both these groups contribute to the pathogenesis of several serious human diseases, including toxic shock syndrome, pneumonia, and sepsis-related infections. Additionally, many members demonstrate emetic activity and are frequently responsible for food poisoning outbreaks. Due to their robust tolerance to denaturing, the enterotoxins retain activity in food contaminated previously with *S. aureus*. The genes encoding the enterotoxins are found mostly on a variety of different mobile genetic elements. Therefore, the presence of enterotoxins can vary widely among different *S. aureus* isolates. Additionally, the enterotoxins are regulated by multiple, and often overlapping, regulatory pathways, which are influenced by environmental factors. In this review, we also will focus on the newer enterotoxins (SEG-SE*Y*), which matter for the role of *S. aureus* as an enteropathogen, and summarize our current knowledge on their prevalence in recent food poisoning outbreaks. Finally, we will review the current literature regarding the key elements that govern the complex regulation of enterotoxins, the molecular mechanisms underlying their enterotoxigenic, superantigenic, and immunomodulatory functions, and discuss how these activities may collectively contribute to the overall manifestation of staphylococcal food poisoning.

Keywords: *Staphylococcus aureus*, superantigen, enterotoxins, food poisoning, regulation, virulence, emesis

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INTRODUCTION

Staphylococcus aureus is a dangerous human pathogen whose virulence potential predominantly relies on the production of an impressive catalog of protein toxins. These can work separately or in concert to cause a multitude of human diseases. Pneumonia, sepsis-related infections, toxic shock syndrome, and food poisoning are diseases that have traditionally been associated in particular with the production of enterotoxins (Lowy, 2003). However, recent studies suggest that the staphylococcal enterotoxins (SEs) have a broader role in the manifestation of a number of other human illnesses, including those associated with the respiratory tract (Pastacaldi et al., 2011; Huvenne et al., 2013) and the development of autoimmune diseases (Principato and Qian, 2014; Li et al., 2015). The SEs are powerful non-specific T-cell stimulators (superantigens)

that cause unregulated activation of the immune response (for detailed reviews see Fraser and Proft, 2008; Spaulding et al., 2013). If this stimulation is sustained, a massive cytokine overload is produced preluding the clinical hallmarks of toxic shock syndrome, which is characterized by the fast onset of fever, organ failure and significant mortality (Lappin and Ferguson, 2009). Unlike the majority of other secreted toxins produced by *S. aureus*, the SEs require only minute quantities to be toxic in humans. Additionally, the SEs have a remarkable tolerance to extreme denaturing conditions, such as low pH (Schantz et al., 1965; Bergdoll, 1983), heating (Evenson et al., 1988; Asao et al., 2003) and proteolytic digestion (Humber et al., 1975; Regenthal et al., 2017). These combined qualities make the SEs, especially SEB, potential bioterrorism agents (Madsen, 2001). Notably, SEB is also classified as a Category B select agent by various United States federal agencies.

In addition to the toxic effects they have on the host, the SEs are potent emesis-inducing toxins. Reports of the involvement of enterotoxin-producing *S. aureus* in staphylococcal food poisoning (SFP) can be dated as far back as the 1900s. However, it was not until the 1930s that a link between the two were made (Dack, 1937). In healthy human individuals, SFP is an acute disease depicted by symptoms including nausea, vomiting, abdominal cramping, diarrhea, typically in the absence of fever, appearing within 3–9 h after the ingestion of food contaminated previously with enterotoxin-producing *S. aureus*. SFP is often self-limiting with recovery occurring 1–3 days after the onset of symptoms (Le Loir et al., 2003). However, symptoms may be more severe in the young, elderly and immunocompromised (Murray, 2005; Argudin et al., 2010). The SEs' ability to traverse the harsh acidic conditions within the gut to reach the intestine means that the advancement of SFP can also occur in the absence of live bacteria. Typically, only high nanogram to low microgram quantities of enterotoxins are needed to induce the symptoms of SFP (Larkin et al., 2009).

Next to *E. coli*, *Shigella*, *Bacillus* spp., and *Clostridium* spp., *S. aureus* is among the leading toxin-producing bacterial causative agents of food poisoning. *S. aureus* is also frequently mentioned in national foodborne illness estimates (Gkogka et al., 2011; Bennett et al., 2013; Thomas et al., 2013; Kirk et al., 2014; Mangen et al., 2015; Park et al., 2015; Van Cauteren et al., 2017), and is identified as a main player in major food poisoning outbreaks worldwide (Asao et al., 2003; Do Carmo et al., 2004; Chiang et al., 2008; Ostyn et al., 2010; Sato'o et al., 2014; Ercoli et al., 2017). In the US alone, it is estimated that *S. aureus* accounts for more than 240,000 foodborne illnesses per year (Scallan et al., 2011). However, considering that SFP can be resolved in individuals without hospitalization, it is not unusual for many cases to go unreported. While SFP rarely develops into a life-threatening disease, its frequency has a significant impact on the economy, resulting in a loss in productivity. It also represents a serious financial burden, especially for the food industry, catering businesses, and public healthcare systems. The implementation of traditional hygiene practices and proper food safety measures are key to preventing foodborne illness (Hussain and Dawson, 2013).

THE SUPERFAMILY OF STAPHYLOCOCCAL ENTEROTOXINS; PROTEINS AND OVERVIEW

The superfamily of SEs and enterotoxin-like (SE*l*s) proteins (**Table 1**) share many common features; they are non-glycosylated, antigenically distinct, low molecular weight (19–29 kDa) single-chain proteins that all fold into homologous globular structures (Thomas et al., 2007). Since the first characterization of the classical SEs (SEA to SEE) in *S. aureus* (Bergdoll et al., 1965, 1971, 1973; Casman et al., 1967; Marrack and Kappler, 1990), advancements in the area of molecular biology during the 1980s led to the identification of a new set of genes encoding closely-related proteins with superantigenic and emetic activities (**Table 1**). This sudden increase in the number of described SEs spurred a move to standardize their nomenclature (Lina et al., 2004). Only enterotoxins with demonstrated emetic potential in monkeys were designated "SE," whereas enterotoxins that failed to do so or have not been evaluated in non-human primate models of emesis are designated enterotoxin like (SE*l*-) toxins (**Table 1**). The only exception to this rule is Toxic Shock Syndrome Toxin-1 (TSST-1), which was originally designated SEF (Bergdoll et al., 1981; Reiser et al., 1983). This toxin's apparent lack of emetic activity, possibly due it being less stable than other SEs (Edwin and Kass, 1989), prompted the name change to TSST-1, which has remained in place ever since. Joining TSST-1, SE*lJ* is the only other tested SE that is non-emetic (Munson et al., 1998; Orwin et al., 2001, 2002). SE*l*X, SE*l*U, SE*l*W, SE*l*V, and SE*l*Y have yet to be tested for emetic activity in non-human primates.

THE SE GENES ARE DISTRIBUTED ACROSS A VARIETY OF DIFFERENT GENOMIC LOCATIONS

When considering the locations of the enterotoxin genes, *selx* (Wilson et al., 2011) and *sely* (Ono et al., 2015) are unique as they are found exclusively on the genome. The *selx* gene can be found in ∼95% of *S. aureus* strains, whereas *sely* appears less frequently and has only been detected in a handful of strains thus far. In contrast, the other enterotoxin genes are sometimes found alone, but more commonly in groups, on a variety of large mobile segments of DNA called mobile genetic elements (MGEs) (Fraser and Proft, 2008; Argudin et al., 2010). These MGEs include prophages, plasmids, transposons, *S. aureus* pathogenicity islands (SaPIs), and the enterotoxin gene clusters (*egc*) (**Table 1**) (for a review on staphylococcal MGEs see, Malachowa and DeLeo, 2010). The *egc* locus is home to an operon of genes encoding SEG, SEI, SEM, SEN, SEO, and two pseudogenes, *φent1* and *φent2* (Jarraud et al., 2001; Monday and Bohach, 2001). Deletion, duplication and recombination events within this cluster make it a major hub for the generation of new types of SEs and

TABLE 1 | Emetic and superantigenic activities of staphylococcal enterotoxins.

Enterotoxin	Genetic element	Superantigenic activity	Emetic activity		Type	Phylogenetic group
			Monkey	Shrew		
SEA	Prophage	Yes	Yes (Bergdoll et al., 1965)	Yes (Hu et al., 2003)	Classical	SEA
SEB	Chromosome, SaPI, plasmid (pZA10)	Yes	Yes (Bergdoll et al., 1965)	Yes (Hu et al., 2003)	Classical	SEB
SEC1	SaPI	Yes	Yes (Schlievert et al., 2000)	nd[1]	Classical	SEB
SEC2	SaPI	Yes	Yes (Bergdoll et al., 1965)	Yes (Hu et al., 2003)	Classical	SEB
SEC3	SaPI	Yes	Yes (Reiser et al., 1984)	nd	Classical	SEB
SED	Plasmid (pIB485)	Yes	Yes (Igarashi, 1972)	Yes (Hu et al., 2003)	Classical	SEA
SEE	Prophage	Yes	Yes (Bergdoll et al., 1971)	Yes (Hu et al., 2003)	Classical	SEA
SEG	*egc*1, *egc*2, *egc*3, *egc*4	Yes	Yes (Munson et al., 1998)	Yes (Hu et al., 2003)	New	SEB
SEH	Transposon (MGEmw2/mssa476 *seh*/D*seo*)	Yes	Yes (Su and Wong, 1995)	Yes (Hu et al., 2003)	New	SEA
SEI	*egc*1, *egc*2, *egc*3	Yes	<100 μg/kg (Munson et al., 1998)	Yes (Hu et al., 2003)	New	SEI
SE/J	Plasmid (pIB485, pF5)	Yes	nd	nd	New	SEA
SEK	Prophages, SaPI1, SaPI3, SaPI5, SAPIbov1	Yes	Yes (Omoe et al., 2013)	Yes (Ono et al., 2017)	New	SEI
SEL	Prophages, SaPIn1, SaPIm1, SaPImw2, SAPIbov1	Yes	Yes (Omoe et al., 2013)	Yes (Ono et al., 2017)	New	SEI
SEM	*egc*1, *egc*2	Yes	Yes (Omoe et al., 2013)	Yes (Ono et al., 2017)	New	SEI
SEN	*egc*1, *egc*2, *egc*3, *egc*4	Yes	Yes (Omoe et al., 2013)	Yes (Ono et al., 2017)	New	SEA
SEO	*egc*1, *egc*2, *egc*3, *egc*4, transposon	Yes	Yes (Omoe et al., 2013)	Yes (Ono et al., 2017)	New	SEA
SEP	Prophage (Sa3n)	Yes	Yes (Omoe et al., 2013)	Yes (Omoe et al., 2005)	New	SEA
SEQ	Prophage, SaPI1, SaPI3, SaPI5	Yes	Yes (Omoe et al., 2013)	Yes (Hu et al., 2017)	New	SEI
SER	Plasmid (pIB485, pF5)	Yes	<100 μg/kg (Ono et al., 2008)	<100 μg/kg (Ono et al., 2008)	New	SEB
SES	Plasmid (pF5)	Yes	<100 μg/kg (Ono et al., 2008)	<100 μg/kg (Ono et al., 2008)	New	SEA
SET	Plasmid (pF5)	Yes	<100 μg/kg (Ono et al., 2008)	<100 μg/kg (Ono et al., 2008)	New	SE/X
SEU	*egc*2, *egc*3	Yes	nd	nd	New	SEB
SE/W (SE/U2)	*egc*4	Yes	nd	nd	New	SEB
SEV	*egc*4	Yes	nd	nd	New	SEI
SE/X	Chromosome	Yes	nd	nd	New	SE/X
SE/Y	Chromosome	Test cell-dependent	nd	Yes (Ono et al., 2015)	New	SE/X

nd, not demonstrated.

variants (Letertre et al., 2003b; Thomas et al., 2006). The acquisition of MGEs generally has a significant impact on core genomes by causing striking differences in genome size and structure. In *S. aureus*, a comparison of the presence of SE genes from several major lineages shows that SE gene composition is strongly linked to specific genetic backgrounds, emphasizing the importance of vertical transmission, rather than horizontal transmission, of SE-encoding MGEs (Goerke et al., 2009). Around 80% of *S. aureus* isolates, including commensal, clinical, and food-poisoning isolates, carry an average of 5–6 SE genes

(Jarraud et al., 2001; Baba et al., 2002; Becker et al., 2003; Holtfreter et al., 2004, 2007; Hait et al., 2014; Lv et al., 2014; Umeda et al., 2017).

THE ENTEROTOXINS CAN BE FURTHER SEPARATED BASED ON NUCLEOTIDE AND AMINO ACID SEQUENCES

The 24 currently identified SEs and SE*l*s, can be further separated into several evolutionary groups based on a comparison of their nucleotide and amino acid sequences; the SEA group (SEA, SED, SEE, SE*l*J, SEH, SEN, SEO, SEP, SES), the SEB group (SEB, SECs, SEG, SER, SE*l*U, SE*l*W, previously known as SE*l*U2), the SEI group (SEI, SEK, SEL, SEQ, SEM, SE*l*V), and the SE*l*X group (TSST-1, SET, SE*l*X, SE*l*Y and members of another group of staphylococcal exotoxins called superantigen-like (SSL) toxins) (for reviews, see Fraser and Proft, 2008; Ono et al., 2015) (**Table 1**). A fifth group, which is not produced by staphylococci, but only represented by a group of functionally and structurally similar superantigenic toxins produced by streptococci, will not be discussed further.

The presence or absence of two specific structural features predominantly defines the superantigenic and enterotoxigenic properties of the SEs and explains differences in activity between the evolutionary groups. First, enterotoxins belonging to the SE*l*X and SEB groups only possess one low affinity α-chain major histocompatibility complex (MHC) II binding site, whereas enterotoxins from the SEA and SEI groups contain one low affinity α-chain MHC II and a second, high affinity β-chain MHC II binding site, which generally equates to superior superantigenic activity (Kozono et al., 1995). Additionally, differences in amino acid composition have given rise to variants of SEB (Kohler et al., 2012), SEC (Bohach and Schlievert, 1987; Couch and Betley, 1989; Marr et al., 1993), SED (Johler et al., 2016), SEG, SEI (Abe et al., 2000; Blaiotta et al., 2004), SEK (Aguilar et al., 2014), SEM, SEN, SEO, SE*l*U, and SE*l*V (Letertre et al., 2003b; Collery et al., 2009). Compared to the parent toxins, variants of SEB (Kohler et al., 2012) and SEC (Deringer et al., 1997) demonstrate altered species tropism or reduced superantigenic activities. The production of these mutations in SEs may be part of a broader strategy of *S. aureus* to adapt to different host species (Marr et al., 1993; Edwards et al., 1997; Johler et al., 2016).

Second, a separate and distinct loop comprising 9–19 varying amino acids flanked by 2 cysteine residues creating a disulfide bridge, was originally thought to be an essential feature of emesis-inducing SE members from the SEA and SEB evolutionary groups. However, mutational analyses of that loop demonstrated that only the disulfide bond between the two cysteine residues, rather than the loop itself, was required for emesis (Hovde et al., 1994). These data are consistent with experiments demonstrating that SEs that lack the loop can still induce emesis in primates (Omoe et al., 2013), leading to the conclusion that there are additional unidentified emesis-associated structural determinant(s) in the SEs.

S. AUREUS HAS A COMPLEX NETWORK OF REGULATORY PATHWAYS TO CONTROL TOXIN PRODUCTION

S. aureus responds to changes in the environment using a combination of quorum-sensing (QS) (Waters and Bassler, 2005) and other two-component systems (TCS), of which at least 16 have been discovered in *S. aureus* to date (Haag and Bagnoli, 2016), as well as many trans-acting regulatory proteins (Bronner et al., 2004). *S. aureus* relies on these systems to quickly make changes in the regulation of genes associated with important physiological features, including drug resistance, metabolism, immune evasion, and virulence. Each system can directly or indirectly control the transcription of specific sets of genes. However, the regulation of one gene may be influenced by multiple systems, leading to additional layers of regulation.

The accessory gene regulator (Agr) QS system, which is activated at high cell densities, is comprised of two transcriptional units transcribed in opposing directions; RNAII, which codes for four genes (*agrA, agrB, agrC,* and *agrD*) (Novick et al., 1995) and RNAIII, a regulatory RNA. These transcripts are controlled by the promoters P2 and P3, respectively. AgrD, which contains the sequence for the autoinducing peptide (AIP), is processed and exported out of the cell by the combined actions of the membrane-associated export protein, AgrB (Ji et al., 1995, 1997; Mayville et al., 1999) and a type I signal peptidase, SpsB (Kavanaugh et al., 2007). AIP acts as the ligand for the membrane bound histidine kinase, AgrC, leading to the phosphorylation of AgrA (Ji et al., 1995; Lina et al., 1998). Activated ArgA binds to the P2 and P3 promoters, resulting in the perpetuation of a positive feedback loop (Koenig et al., 2004).

Expression of *agr* is affected by various trans-activing regulators, such as the Sar family of regulatory proteins, (SarR, SarS, SarT, SarU, SarX, SarZ, SarV, MgrA, and Rot) (Cheung and Projan, 1994; Heinrichs et al., 1996; Cheung et al., 2008), σB (Lauderdale et al., 2009), and SrrAB (Staphylococcal respiratory response AB) (Yarwood et al., 2001; Pragman et al., 2004). Additionally, σB and Rot can affect another important two-component system called SaeRS (Li and Cheung, 2008; Kusch et al., 2011). Importantly, all these regulatory elements respond to various environmental stresses and stimuli; the SaeRS (*S. aureus* exoprotein expression) system responds to membrane attack by antimicrobial molecules produced by the innate host defense (Novick and Jiang, 2003; Kuroda et al., 2007; Geiger et al., 2008; Cho et al., 2015), SarA largely responds to changes in microenvironments (Cheung et al., 2004), σB responds to high temperature, catabolites, alkaline pH, high salinity (Betley et al., 1992; Wu et al., 1996; Kullik and Giachino, 1997; Kullik et al., 1998; Pané-Farré et al., 2006), whereas the SrrAB system has been shown to be particularly crucial for bacterial growth under anaerobic and hypoxic conditions (Yarwood et al., 2001; Pragman et al., 2007; Kinkel et al., 2013; Mashruwala and Boyd, 2017). Lastly, Rot, the global gene regulator (Saïd-Salim et al., 2003) is negatively regulated by RNAIII through an antisense mechanism (Geisinger et al., 2006; Boisset et al., 2007).

REGULATION OF THE CLASSICAL ENTEROTOXINS

It has been described early that there is unequal distribution of SE-associated MGEs among *S. aureus* isolates, and that thus, the host background has profound influences on enterotoxin production (Gaskill and Khan, 1988; Compagnone-Post et al., 1991). Surprisingly, our understanding of how the enterotoxins are regulated is still rather incomplete, but we do know that enterotoxin regulation is strongly dependent on the regulatory systems described above (**Figure 1**). Several Agr-controlled staphylococcal toxins, such as alpha-toxin (Morfeldt et al., 1995) and the family of phenol-soluble modulins (PSMs) (Queck et al., 2008) are produced between the early logarithmic and stationary phases. Early observations showing that the production of SEB (Czop and Bergdoll, 1974; Gaskill and Khan, 1988; Derzelle et al., 2009), SEC (Otero et al., 1990; Regassa et al., 1991), and SED (Bayles and Iandolo, 1989) also occurred between the exponential to stationary phases of bacterial growth (Gaskill and Khan, 1988; Regassa et al., 1991; Zhang and Stewart, 2000) suggested that they could be regulated by Agr. Indeed, isogenic *S. aureus agr* mutants showed significant decreases in SEC and SED production compared to the wild-type strain (Regassa et al., 1991). However, it was later shown that SEB, SEC, and SED is regulated indirectly by other factors. For instance, Agr-dependent regulation of SEB, SEC, and SED occurs via RNAIII-dependent inhibition of Rot (Regassa and Betley, 1993; Tseng et al., 2004; Tseng and Stewart, 2005). In addition to Rot, SEB is also negatively regulated by σB (Ziebandt et al., 2001, 2004; Pané-Farré et al., 2006; Rogasch et al., 2006).

In contrast, the production of bacteriophage-associated SEA is generally constitutive (Thomas et al., 2007), although *S. aureus* strains with distinct high and low SEA expression patterns have been described (Borst and Betley, 1994; Wallin-Carlquist et al., 2010). Since the expression pattern of SEA was found to be different from that of SEB, SEC and SED, it was postulated and confirmed that SEA is regulated independently of Agr (Tremaine et al., 1993). The production of SEA was later discovered to be closely tied to the phage's life cycle (Cao et al., 2012) and to be inducible by bacterial stress (Zeaki et al., 2015).

REGULATION OF THE NEWER ENTEROTOXINS

Information surrounding the regulation of the newer enterotoxins is only beginning to emerge. Unlike most of the classical enterotoxins, it appears that the regulation of several newer enterotoxins including SE*lJ* (Zhang et al., 1998) and SEH (Lis et al., 2012), is Agr-independent. The expression of SFP-associated SEH, which is produced predominantly in the late exponential phase of bacterial growth (Sakai et al., 2008; Lis et al., 2012), was recently shown to be positively regulated by Rot, via direct binding to the *seh* promoter (Sato'o et al., 2015), σB (Kusch et al., 2011), several Sar homologs, and SaeR (Sato'o et al., 2015). Moreover, SaeRS appears to have a positive impact on SE*lX* (Langley et al., 2017) and TSST-1 (Baroja et al., 2016) expression.

In contrast, the production of enterotoxins encoded in the *egc* operon (SEG, SEI, SEM, SEN, SEO, and SE*l*U) is highest in the earliest stages of exponential growth (Grumann et al., 2008) and dependent on σB (Kusch et al., 2011). Interestingly, one study showed that SEK production is dependent on the presence of SEB (Aguilar et al., 2014), whereas SEK and SEQ, which are also found on *sea*-associated phages, can be transcriptionally induced by mitomycin C (Sumby and Waldor, 2003). Taken together, the SEs are regulated by multiple regulatory elements that respond to a variety of different environmental signals. Likely, the delicate balance in enterotoxin expression facilitated by these regulatory elements has a profound impact on the commensal and pathogenic lifestyles of *S. aureus*.

WHICH STAPHYLOCOCCAL ENTEROTOXINS CONTRIBUTE TO SFP?

To control staphylococcal food poisoning and ensure food safety, the roles of both new and classical SEs must be considered. Although a wide variety of SE detection methods have been developed (**Table 2**), molecular detection of SE genes remains the most common method used for investigating the possible contribution of SEs toward SFP. Molecular studies spanning the last two decades have shown that *egc*-encoded genes (*seg*, *seh*, *sei,* or *selj*) are readily detected in *S. aureus* food poisoning isolates around the world (Blaiotta et al., 2004; Grumann et al., 2008; Yan et al., 2012; Viçosa et al., 2013; Chao et al., 2015; Johler et al., 2015; Cheng et al., 2016; Song et al., 2016; Shen et al., 2017; Umeda et al., 2017). Additionally, the detection of non *egc*-encoded enterotoxin genes, such as transposon associated-*seh* (McLauchlin et al., 2000; Ikeda et al., 2005; Jørgensen et al., 2005), plasmid-associated *ser* (Wattinger et al., 2012) and SaPI-associated *seq* (Chiang et al., 2008; Alibayov et al., 2014; Lv et al., 2014; Hu et al., 2017) suggest a role of these newer SEs in SFP.

While PCR is an invaluable tool, confirmation of the physical presence of toxin in food products suspected of contamination is needed to clearly verify their contribution to SFP. The immunological detection of the 5 classical SEs has helped to establish SEA as the top contributor (∼80%) to SFP outbreaks (Pinchuk et al., 2010; Hennekinne et al., 2012), followed by SED, SEB, SEC, and SEE (Hu and Nakane, 2014). In contrast, due to the lack of sensitive detection methods, it has been impossible to draw such conclusions for the newer SEs. However, a steadily increasing number of immunological assays for the non-classical enterotoxins, such as SEG (Nagaraj et al., 2016), SEH (Su and Wong, 1996), SEI (Zhao et al., 2016b), SEK (Aguilar et al., 2014), SEM (Zhao et al., 2017), and SEQ (Hu et al., 2017) have been developed within the last decade. They indicated that one or more of the newer enterotoxins are potential causes of SFP outbreaks. Although few studies have examined the physical presence of multiple enterotoxins, it is most likely that multiple SEs contribute to SFP. The expansion of existing multiplex assays (Liang et al., 2015; Adhikari et al., 2016) would be the most efficient strategy to detect all SEs simultaneously. However, each platform has its advantages and disadvantages (**Table 2**; Wu et al., 2016 for review). An ideal platform to detect all SEs would have

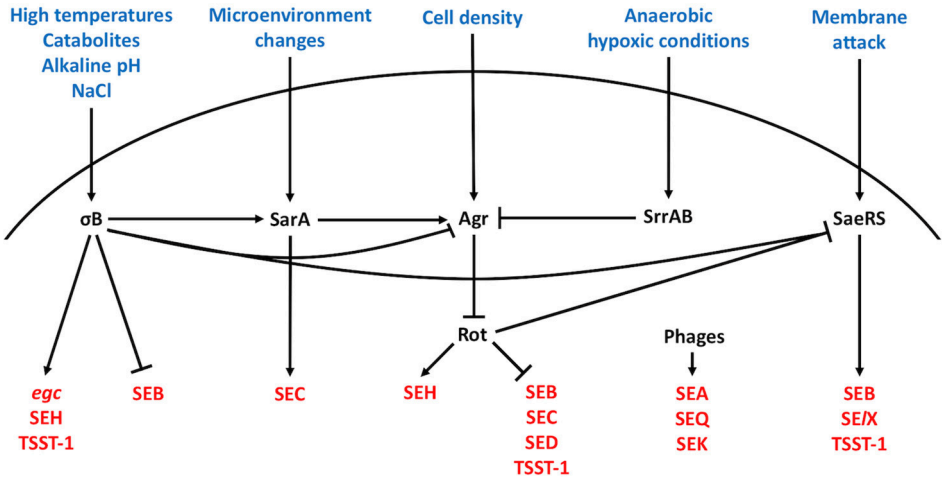

FIGURE 1 | Regulation of staphylococcal enterotoxins. Harsh bacterial growth conditions, changes in the bacterial microenvironment, high cell density, hypoxia, and membrane changes direct enterotoxin expression through the alternative sigma factor, SarA protein family, Agr quorum sensing system, SrrAB protein, and SaeRS two-component system, respectively. The excitatory and inhibitory action of these systems on the other regulators and enterotoxins are summarized. Arrowheads represent upregulation and bars downregulation.

high sensitivity, low cross-reactivity, and universal adaptability. Although creating such a system is not impossible, it would be an extremely difficult task, requiring considerable resources, and vigorous testing.

HUMANS AND LIVESTOCK ARE MAJOR RESERVOIRS FOR THE TRANSMISSION OF ENTEROTOXIN-PRODUCING *S. AUREUS*

S. aureus, a natural colonizer of humans, can be found on the skin (primarily on the hands, chest, and abdomen), gastrointestinal (GI) tract (Ridley, 1959; Armstrong-Esther, 1976; Wertheim et al., 2005), and nasopharyngeal cavities (Williams, 1963). All these sites represent possible reservoirs for the distribution of *S. aureus* causing human disease. Persistent colonization of the anterior nares with *S. aureus*, which currently is estimated to be around 20–30% of the population (Verhoeven et al., 2014), is believed to be the most important risk factor for infection, especially regarding health-care associated diseases (Von Eiff et al., 2001). While colonization of the GI tract by *S. aureus* has received significantly less attention, recent studies emphasize its underappreciated role in the association with and transmission of *S. aureus* disease (Nowrouzian et al., 2011, 2017; Senn et al., 2016; Gagnaire et al., 2017). With regards to SFP, studies investigating the presence of enterotoxin genes in *S. aureus* isolates sampled from the nose (Nashev et al., 2007; Collery et al., 2009; Wattinger et al., 2012; Ho et al., 2015) and gut (Lis et al., 2009; Shin et al., 2016) indicate that these two sites are important sources of enterotoxin-producing *S. aureus*.

S. aureus is particularly renowned for its ability to acquire and develop resistance to multiple antibiotics, which is a key factor contributing to the difficultly of treating infections caused by this pathogen. A majority of *S. aureus* infections are caused by methicillin-resistant strains (MRSA), which, historically, have been associated with disease in hospitalized patients in a variety of public healthcare settings [hospital-associated (HA)-MRSA]. However, in the early 1990s, a new breed of genetically distinct MRSA strains started to appear in the community [community-associated (CA)-MRSA] (Otto, 2010). Compared to the HA-MRSA strains, CA-MRSA strains are exceptionally pathogenic (Chambers, 2001; Cameron et al., 2011) because of the enhanced production and acquisition of a broad set of virulence factors that contribute to fitness, colonization and virulence (Otto, 2012). Additionally, MRSA infections in the community can be caused by strains initially associated with livestock [livestock-associated MRSA (LA-MRSA)] (Huijsdens et al., 2006; Lewis et al., 2008; Nemati et al., 2008). For instance, carriage, or infections caused by *S. aureus* in dairy cattle (e.g., mastitis) can lead to the contamination of dairy products and raw meat. In particular, unprocessed foods hold a substantial risk for the introduction of resistant microbes into the food chain, which can have a considerable economic impact, especially in countries with industrialized dairy sectors (Le Loir et al., 2003). Interestingly, epidemiological studies have indicated that LA-MRSA isolates belong to genetic lineages different from their HA- and CA-MRSA counterparts (for detailed reviews, see Fluit, 2012; Cuny et al., 2015; Smith, 2015) and harbor unique genes that are essential for host adaptation (Lowder et al., 2009; Guinane et al., 2010; Price et al., 2012).

Unsurprisingly, several recent studies reported high levels of multiple antibiotic resistance in LA-MRSA (Kérouanton et al., 2007; Ge et al., 2017; Sahibzada et al., 2017; Abdi et al., 2018; Suleiman et al., 2018), but unlike other enteric pathogens, such as *Salmonella* and *E. coli*, for which antimicrobial resistance can impose serious health risks in humans (Doyle, 2015), antibiotic resistance in HA-, CA-, or LA-MRSA isolates had little influence

TABLE 2 | A summary of detection strategies for staphylococcal enterotoxins.

Method of detection	Description	Comments	References
Animals	Emesis in kittens		Fulton, 1943
	Emesis in house musk shrews	Animal testing is generally labor intensive and expensive	Hu et al., 1999
	Emesis in dogs	Inter-animal and species differences can affect results	Kocandrle et al., 1966
	Emesis in pigs and piglets	Low sensitivity in some species	Taylor et al., 1982; Van Gessel et al., 2004
	Emesis in ferrets		Wright et al., 2000
	Emesis in monkeys		Bergdoll et al., 1965; Sugiyama and Hayama, 1965
	Skin test in guinea pigs		Scheuber et al., 1983
	Mouse, rat, and rabbits[a]		Horn et al., 2013
Serological testing	Gel diffusion/agglutination tests	Semi-quantitative. Lack in specificity and sensitivity have prevented these assays from being employed for routine detection of SEs	Read et al., 1965; Salomon and Tew, 1968
Immunoassays	Colorometric	Colorometric method is most commonly used for SE protein detection	Saunders and Bartlett, 1977
	Fluorescent (including Quantum dots and Lanthanide ion chelate-doped nanoparticles)		Tempelman et al., 1996; Goldman et al., 2002
	Chemiluminescent	All methods are highly sensitive and specific and provide low background signals	Luo et al., 2006
Coupled immunoassays	Electrochemiluminescent	Easy and rapid to operate, low costs Can detect presence of over a wide linear range and in complex samples	Kijek et al., 2000; Sun et al., 2010
	Surface plasmon resonance		Rasooly and Rasooly, 1999; Nedelkov et al., 2000
	Surface-Enhanced Raman Scattering		Pekdemir et al., 2012
	Electrochemical mass		Harteveld et al., 1997
Molecular	Colony blot hybridization	Simultaneous detection of several SE genes with different primers	Neill et al., 1990
	Polymerase chain reaction (PCR)		Wilson et al., 1991
	Multiplex PCR	Fast and can be applied to detect SE genes in most kinds of food	Shylaja et al., 2010
	Real-time PCR	Methods do not detect the presence of protein toxins	Letertre et al., 2003a
	Reverse-transcriptase PCR		Matsui et al., 1997
	Loop-mediate isothermal amplification (LAMP)		Nkouawa et al., 2009
Chromatography	Liquid chromatography tandem-mass spectrometry (LC-MS/MS	Does not require the isolation of toxins from food. Highly sensitive. However, samples with high protein levels may suppress electrospray.	Kientz et al., 1997
	Liquid chromatography Electrospray ionization mass spectrometry (LC-ESI/MS)		Callahan et al., 2006
Aptamer-based bioassays	DNA and RNA	Highly specific, comparable to antibodies. Easily produced by chemical synthesis, high purity and easily modified with chemical tags. Can be coupled with other techniques.	Bruno and Kiel, 2002
	Peptide		Soykut et al., 2008
	Molecularly imprinted polymers		Gupta et al., 2011

[a] *No emetic reflexes observed in these species.*

on the ability of *S. aureus* to cause SFP (Sergelidis and Angelidis, 2017). These observations are consistent with the notion that SFP is not a disease that is typically treated with antibiotics, since the enterotoxin-driven manifestation of SFP can progress in the absence of bacteria.

MECHANISMS UNDERLYING ENTEROTOXIN-INDUCED EMETIC AND DIARRHEAL ACTIVITY

Progress in understanding the molecular mechanisms underlying the enterotoxigenic effects of the SEs has been hampered by a lack of relevant animal models. Small rodents, such as mice and rats, are non-emetic and generally less susceptible to the enterotoxigenic effects of the SEs (Bergdoll, 1988) whereas non-human primates, which are considered the gold standard for testing the emetic activity of enterotoxins, are costly and riddled with complex requirements in animal care and husbandry. However, the house musk shrew, *Suncus murinus*, was recently identified as a suitable animal model and an alternative to using monkeys (Hu et al., 2003). Studies in the shrew confirmed that a network of branched connections linking multiple organs of the body with the brain, called the vagus nerve, was an essential element for SE-induced emesis, recapitulating earlier observations from monkeys (Sugiyama and Hayama, 1965). Further studies in shrews revealed that the MHC II-independent release of 5-hydroxytryptamine (5-HT/Serotonin) from mast cell granules by SEs was crucial for SE-induced emesis (Ono et al., 2012). Other agonists involved in the emetic response have also been reported (Scheuber et al., 1987; Alber et al., 1989; Jett et al., 1990). In addition to mast cells, the SEs appear to have an affinity for epithelial cells (Hamad et al., 1997; Shupp et al., 2002; Danielsen et al., 2013; Zhao et al., 2016a) and goblet cells (Hirose et al., 2016). Unlike mast cells, SEs use epithelial cells (Danielsen et al., 2013) and mucus-producing goblet cells (Hirose et al., 2016) as gateways in order to traffic across the intestinal epithelia to reach other final targets. Importantly, the movement of enterotoxins through epithelial cells is thought to be a glycolipid-dependent transcytosis process that may be facilitated in the presence of other *S. aureus* virulence determinants (Edwards et al., 2012). Interestingly, a conserved stretch of 10-amino-acid peptides, located within the longest alpha-helical chain between the A and B domains of the enterotoxins, is an important structural determinant that promotes translocation (Shupp et al., 2002; **Figure 2**).

In contrast to strong induction of emesis, the clinical symptoms of diarrhea are oftentimes less apparent in SFP, which may be in part due to the inability of some SEs, such as SEA and SEC, to cause fluid exudation and dilation of the intestinal segments (Maina et al., 2012). However, the symptoms of diarrhea sometimes observed with SEB intoxication may be due to the inhibition of water and electrolyte reabsorption in the small intestine (Sullivan, 1969; Sheahan et al., 1970). To this date, exactly how the SEs cause diarrhea is still far from understood. For a detailed review on other aspects of SE-induced emesis, see (Hu and Nakane, 2014).

THE SUPERANTIGENIC ACTIVITIES OF THE ENTEROTOXINS

The molecular details underlying the superantigenic activity of the SEs have been dissected by numerous X-ray crystallography, structural and mutational analyses. Unlike with conventional antigens, the non-specific activation of T cells by SEs occurs independently of antigen processing and presentation to the T cells by antigen-presenting cells (APCs). Instead, SEs act as a bridge between APCs and T cells. In the majority of cases, SEs first bind to the MHC class II molecules found on APCs and coordinate binding to one or more variable beta (Vβ) chain(s) of T-cell receptors (TCRs) (Kappler et al., 1989; White et al., 1989; Choi et al., 1990; Jarraud et al., 2001). However, these molecular interactions are not exclusive and other receptors have been described to be involved. For instance, the variable alpha (Vα) chain can be targeted by SEH (Saline et al., 2010). Moreover, maximal superantigenic activity of SEB is dependent on additional co-stimulatory receptors, CD28 and B7-2, on T cells and APCs, respectively (Arad et al., 2011; Levy et al., 2016). Interestingly, the same CD28 binding site can be found on other SEs, such as SEA and TSST-1 (Arad et al., 2011). Regardless of the mechanism of cross-linking, characteristic for SE activity is a polyclonal activation of a large pool of $CD4^+$ and $CD8^+$ T cells (∼20% of the total T cells) (Marrack et al., 1990; Miethke et al., 1992; Leder et al., 1998) followed by a massive release of an assortment of T helper 1 (Th1) cytokines, such as tumor necrosis factor (TNF) α, interleukin 1 (IL-1), IL-2, and interferon (IFN) γ (Carlsson et al., 1988; Tiedemann and Fraser, 1996), all of which contribute to the SE superantigenic effect (for a detailed reviews, see Krakauer, 2013; Krakauer et al., 2016).

THE ENTEROTOXINS ARE IMMUNOMODULATORS OF MULTIPLE IMMUNE CELL TYPES

The superantigenic and enterotoxigenic activities of the SEs are the best studied mechanisms underlying their pathogenicity. However, recent studies show that the SEs possess functions in addition to these conventional activities. For example, both TSST-1 and SE*l*X (Wilson et al., 2011) show similarity to another family of staphylococcal exotoxins, called the staphylococcal superantigen-like (SSL) toxins (reviewed in Fraser and Proft, 2008). Although the SSL toxins lack the ability to induce Vβ-specific T-cell proliferation, they have diverse roles in immune evasion, including the ability to interfere with complement activation and neutrophil function (reviewed in Langley et al., 2010). Recently, it was discovered that SE*l*X has a unique sialic acid-binding motif. This motif allows SE*l*X to interact with adhesion molecules on neutrophils involved in immune recognition and cell activation (Langley et al., 2017; Tuffs et al., 2017). Importantly, the ability of SE*l*X to bind neutrophils, which are considered the first line of defense against *S. aureus* (Spaan et al., 2013), was crucial for disease progression in a rabbit model of necrotizing pneumonia. Together, these studies describe an

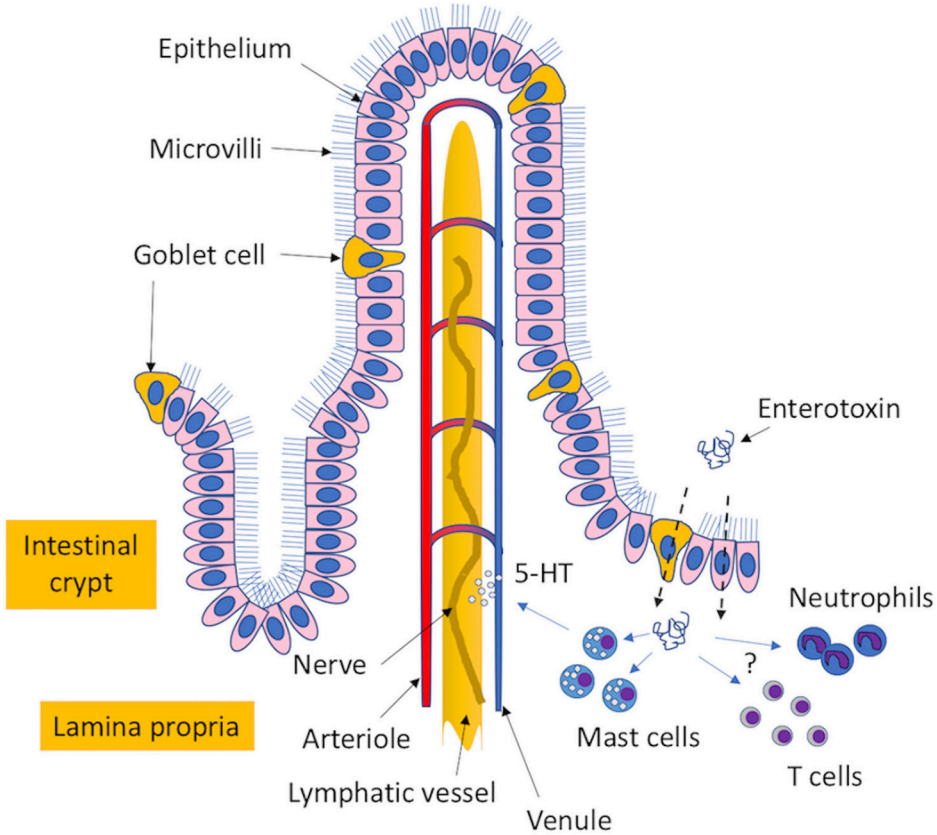

FIGURE 2 | Proposed mechanism of enterotoxin-induced emesis. The enterotoxins transit through mucus-expelling goblet cells and epithelial cells in the intestinal epithelium to reach the lamina propria. Here, the enterotoxins can interact with mast cells to induce the release of 5-hydroxytryptamine (5-HT/serotonin precursor), which interacts with the vagus nerve to cause an emetic response. Additional cellular targets that may have possible roles in the induction of enterotoxigenic disease include different types of T cells and neutrophils.

unusual member of the SE family that has both superantigenic and SSL functions.

Neutrophils are the latest among a growing list of immune cell types recognized to be targeted directly or indirectly by the SEs. Others include γδ T cells (Maeurer et al., 1995; Morita et al., 2001), invariant natural killer T (*i*NKT) cells (Rieder et al., 2011; Hayworth et al., 2012), B cells (Stohl et al., 1994), mast cells (Scheuber et al., 1987; Lotfi-Emran et al., 2017), and mucosa-associated invariant T (MAIT) cells (Shaler et al., 2017). Activation of these cell types by SEs can have a considerable impact on the immune system, which may lead to non-conventional overstimulation of the immune system, as exemplified by B cell proliferation and differentiation into plasma cells (Stohl et al., 1994). Additionally, excessive inflammation, as a result of the direct activation of *i*NKT cells and γδ T cells, can cause the production of SE-associated inflammatory disease in the lungs (Rieder et al., 2011) and systemic infection, as demonstrated in mouse infection models (Szabo et al., 2017).

In contrast to the overstimulation of the immune response by SEs, the activation of MAIT cells appears to have the opposite effect (Shaler et al., 2017). MAIT cells have significant roles in innate host defense against a variety of pathogens (Napier et al., 2015). Notably, the activation of MAIT cells by SEs was shown to be induced in a TCR-independent manner (Shaler et al., 2017). While direct activation of the MAIT cells by SEs could not be excluded, MAIT cell activation was mediated mostly by IL-12 and IL-18 released from the direct activation of conventional T cells by SEs (Shaler et al., 2017). Following a period of hyper-activation, these MAIT cells rapidly undergo exhaustion and are unable to respond further, leaving behind a suppressed and severely crippled arc of innate host defense.

COULD ENTEROTOXICITY BE DEPENDENT ON T-CELL IMMUNOMODULATION?

Whether the superantigenic function is needed for the enterotoxigenic activity of the SEs is an interesting question. Shock and fever, hallmarks of superantigen-induced disease, is generally low or absent in patients with SFP (Dinges et al., 2000), arguing against the activation of a systemic immune response. However, it was shown that 5 times more of an SEA protein derivative, which lacked superantigenic but retained

emetic activity, was required to induce emesis in a monkey model compared to unaltered SEA (Hoffman et al., 1996). This observation implies that both superantigenic and enterotoxicity activities are likely needed for a maximal emetic response.

Another aspect of immune interaction that may need to be further investigated is the potential role of T cells in SE enterotoxic activities. MAIT cells for example, which have been shown to have a protective role against GI bacterial disease (Powell and Macdonald, 2017; Salerno-Goncalves et al., 2017), represent ∼10% of intestinal T cells (Treiner et al., 2003; Dusseaux et al., 2011) and ∼50% of T cells in the intestines express γδ TCRs (Carding and Egan, 2002). Furthermore, γδ T cells that are present in the gut mucosa play an important role in mucosal immunity (Agace, 2008). Additionally, given that the SEs are highly potent at very low concentrations, enhanced expression of SEs may not be essential for the advancement of SE-mediated disease. In fact, when regulatory T cells (Tregs) are stimulated with lower concentrations of SEC, an immunosuppressed phenotype can be induced that may directly benefit *S. aureus* colonization and disease progression (Lee et al., 2017). In the healthy gut, Tregs play a crucial role in the maintenance of intestinal homeostasis by controlling inappropriate immune responses (Luu et al., 2017). Therefore, it is tempting to speculate that the combined targeting of MAIT cells, γδ T cells and Tregs in the gut by SEs may promote the pathogenesis of SFP. Whether MAIT, γδ T cells, and Tregs play any roles in SFP requires much more detailed investigation.

CONCLUSIONS

Although the classical enterotoxins have historically been considered the predominant contributors to SFP, a number of molecular studies suggest that many of the newer SEs also have a prominent role. However, in order to better determine which SEs are responsible for SFP, it is best for studies investigating SFP outbreaks to employ methods that can detect all SE genes as well as the physical presence of toxin in suspected contaminated foods. The ability to culture and accurately characterize SFP-causing *S. aureus* will significantly help understand true incidence and prevalence of SFP. It should also be noted that the inability to detect SEs in contaminated foods does not exclude that they contribute to SFP. Therefore, it is just as vital that we have a deeper understanding of what promotes SE production, especially in food environments. While it is accepted that multiple regulatory networks can have a significant impact on enterotoxin expression, it remains poorly understood how specific enterotoxins, especially the newer enterotoxins, are regulated.

In this review, we also provided an overview of the molecular mechanisms that contribute to SFP. Yet, compared to what we know about staphylococcal superantigen-associated disease, our comprehension of the structural elements and mechanisms by which SEs induce SFP has remained limited, especially considering that SFP is a common disease that continues to affect millions worldwide. A key gap in our knowledge is whether the superantigenicity of the SEs plays a pathogenic role in SFP. There is evidence that suggests that the manifestation of SFP does not solely rely on the enterotoxic function of SEs. Furthermore, we highlighted that different immune and non-immune cell types are susceptible to immunomodulation by the SEs. Any possible interaction between the SEs and these cell types, especially in the gut environment, is worth exploring. Overall, the molecular details involved in SE-mediated enterotoxigenic disease are slowly being uncovered; however, many basic questions remain. Future challenges therefore will consist of deciphering the series of events that lead to disease and whether there are other key cellular players, and identifying an appropriate animal model that is amenable to genetic manipulation.

AUTHOR CONTRIBUTIONS

EF, GC, and MO: contributed to the drafting of the manuscript and approved the final version.

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