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Staphylococcal Food Poisoning: a current review

Lebensmittelintoxikationen durch S. aureus: eine aktuelle Literaturübersicht

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Summary

Staphylococcal Food Poisoning is one of the most prevalent causes of food-borne intoxication worldwide. It is typically self-limiting, presenting with violent vomiting following a short incubation period. Staphylococcal Food Poisoning is caused by ingestion of staphylococcal enterotoxins preformed in food. These toxins are able to cause massive T-cell proliferation and were classified as members of the pyrogenic exotoxin superantigen family. With the rise of genomic studies and the development of a wide range of new molecular techniques, research on Staphylococcal Food Poisoning is advancing quickly, revealing an immense variety of intriguing results. In this review, we focus on providing an overview of the vast field of current research on this intoxication.

Keywords: Staphylococcal enterotoxins, food poisoning, outbreak, regulatory mechanisms, superantigen

Zusammenfassung

Von Staphylokokken ausgelöste Lebensmittelintoxikationen gehören weltweit zu den häufigsten Ursachen für Lebensmittelvergiftungen. Sie verlaufen üblicherweise selbstlimitierend und rufen nach einer kurzen Inkubationszeit heftiges Erbrechen hervor. Eine Staphylokokken bedingte Lebensmittelintoxikation wird durch den Verzehr zuvor im Nahrungsmittel gebildeter Staphylokokken Enterotoxine verursacht. Diese Toxine sind in der Lage eine massive T-Zell-Proliferation auszulösen und wurden den pyrogenen Exotoxin-Superantigenen zugeordnet. Die Zunahme genomischer Studien und die Entwicklung eines breiten Spektrums neuer molekularer Techniken beflügelt die Forschung an Lebensmittelintoxikationen durch Staphylokokken und enthüllt eine immense Vielfalt faszinierender Ergebnisse. In der vorliegenden Übersichtsarbeit konzentrieren wir uns darauf einen Überblick über das weitläufige Gebiet der gegenwärtigen Forschung in diesem Bereich zu liefern.

Schlüsselwörter: Staphylokokken Enterotoxine, Lebensmittelvergiftung, Ausbruch, regulatorische Mechanismen, Superantigen

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Significance of Staphylococcal Food Poisoning

Staphylococcal Food Poisoning (SFP) is one of the most prevalent causes of food-borne intoxication worlwide. As clinical symptoms are often self-limiting, only 10 % of SFP patients are admitted to a hospital or consult a physician (Holmberg and Blake, 1984; Thomas et al., 2007). Therefore, individual cases of SFP are seldom reported and the organism is primarily isolated in large outbreaks. A list of recent publications describing SFP outbreaks is given in Table 1.

A study of the USDA Economic Research Service estimated *S. aureus* to be responsible for 1.2–1.5 million cases of food poisoning per year, causing annual costs of $1.2 billion (Buzby et al., 1996).

Clinical symptoms

Typically, SFP is a self-limiting disease, presenting with emesis following a short incubation period. Symptoms start 30 min to 6 h after ingestion of staphylococcal enterotoxins (SEs) and spontaneously subside after 24 h (Le Loir et al., 2003).

In a summary of clinical symptoms of 2,992 SFP patients the key symptom described was vomiting (82 %). Nausea was observed in 74 %, diarrhea in 68 %, and abdominal pain in 64 % of the cases. Diarrhea is typically watery, but may also contain blood, and is always accompanied by emesis. In rare cases SFP can result in fatal dehydration and electrolyte imbalances. Fatality rates range from 0.03 % for the general public to 4.4 % in children and the elderly (Doyle and Beuchat, 2007).

The emetic activity of SEs was investigated in the rhesus monkey by testing emetic responsiveness following destruction of specific neural structures and/or visceral deafferentation. Taken together, vagotomy and abdominal sympathectomy suppress the emetic response to ingestion of SE, even when lethal doses of SEB are administered. However, neither sympathectomy nor vagotomy alone is able to inhibit emesis. Vagotomy merely provided increased tolerance to SE. These results suggest the site of emetic activity to be located in the abdomen and the stimulus to be transmitted to the brain via these nerves (Thomas et al., 2007).

SE Nomenclature

SEs belong to the group of exotoxins and act in the gastrointestinal tract (Dinges et al., 2000). They possess superantigen character and can therefore unspecifically activate T-cells (Becker et al., 2007). Over the years, nomenclature was changed to adapt to the scientific state of the art.

In 1960, Casman suggested two immunologically distinct types of toxins – F (food poisoning) and E (enteritis). This system was discarded, because many strains could not be assigned to one category only (Casman, 1960; Lina et al., 2004).

In 1962, an alphabetical nomenclature system for SE was introduced. Enterotoxins previously designated F (food poisoning) and E (enteritis) equal the current denomination SEA and SEB with the prototype strains ATCC 13565 (previously “196E”) and ATCC 14458 (previously “243”) (Casman et al., 1963; Doyle and Beuchat, 2007).

During the following years, further superantigens were described and assigned alphabetically (SEC, SED etc.). Slightly modified, the system is still valid today. The International Nomenclature Committee for Staphylococcal Superantigens (INCSS) proposed guidelines for the description of enterotoxins. Before new superantigens or superantigen-like toxins can be described, the expression of the gene has to be verified and the protein must be characterized. Moreover, the INCSS proposed that any new staphylococcal enterotoxin must be verified for emetic activity by oral administration in a classic, non-human primate assay. Toxins that lack emetic properties in the monkey feeding assay or have not been tested yet, should be designated “staphylococcal enterotoxin-like superantigens” (SEl-SAg) (Lina et al., 2004; Larkin et al., 2009).

TABLE 1: *Recent outbreaks of SFP.*

Year	Country	Incriminated food	SE-type[1])	Number of patients	Reference
2009	France	Soft cheese from unpasteurized milk	SEE	23	Ostyn et al., 2010
2008	Switzerland	Raw goat milk	SED	3	Giezendanner et al., 2009
2008	Japan	Crêpes	SEA, SEC	74	Kitamoto et al., 2009
2007	Austria	Pasteurized milk products	SEA, SED	40	Schmid et al., 2009
2006	Austria	Boiled rice, chicken wings	not stated	113	Schmid et al., 2007
2005	India	Potato balls	SEB, SED	>100	Nema et al., 2007
2003	Norway	Mashed potato made with raw milk	SEH	8	Jørgensen et al., 2005
2000	Japan	Low fat milk	SEA	13 420	Asao et al., 2003
2000	Japan	Reconstituted milk	SEA, SEH	>1000	Ikeda et al., 2005
2000	Australia	Chicken	not stated	>18	Cowell et al., 2002
1999	Japan	Scrambled egg	SEA	21	Miwa et al., 2001
1998	Brazil	Various	SEA	ca. 180	Colombari et al., 2007
1998	Brazil	Chicken, roasted beef, rice, beans	SEA	ca. 4000	Do Carmo et al., 2004
1997	USA	Precooked ham	SEA	18	Ward et al., 1997
not stated	Netherlands	Noodle dish	SEA	ca. 100	de Jong et al., 2004

[1]) SE type = type of staphylococcal enterotoxin incriminated.

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The denomination of "SEF" for the Toxic Shock Syndrome Toxin-1 (TSST-1) was dropped when the toxin was confirmed to lack emetic activity. Therefore, SEF is missing in the current alphabetical list of toxins (Betley et al., 1990; Doyle and Beuchat, 2007).

The designation of SEs according to serological criteria is limited by the fact that the antigenic properties of the protein of some SEs do not match their molecular and biological uniqueness. Due to minor differences in immunological reactivity, serotype SEC can be subdivided into at least three subtypes (SEC1, SEC2, SEC3) that might differ significantly in sequence within each subtype (Doyle and Beuchat, 2007).

In 2006, Uchiyama described groupings of all staphylococcal superantigens including TSST-1 based on amino acid sequence. Groups are depicted in Table 2 (Larkin et al., 2009).

In the literature, "classical" or "major" SEs are often differentiated from newly described SEs and SEl-SAgs, discovered in recent genomic studies. While 94 % of SFP causing *S. aureus* strains produce one or more classical SEs, the significance of most newly described SEs in SFP is still unclear. In many outbreaks, more than one SE can be detected in the same patient, thus aggravating the search for the causative SE (Wieneke, 1974; Becker et al., 2007).

SE Structure & Stability

SE are water-soluable, short proteins (194–245 amino acids) and belong to the family of pyrogenic toxin superantigens (PTSAgs) that also includes the toxins responsible for the Staphylococcal Scalded Skin Syndrome (exfoliative toxin A and B), as well as the Toxic Shock Syndrome toxin TSST-1 (Thomas et al., 2007). They share common phylogenetic relationships, structure, function, and sequence homology (Balaban and Rasooly, 2000).

Despite the sequence diversity of SEs, X-ray cristallographic analyses revealed remarkably similar three-dimensional topologies. Their similar structure is also evident by cross-reactivity between SEA and SEE, as well as SEB and SEC (Jay et al., 2005; Larkin et al., 2009).

SEs, as well as TSST-1, exhibit a common two-domain structure consisting of an amino-terminal and a larger carboxy-terminal domain (Doyle and Beuchat, 2007). The two domains are separated by a short, shallow cavity at the top of the molecule and by a large groove extending all the way along the back of the molecules (Thomas et al., 2007).

The amino-terminal domain contains residues near the N terminus, but not the N-terminal residues themselves, and shows an oligonulceotide-oligosaccharide-binding fold. This conformation consists of a β-barrel capped at one end by an α-helix and might play a significant role in the function of the toxin (Doyle and Beuchat, 2007). This is also indicated by the fact that the oligonucleotide-oligosaccharide-binding fold family includes the B subunits of the AB5 heat-labile enterotoxins, cholera toxin, pertussis toxin, and Verotoxin (Mitchell et al., 2000).

TABLE 2: *Amino acid sequence classification of SE and TSST-1 into five homology groups according to Uchiyama (Larkin et al., 2009).*

Groups	Superantigens
Group 1	SEA, SED, SEE, SElJ, SElN, SElO, SElP
Group 2	SEB, SEC, SEG, SElR, SElU
Group 3	SEI, SElK, SElL, SElM, SElQ
Group 4	TSST-1
Group 5	SEH

The carboxy-terminal domain is a five-strand antiparallel β-sheet wall overlaid with a group of α-helices forming a β-grasp motive, similar to the immunoglobulin-binding motifs of streptococcal proteins G and L, ubiquitin, and 2F2-2S ferredoxin as well as the Ras-binding domains of the Ser/Thr-specific protein kinase Raf-1 (Doyle and Beuchat, 2007). Structural similarities among SEs and other bacterial proteins suggest the evolution of SEs through the recombination of two smaller β-strand motives (Mitchell et al., 2000; Thomas et al., 2007).

The top of the amino-terminal domain contains a cysteine loop, a conserved stucture among all SE, and a disulfide linkage, that is missing in the either weak or nonemetic SEI and SElL. Emetic activity seems to require preservation of the structure in the area of the conserved disulfide loop (Doyle and Beuchat, 2007). While the disulfide linkage itself does not seem to be necessary for enterotoxigenicity, it might stabilize a conformation within or adjacent to the disulfide loop (Thomas et al., 2007).

Protease-generated fragments of SEA, SEB, or SEC1 were analyzed to define molecular regions of SEs responsible for enterotoxigenicity. The results indicated that only large fragments containing central and C-terminal portions of the SE are able to cause emesis. Moreover, N-terminal residues of the SEs are not required for emetic activity. SEC1 modified by removal of the 59 N-terminal residues retained emetic ability, while smaller fragments of SEC1 and other SEs were inactive (Doyle and Beuchat, 2007).

SEs are exotoxins secreted in the medium and display high tenacity in the face of stressors that reliably inactivate the organism. This is of particular interest, as loss of serological recognition does not assure loss of emetic activity. SE are highly stable and can keep their emetic activity in the gastrointestinal tract as they resist most proteolytic enzymes, including pepsin and trypsin (Le Loir et al., 2003).

SE Superantigen Character

SE act as superantigens, causing massive T-cell proliferation. Although superantigen and emetic activity of SEs are two separate features localized on separate domains of the protein, a strong correlation of these activities was shown. In most cases, genetic mutation leading to loss of T-cell stimulatory activity also leads to loss of enterotoxigenic activity (Harris et al., 1993).

Superantigens react with the MHCII (major histocompatibility complex class II) of antigen presenting cells and the T-cell receptor (TCR) of lymphocytes. The interactions are relatively nonspecific and occur outside the conventional antigen binding sites. Therefore, superantigens are not processed and activate a much higher percentage of the T-cell population than conventional antigens (Doyle and Beuchat, 2007; Larkin et al., 2009).

SE bind to conserved elements on MHC II with an affinity of 10^{-8} to 10^{-6} M, depending upon MHC isotype and use of either whole cells of purified receptor. Generally, interactions of SEs are better with human, instead of mouse, MHCII. Human leukocyte antigen (HLA)-DR acts as a superior receptor than HLA-DP or HLA-DQ and

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murine IE binds SE better than IA (Larkin et al., 2009).

Most SE interact with the TCR V-beta (beta chain variable region) element, except for SEH, binding to the V-alpha region of the receptor.

As HLA and human TCR specificity has been extensively reviewed before, readers are referred to three recent publications (Doyle and Beuchat, 2007; Thomas et al., 2007; Larkin et al., 2009).

Encoding Regions

The coding regions for SEs and SEl-Ags can be located on the chromosome, on plasmids, or on pathogenicity islands. The *sea* gene is located on a mobile genetic element, carried by a lysogenic phage. The *seb* and *sec* genes are located on *S. aureus* pathogenicity islands (SaPI), exhibiting phage-like features (Novick, 2003). The *sed* gene is localized on pIB485, a 27.6 kb plasmid (Balaban and Rasooly, 2000).

While many SEs and SEl-Ags are encoded by genes located on mobile genetic elements, SEG and SEI, as well as SElM, SElN, and SElO are encoded by the *egc* (enterotoxin gene cluster) operon (Jarraud et al., 2001; Novick, 2003; Becker et al., 2007).

Studies with prevalence data for SE genes in isolates from different matrices

S. aureus isolated from various matrices differ in distribution of SE genes. The studies listed in Table 3 vary widely in terms of approach, preselection of samples and enterotoxin genes screened for. We therefore refer directly to the cited publications in order to abstain from misleading simplifications.

Classical SEs

The classical SEs are responsible for almost all clinical cases of SFP and 94 % of outbreak strains were reported to possess at least one of the classical SEs (Becker et al., 2007).

TABLE 3: *References to prevalence and distribution of enterotoxin genes in S. aureus isolated from various matrices.*

Source	Country	Reference
SFP outbreaks	Taiwan	Chiang et al., 2008
	France	Kérouanton et al., 2007
Nasal swab	Germany	Becker et al., 2003
	Spain	Fueyo et al., 2005
	Poland	Bania et al., 2006
Porcine carcasses	Switzerland	Nitzsche et al., 2007
Hare carcasses	Switzerland	Kohler et al., 2008
Bovine mastitis milk	USA	Srinivasan et al., 2006
	Hungary	Peles et al., 2007
	Germany	Zschöck et al., 2005
	Japan	Katsuda et al., 2005
	Switzerland	Stephan et al., 2001
Foodstuffs	Czech Republic	Růzicková et al., 2008
	Poland	Bania et al., 2006
Milk and milk products	Switzerland	Scherrer et al., 2004
	Italy	Morandi et al., 2007
	Brazil	Rall et al., 2008

SEA

SEA is the most common SE recovered from food-poisoning outbreaks in the US (77.8 % of all outbreaks). Its high emetic power was shown in an outbreak of SFP due to contaminated chocolate milk in the U.S., in which a total dose of only 200 ng SEA was sufficient to cause gastroenteritis. SEA shares high sequence homology with SEE (81 %) and SED, indicating that these enterotoxins are closely related (Balaban and Rasooly, 2000).

Studies indicate the lyosgenic phage carrying *sea* to have integrated into the bacterial chromosome by circularization and reciprocal crossover. The expression of *sea* starts in the mid-exponential phase of growth. However, unlike *seb, sec,* and *sed,* expression of *sea* is not controlled by the accessory gene regulator *agr* (Balaban and Rasooly, 2000).

Among the known staphylococcal superantigens, SEA binds with the highest affinity to HLA-DR and contains two binding sites. The higher affinity site on SEA is located within the C-terminus and enables Zn^{2+}-dependent binding of three SEA residues (His187, His226, Asp227) to His81 of HLA-DRβ. The Zn^{2+}-dependent binding motif allows for very efficient binding to MHCII and is also present in SED and SEE. The lower affinity site within the N-terminus (Phe47) interacts with Gln18 of HLA-DRα. Thus, SEA binds as a dimer to HLA-DR, crosslinking two MHCII molecules necessary for cytokine expression (Larkin et al., 2009).

SEB

SEB causes approximately 10 % of SFP outbreaks (Balaban and Rasooly, 2000). The production of SEB and TSST-1 in the same strain is mutually exclusive, as the pathogenicity islands SaPI3 and SaPI1, encoding *seb* and *tst,* share a common insertion site (Novick, 2003). While *seb* was shown to be located in the chromosome in clinical cases of SFP, the gene is carried by a 750 kb plasmid in some strains (Balaban and Rasooly, 2000).

TSST-1 and SEB share the same contact residues on the α-chain of MHCII. However, the complexes the toxins form with HLA-DR1 show crystal structures that indicate different binding mechanisms. SEB interacts exclusively with the α-chain of MHCII, whereas TSST-1 can bind to the α- and β-chain of MHCII, as well as the C-terminus of certain bound peptides (Larkin et al., 2009).

TSST-1 and SEB do not only function as superantigens, but represent transcription factors as well. They are autorepressors and act as global repressors of most exoprotein genes at the level of transcription (Novick, 2003).

In comparison with other SEs, SEB exhibits relatively high sensitivity to pepsin under conditions of acidic stress. However, SEB remains biologically active in the stomach, as pH-values rise due to mixing of food and gastric acid following food intake (Le Loir et al., 2003).

SEC

The three antigenetically distinct SEC subtypes SEC1, SEC2, and SEC3 share 91–99 % sequence identity and exhibit strong cross-reactions, while differing in toxicity (Lina et al., 2004). Moreover, unique host-specific SEC were found in *S. aureus* isolated from different animal species. This finding indicates toxin heterogeneity due to selection for modified SEC sequences that facilitate sur-

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vival in the respective host (Balaban and Rasooly, 2000).

SE are able to bind a wide variety of molecules, while exhibiting toxin-dependent preferences. Remarkably, SEC is the only classical SE preferably binding HLA-DQ, instead of HLA-DR (Thomas et al., 2007).

SED

The gene encoding SED is localized on pIB485, a 27.6 kb plasmid. Isolated in 37.5 % of outbreaks, SED is a very common cause for SFP, second only to SEA. Similar to SEA, SED is dependent on Zn^{2+} for high affinity binding to HLA-DR. SED exhibits the unique ability to form homodimers in the presence of Zn^{2+}, facilitating multimer interactions with MHCII (Balaban and Rasooly, 2000).

SEE

SEE shares 81 % sequence homology with SEA (Balaban and Rasooly, 2000). Moreover, both SEE and SEA preferably bind HLA-DR (Thomas et al., 2007).

Newly described SEs

For a long time, the classical SEs, comprised of SEA to SEE, used to be the only known enterotoxins in *S. aureus.* With the rise of genomic studies in recent years, various "new" SEs and SEl-SAgs were described. Their occurrence and role in disease is still unclear, because the emetic activity of many of these newly described superantigens has not been assessed in the monkey model. Moreover, classical and newly described superantigens are often detected in the same strain, thus exacerbating interpretation of their role in disease (Pereira et al., 1996; Ikeda et al., 2005).

To date, an emetic response in the primate feeding model was reported for SEG, SEH, and SEI (Su and Wong, 1995; Munson et al., 1998). However, SEI only caused emesis in one of four tested rhesus monkeys, while eliciting diarrhea and prostration in the remaining animals. The impaired emetic potency of SEI may be due to primary structural differences: the enterotoxin lacks a disulfide loop and contains an insertion of eight amino acids near the C terminus (Munson et al., 1998).

SelP was reported to elicit an emetic response after intraperitoneal application of relatively high doses (50–150 µg/animal) to the house musk shrew (Hu et al., 2003).

SElQ and SElL were shown to lack emetic activity in a monkey feeding assay (Orwin et al., 2002; Orwin et al., 2003).

The involvement of newly discovered SEs and SEl-Ags in SFP outbreaks, in which classical SEs could not be detected, is controversially discussed. Some *S. aureus* strains recovered from presumptive cases of SFP were shown to possess genes encoding newly described SEs and SEl-Ags, while classical SEs could not be identified (McLauchlin et al., 2000; Omoe et al., 2005). Especially SEH was associated with a number of outbreaks of SFP (McLauchlin et al., 2000; Jørgensen et al., 2005; Becker et al., 2007).

However, in most cases, causative relations of clinical cases of SFP and newly described SEs or SEl-SAgs remain to be established. First, emetic activity of SEl-SAgs was not shown in a monkey feeding assay, thus impeding assessment. Second, the presence of genes encoding SEs and SEl-SAgs does not necessarily imply subsequent transcription and translation, as shown for *seg* and *sei* (McLauchlin et al., 2000; Omoe et al., 2002; Omoe et al., 2005). Third, methods chosen to test for SEs must be critically assessed. Some studies did not test for all classical SEs (Omoe et al., 2005). Moreover, the results of the screening for classical SEs may have been false negative. SEA and SED were shown to have lost serological activity after heat treatment, and therefore serological recognition in the test kit, while still being emetically active in the kitten *in vivo* assay (Le Loir et al., 2003).

SE Regulation

As a complex network of interacting regulators influences expression of the genes coding for SEs, there are no universally valid rules in *S. aureus* enterotoxin regulation.

SEA, the most common enterotoxin causing SFP is being expressed constitutively. So far, there is no data on regulatory mechanisms controlling SEA production (Thomas et al., 2007). The remaining classical enterotoxins SEB-SEE differ in expression regarding mechanism of gene regulation and temporal regulation. While SEA is produced throughout log phase of growth, the maximum concentration of SEB, SEC, and SED is produced during the transition from exponential to stationary phase of growth, indicating regulation by *agr* Moreover, the classical SEs differ in toxin yield, with SEB and SEC being expressed in more than ten times greater quantities than SEA, SED, and SEE (Derzelle et al., 2009).

One major problem in the evaluation of studies investigating regulatory mechanisms derives from the fact that most studies were executed *in vitro* using the same strain – NCTC8325. This strain and its derivates exhibit a 11-base deletion in *rsbU,* which encodes a phosphatase activating σ^B. The decisive role of σ^B in regulation of the *S. aureus* virulon is well established and will be described in more detail below (see sigma factor SigB). Moreover, there are important differences in regulatory mechanisms among *S. aureus* strains (Novick, 2003).

agr

The quorum sensing dependent *agr* (accessory gene regulator) system, is involved in the response of *S. aureus* to environmental stimuli. It is a two-component regulatory system, which responds to an autoinducer peptide (Tseng et al., 2004). Expression of this global regulator coincides temporarily with maximum expression of most SE, excluding SEA and SED, which are expressed earlier (Doyle and Beuchat, 2007).

In general, the activation of *agr* was shown to inhibit expression of genes encoding certain cell-wall associated proteins and increasing expression of genes encoding exoproteins during the post-exponential phase of growth (Bronner et al., 2004; Tseng and Stewart, 2005).

The *agr* system regulates *seb, sec,* and *sed* on the level of transcription. In mRNA mutants, steady-state levels were reduced 4-fold for *seb,* 5.5-fold for *sed,* and 2 to 3-fold for *sec* (Zhang and Stewart, 2000). Reductions in enterotoxin protein synthesis were even more pronounced, showing 16 to 32-fold reductions in SEC and 5-fold reductions in SED, as evidenced by Western blot analysis (Tseng et al., 2004).

Transcription can be initiated by three promoters (P1, P2, P3). P1 transcribes *agr.* The P2 transcriptional unit RNAII encodes the proteins AgrA, AgrB, AgrC and AgrD. These proteins form a quorum sensing system and

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are required for the transcription of P2 and the activation of P3 (Bronner et al., 2004; Doyle and Beuchat, 2007). The partially translated P3 transcript, RNAIII, is the effector of the *agr* locus (Bronner et al., 2004).

The mechanism of action of the *agr* locus is depicted in Figure 1. The auto-inducing peptide AIP represents the activating molecule for the *agr* system. The AgrD-encoded propeptide, derived from AgrD-residues 46–53, was suggested to be processed and secreted by AgrB (Novick, 2003). AIP binds to an extracellular loop of the transmembrane-histidin-kinase AgrC, a membrane bound receptor recognizing increased levels of AIP in the environment. The following autophosphorylation was proposed to allow phosphorylation of the response regulator AgrA. In combination with SarA this leads to activation of the *agr* promoters P2 and P3 and the expression of RNAII and RNAIII (Novick, 2003; Cheung et al., 2004; Doyle and Beuchat, 2007).

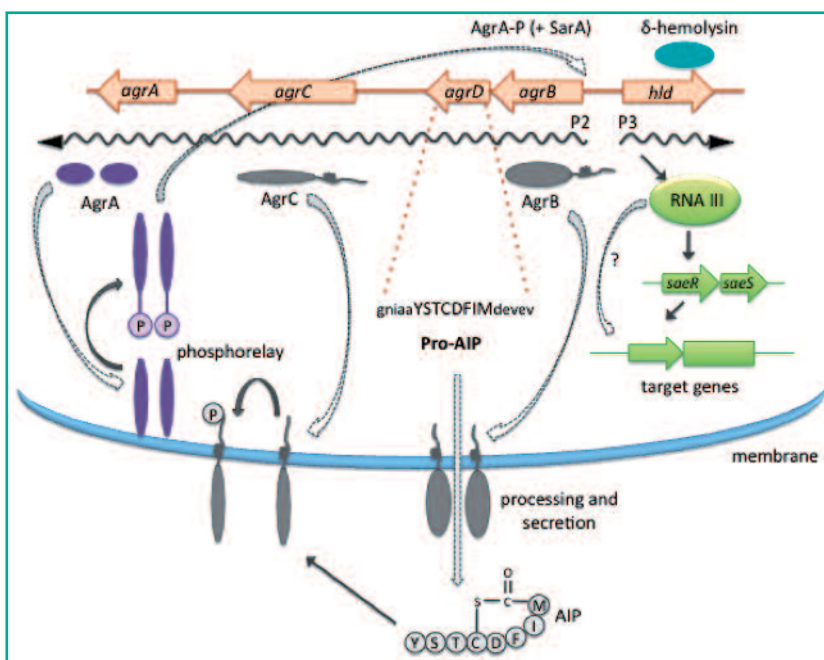

FIGURE 1: *The agr locus in S. aureus modified after Doyle and Novick (Novick, 2003; Doyle and Beuchat, 2007). The auto-inducing peptide AIP represents the activating molecule for the agr system. The AgrD-encoded propeptide, derived from AgrD-residues 46-53, was suggested to be processed and secreted by AgrB. AIP binds to AgrC, a membrane bound receptor recognizing increased levels of AIP in the environment. The following autophosphorylation allows phosphorylation of the response regulator AgrA. In combination with SarA this leads to activation of the agr promoters P2 and P3 and the expression of RNAII and RNAIII.*

sae

The *sae* (*S. aureus* exoprotein expression) locus is a two-component regulatory system constituted by the two co-transcribed genes *saeR* and *saeS* (Bronner et al., 2004). While it is a positive effector of cell-free α- and β-hemolysins, coagulase, nuclease and protein A, it does not affect SEA (Doyle and Beuchat, 2007).

The SarA protein family

The SarA protein family includes the SarA homologs SarA, SarR, SarS, SarT, SarU and SarV, as well as MgrA (also called Rat) and Rot (Cheung et al., 2004).

The **sarA** (staphylococcal accessory regulator A) locus binds several promoters, including *agr, hla, spa* and *fnbA*. It interacts with an intergenic region between *agr* promoters P2 and P3, which upregulates expression of RNAIII, thus influencing the expression of *agr* regulated genes. Moreover, transcriptional gene fusion has shown that *sarA* upregulates *tst* and *seb* (Tseng et al., 2004; Doyle and Beuchat, 2007).

Rot (repressor of toxins) belongs to the family of SarA transcription factors. Recent studies revealed the term "repressor" to be misleading, as Rot does not only repress transcription of various exotoxins, but also acts as positive regulator of 86 genes and upregulates the expression of *seb* (Bronner et al., 2004; Doyle and Beuchat, 2007). Moreover the postexponential increase in *sed* transcription was proposed to result from Agr-mediated reduction in Rot activity (Tseng et al., 2004).

Sigma factor (SigB)

Alternative sigma factors play an important role in the response to environmental stimuli. *S. aureus* possesses only one alternative sigma factor – sigB σ^B, which can be activated by environmental stress and energy depletion (Novick, 2003). SEB expression is negatively regulated by σ^B in an *agr*-independent mechanism. Therefore, induction of σ^B by environmental stress leads to decreased expression of *seb* (Doyle and Beuchat, 2007).

For a more detailed review on regulation of enterotoxins and virulence determinants in *S. aureus* in general, readers are referred to three recently published reviews (Novick, 2003; Bronner et al., 2004; Cheung et al., 2004).

Use of mRNA based techniques in assessment of SE expression and poisoning risk

Reverse transcription real-time PCR is a valuable tool in monitoring gene expression under various growth conditions. It allows for rapid assessment of SE and SEl-SAg transcript levels in *S. aureus* strains.

Derzelle et al. showed that temporal expression profiles of the SE and SEl-SAg encoding genes follow four distinct patterns during cell growth under optimal conditions, thus providing hints on possible regulatory mechanisms. No change in transcript levels for *sea, see, selj, selk, selq,* and *selp* was detected. Only a small decrease in mRNA abundance was shown for *seg, sei, selm, seln, selo,* and *selu,* whereas a massive increase in expression at the end of the exponential growth phase was observed in *seb, sec,* and *seh.* A slight post-exponential induction of expression was noted for *sed, selr, sell* (Derzelle et al., 2009).

Lee at al. determined the expression levels of enterotoxin genes in *S. aureus* strains isolated from food and clinical samples using reverse transcription real-time PCR. Various levels of enterotoxin expression were found, dependent on the species and the enterotoxin (Lee et al., 2007).

If mRNA content is correlated with the amount of SE and SEl-SAg produced, assessment of the expression levels

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of enterotoxin genes could be used to evaluate poisoning risk of individual strains (Lee et al., 2007; Derzelle et al., 2009).

Detection of *S. aureus* and SEs

Screening for coagulase-positive staphylococci in food and animal feeding stuffs is performed by using the ISO 6888 reference protocol.

Various publications describe techniques used to detect *S. aureus* enterotoxins in food. For information on detection of *S. aureus* enterotoxins in food, readers are referred to the various publications and reviews focusing on SE detection techniques (Bennett, 2005; Becker et al., 2007; Derzelle et al., 2009).

Food safety & process hygiene criteria

Food and process hygiene criteria for the European Economic Area were determined in commission regulation (EC) No 2073/2005 of 15 November 2005 on microbiological criteria for foodstuffs.

"Food safety criterion" means a criterion defining the acceptability of a product or a batch of foodstuff applicable to products placed on the market.

"Process hygiene criterion" means a criterion indicating the acceptable functioning of the production process. Such a criterion is not applicable to products placed on the market. It sets an indicative contamination value above which corrective actions are required in order to maintain the hygiene of the process in compliance with food law.

Food safety criterion referring to SE

The food safety criterion, determining the limit for SE in cheeses, milk powder, and whey powder products placed on the market during their shelf life, is described in Table 4 (2073/2005, Annex I 1.21).

TABLE 4: *Food safety criterion referring to SE in cheeses, milk powder and whey powder.*

Sampling plan n	Sampling plan c	Limits	Analytical reference method
5	0	not detected in 25 g	European screening method of the Community Reference Laboratory for Milk

n = number of units comprising the sample; c = number of sample units giving values over limit

Process hygiene criteria referring to coagulase-positive staphylococci

The process hygiene criteria described in Table 5 are valid for coagulase-positive staphylococci in milk and milk products, as well as fishery products of the following food categories (2071/2005, Annex I 2.2./2.4.):

2.2.3.: Cheeses made from raw milk

2.2.4.: Cheeses made from milk that has undergone a lower heat treatment than pasteurisation[1]) and ripened cheeses made from milk or whey that has undergone pasteurisation or a stronger heat treatment[1])

TABLE 5: *Process hygiene criteria.*

Food category	Sampling plan n	Sampling plan c	Limits (CfU/g) m	Limits (CfU/g) M	Stage, where the criterion applies
2.2.3.	5	2	10^4	10^5	At the time during the manufacturing process when the number of staphylococci is expected to be highest
2.2.4.	5	2	100	1000	
2.2.5.	5	2	10	100	End of the manufacturing process
2.2.7.	5	2	10	100	
2.4.1.	5	2	100	1000	

n = number of units comprising the sample; c = number of sample units giving values between m and M

2.2.5.: Unripened soft cheeses (fresh cheeses) made from milk or whey that has undergone pasteurisation or a stronger heat treatment[1])

2.2.7.: Milk powder and whey powder, except for products intended for further processing in the food industry

2.4.1.: Shelled and shucked products of cooked crustaceans and molluscan shellfish

The analytical reference method used for cheeses from raw milk (2.2.3.) is the EN/ISO 6888-2 protocol, whereas the remaining food categories (2.2.4., 2.2.5., 2.2.7. and 2.4.1.) are analyzed using EN/ISO 6888-1 or -2.

In case of unsatisfactory results, an improvement in production hygiene is necessary. Moreover, an improvement in the selection of raw materials is required for foodstuffs of food categories 2.2.3. and 2.2.4. If values $>10^5$ CfU/g are detected in foodstuff of food categories 2.2.3–2.2.5. und 2.2.7., the batch has to be tested for staphylococcal enterotoxins.

[1]) Excluding cheeses where the manufacturer can demonstrate, to the satisfaction of the competent authorities, that the product does not pose a risk of staphylococcal enterotoxins.

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