MiniReview

Understanding the mechanism of action of the exfoliative toxins of

*Staphylococcus aureus*

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Abstract

The exfoliative toxins of *Staphylococcus aureus* are responsible for the staphylococcal scalded skin syndrome, a blistering skin disorder that particularly affects infants and young children, as well as adults with underlying disease. Their three-dimensional structure is similar to other glutamate-specific trypsin-like serine proteases with two substrate-binding domains and a serine-histidine-aspartate catalytic triad that forms the active site. However, unlike other serine proteases, the exfoliative toxins possess a highly charged N-terminal α-helix and a unique orientation of a critical peptide bond, which blocks the active site of the toxins so that, in their native state, they do not possess any significant enzymatic activity. The target for the toxins has recently been identified as desmoglein-1, a desmosomal glycoprotein which plays an important role in maintaining cell-to-cell adhesion in the superficial epidermis. It is speculated that binding of the N-terminal α-helix to desmoglein-1 results in a conformation change that opens the active site of the toxin to cleave the extracellular domain of desmoglein-1 between the third and fourth domains, resulting in disruption of intercellular adhesion and formation of superficial blisters. Elucidating the mechanism of action of the toxins and identifying desmoglein-1 as their specific epidermal substrate has not only given us an insight into the pathogenesis of the staphylococcal scalded skin syndrome, but also provided us with useful information on normal skin physiology and the pathogenesis of other toxin-mediated diseases. It is hoped that this knowledge will lead to development of rapid screening and diagnostic tests, and new antitoxin strategies for the treatment and prevention of the staphylococcal scalded skin syndrome in the near future.

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Keywords: Staphylococcal scalded skin syndrome; *Staphylococcus aureus*; Exfoliative toxin; Desmoglein; Serine protease

1. Introduction

This year marks the 125th anniversary since the first description of staphylococcal scalded skin syndrome (SSSS) by a German physician who observed the condition in young children in a Czechoslovakian foundling asylum in 1878 [1]. It took almost a hundred more years to discover the toxins responsible [2] and their epidermal target was only identified three years ago [3]. The exfoliative toxins are responsible for a spectrum of disease ranging from localised blisters to extensive exfoliation, which has previously been called dermatitis exfoliativa, pemphigus neonatorum, Lyell’s disease and Ritter’s disease [4,5]. SSSS is rarely fatal in children but carries a mortality of over 50% in adults who usually have serious underlying medical problems [6]. Treatment for SSSS remains supportive care and antistaphylococcal antibiotics despite the condition being toxin-mediated [7]. However, recent developments in our understanding of the structure and action of the exfoliative toxins and the identification of their specific epidermal substrate have opened exciting prospects for further research, ranging from development of antitoxin peptides that prevent exfoliation to specific targeting of therapeutic molecules to the epidermis. The aim of this article is to review the recent developments in our understanding of the mechanism of action of the exfoliative toxins and the pathogenesis of SSSS, and to identify potential areas for future research.

2. The disease

The exfoliative toxins of *Staphylococcus aureus* are responsible for the skin lesions of SSSS [8]. It is not clear
how this process benefits the organism, but it has been suggested that damaging the protective epidermis allows the organism to propagate and invade deeper tissues [3]. The severity of the skin lesions varies from a few localised blisters to generalised exfoliation affecting the entire body surface area and depends on the presence or absence of protective antitoxin antibodies [4]. In the localised form, also known as bullous impetigo, *S. aureus* enters a break in the skin barrier and produces the toxin locally to produce blisters filled with clear to purulent fluid [9], but haematogenous spread is limited by the presence of antitoxin antibodies [10]. Streptococci can cause similar lesions, but it has been suggested that the two can be distinguished clinically because the latter begin with small vesicles that evolve into characteristic irregular, honey-coloured golden crusted plaques, while localised SSSS lesions form fragile blisters that burst to leave a tender erythematous base that dries to a thin shiny surface [11]. However, in practice, this is not always possible, and the two organisms often co-exist in the lesions. In neonates, the lesions are often found around the umbilicus or the perineum, whilst in older children, they are more common on the extremities [11]. In the generalised form, *S. aureus* usually resides at a distal colonised site (e.g. nose, umbilicus, axilla, or perineum), or an infective site (e.g. wound, abscess, conjunctivitis, pyomyositis, pneumonia, or osteomyelitis), but often a focus is not found [4,6]. The toxins are released into the bloodstream and lack of protective antitoxin antibodies allows the toxins to reach the epidermis where they act locally to produce the characteristic skin lesions [10]. The condition typically begins with fever and tender erythema, which progresses to the formation of large, fragile-roofed superficial blisters which rupture on slightest pressure to leave extended areas of denuded skin (Fig. 1) [12]. Neonates and young infants are particularly susceptible to lack of the protective skin barrier, which may cause excessive protein and fluid losses, hypothermia and secondary infection [4,13,14]. In general, however, the infection usually resolves with appropriate treatment and mortality remains below 5% [6,11,13]. In contrast, adults who develop generalised SSSS invariably have an underlying medical problem, particularly immunodeficiency or renal failure, and *S. aureus* bacteraemia is common, with a mortality of over 50% despite antibiotic treatment [6].

The diagnosis of SSSS currently relies mainly on recognition of the characteristic appearance of the rash with fever [7]. Isolating *S. aureus* from the skin lesion does not support the diagnosis of SSSS [15]. We have recently shown that, of 54 isolates of *S. aureus* from skin lesions of children aged 1 week to 7 years who presented with fever and the characteristic superficial exfoliation of SSSS affecting at least 10% of the body surface area with a positive Nikolsky sign (gentle rubbing of uninvolved or healed skin results in dislodgement of the superficial epidermis [16]), only 17 (31%) were shown by polymerase chain reaction and Western blot analysis to produce exfoliative toxin [15]. In the remaining 37 isolates (69%), there was no evidence of exfoliative toxin production. *S. aureus* is a common skin commensal and it is not uncommon for a person to harbour more than one strain of *S. aureus*. It is, therefore, possible that the isolated strain was not responsible for toxin production or the initial clinical diagnosis was incorrect [15]. This finding is important because current diagnostic tests for SSSS, which include polymerase chain reaction, enzyme-linked immunosorbent assays, Ouchterlony immunodiffusion, radioimmunoassays and reverse passive latex agglutination, as well as the gold standard...
newborn mouse model, all require isolation of the organism from the patient [15]. The most useful investigation, therefore, remains a biopsy of the skin lesion showing midepidermal cleavage with minimal inflammation [7], which will differentiate SSSS from a wide range of differential diagnoses (Table 1).

Management of SSSS is currently based mainly on personal experience and anecdotal reports, due to a lack of objective clinical trials. We have attempted to develop an algorithm for out-patient management of children presenting with fever and an exfoliating rash, but this has not been validated in clinical practice [7]. Children with localised SSSS can be treated with oral antibiotics which should cover both S. aureus and streptococci [11,17]. Topical antibiotics may also be useful in localised lesions because the organisms are often present in significant numbers and produce the toxins locally [5,7]. Children with generalised SSSS, particularly neonates, need careful monitoring for dehydration, hypothermia, pain and evidence of secondary skin infection, particularly due to Pseudomonas species, which can be fatal [13,14]. Treatment involves appropriate intravenous antibiotics against penicillin-resistant staphylococci such as methicillin, nafcillin, dicloxacillin and flucloxacillin, adequate analgesia, and intravenous fluids if oral intake is reduced because of extensive perioral lesions, for example. It should be noted that there have been several cases of SSSS due to methicillin-resistant S. aureus, and this possibility must be considered if the patient is not improving after 48 h of antibiotic treatment [18]. Steroids are contraindicated on the basis of both experimental [19] and clinical [20] evidence. In severe cases with extensive exfoliation, broad-spectrum antibiotic cover for secondary infections and liaison with the local burns unit may be advisable [7]. There is some evidence that subinhibitory concentrations of clindamycin, a protein synthesis inhibitor, can significantly decrease production of exotoxins such as toxic shock syndrome toxin-1 and other superantigens by S. aureus and Streptococcus pyogenes and may be useful for the treatment of toxic shock syndrome [21–23]. Further studies are required to determine whether such a treatment strategy might also be useful for the treatment of SSSS. It should be noted, however, that the combination of flucloxacillin and gentamicin is not only highly bactericidal against S. aureus but can also inhibit exotoxin production by more than 95% [23].

### Table 1

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<th>Differential diagnoses for generalised SSSS</th>
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<td>Bullous lichen planus</td>
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<td>Subcorneal pustular pustulosis</td>
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### 3. Risk factors

Infants and young children are more likely to develop generalised SSSS compared to adults [4]. Initial studies that led to the eventual identification of the exfoliative toxins showed that mice less than 5 days old developed exfoliation after inoculation with a toxigenic S. aureus strain, while those over 7 days old did not, suggesting a specific maturation process that protects adults from developing generalised SSSS [2]. Speculated reasons for the higher incidence of SSSS in children include high prevalence of commensal staphylococcal carriage in children, an immature immune system and poor renal clearance of the toxin [8]. Nasal carriage of S. aureus occurs in around a third of the general population [24,25], but varies according to age, ethnic origin and certain dermatological conditions, including atopic dermatitis and psoriasis [4]. In neonates, staphylococcal colonisation also occurs on the skin, perineum, wound sites, umbilicus, perineum and circumcision wounds, with up to 60–90% of newborn babies discharged from hospitals being commensal carriers of S. aureus [4]. Around 5% of all S. aureus strains produce exfoliative toxin, but only a small proportion of carriers develop SSSS, suggesting that other factors are important for developing the condition [8].

Another hypothesis is that older children and adults might be protected from the generalised form of SSSS because of maturation of the immune system, which is immunologically immature in neonatal mice and humans [26]. One study showed that inoculation of small doses of toxigenic S. aureus resulted in exfoliation only in neonatal mice that had not previously been immunised with purified exfoliative toxin extracts [10]. The same study also found that more than 50% of children over the age of 10 years had antibodies that recognised exfoliative toxin, which are thought to protect them against generalised exfoliation [10]. Furthermore, adult cases of SSSS have often been described among immunocompromised patients and those receiving immunosuppressive medication [6]. However, Plano and colleagues recently showed that adult mice that had been thymectomised within 24 h of birth (and, therefore, lacked mature T cells) and adult mice with severe combined immunodeficiency (SCID) lacking both mature T and B cells (and, therefore, not able to produce protective antibodies) were not susceptible to exfoliation.
(defined as a positive Nikolsky sign and/or blister formation at 16 h after subcutaneous toxin injection) [27]. These findings were further supported by observations that intravenous injection of adult spleen cells into neonatal mice did not protect against exfoliation when exposed to exfoliative toxin and suggest that the adaptive immune response, which develops after the first week of life in mice, does not play a significant role in protecting adults from exfoliation [27].

While the role of the host immune system in SSSS requires further elucidation, it is clear that renal function plays a critical role in determining susceptibility to the generalised form of the disease, since more than 75% of adults who develop generalised SSSS have impaired renal function [6]. Murine studies have shown that newborn mice excrete only one-fifteenth of a test dose of intravenous exfoliative toxin within 3 h compared to a third of the test dose by adult mice [28]. In addition, nephrectomised, but not hepatectomised, adult mice will develop exfoliation when challenged with exfoliative toxin [28]. More recently, Plano’s group showed that serum toxin levels raised, but not hepatectomised, adult mice will develop exfoliation when challenged with exfoliative toxin [28]. In addition, nephrectomised, but not hepatectomised, adult mice will develop exfoliation when challenged with exfoliative toxin [28].

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4. The toxins as enzymes

The association between SSSS and *S. aureus* was suspected soon after the condition was described over a hundred years ago [29] but it was not until 1970 that Melish and Glasgow were able to show that an exoprotein of *S. aureus* was responsible for the exfoliation in newborn mice [2]. This exotoxin was soon isolated, sequenced, characterised and cloned into other bacteria such as *Escherichia coli* [30–36]. *S. aureus* produces at least four antigenically distinct toxin serotypes of which two, exfoliative toxins A (ETA) and B (ETB), are responsible for most human cases of SSSS [4]. Epidemiological studies have shown that ETA is the predominant serotype in Europe and the USA, while ETB is more prevalent in Japan [4]. ETA consists of 242 amino acids, has a molecular mass of 26950 Da, is heat-stable and the gene is located in chromosomes, while ETB consists of 246 amino acids, has a molecular mass of 27274 Da, is heat-labile and the gene is plasmid-located [13]. *S. aureus* also produces exfoliative toxin C (ETC), a 27-kDa heat-labile toxin that was isolated from a horse with skin infection and shown to produce intraepidermal splitting in both newborn mice and chicks [37]. Recently, another serotype, termed ETD, was identified whilst screening the genome of clinical *S. aureus* isolates from diseased patients with probes for the *eta* and *eth* genes [38]. ETD is a 27-kDa protein with a 40% sequence similarity to ETA, 59% to ETB and 13% to ETC. The toxin produces exfoliation in newborn mice but not in 1-day-old chicks. Intriguingly, two of the three ETD-producing strains identified in this study were isolated from wound infections and not SSSS and, of 88 *S. aureus* isolates from lesions of impetigo in Japanese patients, only one produced ETD [38]. The authors speculate that ETD is not strongly associated with SSSS, but may play a wider pathogenic role in staphylococcal infections, such as disrupting the skin epithelial barrier and allowing the organism to spread or invade local tissues. In piglets, a group of toxins similar to the *S. aureus* exfoliative toxins but produced by *Staphylococcus hyicus* is responsible for exudative epidermitis, characterised by exudation, exfoliation and blister formation with skin erosions [39]. At least three antigenically distinct, 27–30-kDa *S. hyicus* exfoliative toxins have been identified and shown to cause midepidermal cleavage in piglets aged less than 5 weeks and 1-day-old chicks, but not in older pigs, 15-day-old chicks, mice or guinea pigs [39,40].

Initial sequence analysis of the exfoliative toxins revealed a 25% homology to staphylococcal V8 protease, including a serine-histidine-aspartate catalytic triad present in all serine proteases – mutation of any of these three amino acids results in loss of exfoliative activity in the newborn mouse model [13]. In vitro studies involving incubation of the toxins with either neonatal mouse epidermal extract [41] or A431 skin cells [42] result in induction of protease activity in the supernatant, which can be abolished in the A431 cell supernatant by preincubation of the toxin with a serine protease inhibitor [42]. Computer models based on the three-dimensional structures of other glutamate-specific trypsin-like serine proteases such as α-thrombin, chymotrypsin, *Streptomyces griseus* protease, and *Achromobacter protease* [43], and recent crystallographic studies for both ETA [44,45] and ETB [46] provided further support that the toxins act as, albeit atypical, serine proteases (Fig. 2). Both toxins have two domains, S1 and S2, each consisting of six-strand β-barrels common
to all members of the trypsin family, and a C-terminal α-helix. The catalytic triad forming the active site is located on the interface of the two barrels. The toxins additionally possess threonine(190) and histidine(213) in the core of the N-terminal S1 pocket that are conserved in all glutamate-specific serine proteases [44,45]. However, unlike other members of the trypsin family, the exfoliative toxins have a distinct, highly charged (eight of 15 residues in ETA and six of 11 residues in ETB) N-terminal α-helix that lies near the base of the S1 pocket. Furthermore, the proline(192)-glycine(193) bond in ETA and its equivalent valine(183)-glycine(184) in ETB are flipped 180° relative to other serine proteases. This allows the proline(192) in ETA and valine(183) in ETB to form a hydrogen bond with their respective active site serine residues, thus blocking the active site – this explains why the toxins are inactive in their native state.

It has been proposed that binding of the highly charged N-terminal α-helix to a specific epidermal receptor could flip the proline-glycine bond in ETA and valine-glycine in ETB to allow a conformational change that exposes the active site, which can then bind and cleave the protein between the third and fourth extracellular domains after glutamic acid residue 381 (counting from the initiating methionine residue of human desmoglein-1). By comparison with E- and N-cadherins whose three-dimensional structures are known, it is speculated that calcium binding to these sites stabilizes the rigidity and fixes the orientation of desmoglein-1, thereby allowing it to perform its function as part of the extracellular cytoskeleton. Cleavage at such positions is thought to lead to the formation of the skin blisters seen in pemphigus foliaceus.

A major setback in exfoliative toxin research until recently was the lack of any significant in vitro enzymatic activity towards a wide range of substrates tested and a failure to prevent exfoliation in newborn mice by different metabolic inhibitors [4]. However, in a series of elegant experiments, Amagai and colleagues have recently identified the epidermal target for the exfoliative toxins following observations that the skin lesions of SSSS were clinically and histologically identical to pemphigus foliaceus (Fig. 3), an autoimmune skin condition in which autoantibodies attack desmoglein-1, a transmembrane desmosomal glycoprotein in the cadherin gene superfamily, which plays an important role in maintaining keratinocyte cell-to-cell adhesion in the superficial epidermis [3]. The group showed that injecting small quantities of purified exfoliative toxin into the neck of newborn mice produced identical blisters to pemphigus foliaceus and, using immunofluorescence staining and Western blot analysis, they were able to demonstrate that the blister formation was specifically due to degradation of desmoglein-1. The toxins cleave human and mouse desmoglein-1 between the third and fourth extracellular domains after glutamic acid residue 381. Reproduced with permission from ACS Publications [36].
a critical site would result in dysfunction of the molecule and loss of intercellular adhesion within the epidermis.

The reaction between the exfoliative toxins and desmoglein-1 does not require any other factor since incubation of the toxins with recombinant extracellular domain of desmoglein-1 only resulted in a dose-dependent degradation of the protein [3,4,7]. Furthermore, replacing the serine residue of the active site with alanine resulted in the toxins still being able to bind but unable to cleave desmoglein-1, supporting previous speculations that the toxins act as serine proteases. Using wild-type ETA and mutant ETA that is able to bind but unable to cleave desmoglein-1, the authors were able to estimate the dissociation constant of the reaction between ETA and desmoglein-1 at approximately 8 μM, which is within the range of a hydrolytic reaction whose specificity is due to relatively strong binding in the catalytic site with a relatively low K_m [48]. Co-immunoprecipitation studies between ETA and desmoglein-1 and between ETA and other closely related epidermal antigens such as desmoglein-3 and E-cadherin also confirm that ETA binds specifically to desmoglein-1 only and dissociates after hydrolysis of the target peptide bond, consistent with enzyme recycling [48].

Desmoglein-1 is found throughout the epidermis and mucous membranes but blisters are only formed in the superficial epidermis in both SSSS and pemphigus foliaceus [3]. This observation can be explained by the ‘desmosome compensation’ hypothesis, which suggests that desmoglein-3, which is found in the deep epidermis and in mucous membranes but not in the superficial epidermis, will compensate for desmoglein-1 and maintain the integrity of the structure, if the function of the latter is compromised [49]. This hypothesis would also explain why the mucous membrane is not affected in SSSS.

5. The toxins as superantigens

The exfoliative toxins are unique in that they possess both enzymatic and superantigenic activity, although this still remains controversial [5]. Superantigens are able to bind directly to the major histocompatibility complex on the surface of antigen-presenting cells outside the antigen-binding groove and cross-link with the variable V_β region of the β-chain of the T cell receptor to potentially activate up to 20% of all T cells. The superantigenic activity of the toxins is considered to be separate from their enzymatic activity since mutation of the active site serine(195) to alanine in ETA results in loss of exfoliative activity but not in mitogenic activity [44]. Previous reports that the superantigenic activity of the exfoliative toxins was due to contamination by other superantigens is unlikely to be true since cloning ETA into a non-superantigenic strain of S. aureus resulted in superantigenic activity in the supernatant [44].

Current evidence suggests that the exfoliative toxins possess a unique and specific superantigenic activity because they induce selective polyclonal expansion of V_βs 3, 12, 13.2, 14, 15 and 17 (but not V_β 2) and only those murine V_β T cells that are highly homologous to human forms are induced [50]. ETA is able to activate murine macrophages to release high levels of tumour necrosis factor-α, interleukin-6 and nitric oxide to cause contact-dependent cytotoxicity in transformed embryo fibroblast cells [51]. When compared to ETA, ETB is considered to be more pyrogenic and enhances susceptibility to lethal shock in rabbits [50]. ETB is also more frequently isolated in generalised compared to localised SSSS and can cause generalised SSSS in apparently healthy adults [52]. Furthermore, flow cytometry analysis revealed that T cells stimulated with ETB show a corresponding population of T cell receptors on their surface bearing the appropriate V_β [50]. On the other hand, ETA appears to decrease the number of expected V_β receptors on the surface of T cells, suggesting that ETA may down-regulate T cell receptors on the expanded set of T cells, a process also thought to occur with other superantigens [53]. Despite these differences, both ETA and ETB produce identical skin lesions in humans and mice. Thus, although there is little evidence that the superantigenic activity is important in the pathogenesis of SSSS, the toxins could play a role in other diseases where superantigens are thought to be involved, such as Kawasaki disease, atopic dermatitis, psoriasis, various autoimmune disorders, and sudden infant death syndrome [4,5].

6. The toxins in the future

Progress in our understanding of SSSS is improving at an exciting pace. The toxins responsible for the exfoliation have been identified, characterised and their structures elucidated. More recently, their specific epidermal target has been identified and this has opened an exciting new avenue for further research into the condition. In particular, by analysing the three-dimensional structure of the exfoliative toxins complexed with desmoglein-1, structural biologists should be able to confirm their speculated mechanism of action.

Until recently, research on SSSS involved injecting exfoliative toxin into live newborn animals. Now this process can be duplicated in the laboratory by incubating the toxin with desmoglein-1 only and measuring degradation of the latter. Such a simple and rapid laboratory assay can be used to compare differences in various properties of the different toxin serotypes, such as temperature and requirement for calcium. In particular, it may explain how ETC and S. hyicus exfoliative toxin A are able to induce exfoliation without conserving the serine-histidine-aspartate active site. In addition, site-directed mutagenesis can be used to develop mutant toxins to study different properties of the toxins, such as their species specificity and their...
and a synthetic peptide based on the conserved region (KKKVTAQELD) was able to significantly reduce transcytosis [56]. The exfoliative toxins may also possess such a conserved region, which may provide a target for future vaccine development to prevent SSSS.

7. Conclusion

Staphylococcal skin infections remain one of the most common childhood conditions. Of these, the staphylococcal scalded skin syndrome produces the most dramatic changes with exfoliation of almost the entire body surface in severe cases. While most cases are easily treated, it remains a potentially fatal condition, particularly in adults with underlying disease. SSSS is caused by the staphylococcal exfoliative toxins, which have an exquisite ability to target and destroy a specific protein in the epidermis. Identification of desmoglein-1 as the epidermal target has explained many of the unusual features of the toxins compared to other serine proteases and opened a new area for basic and clinical research, including development of new diagnostic tests and specific antitoxin therapies. Furthermore, understanding the mechanism of action of the exfoliative toxins will not only allow us to understand the pathogenesis of SSSS, but also provide useful information on normal skin physiology and other toxin-mediated diseases. The toxins are also likely to have other useful benefits in dermatology and therapeutics in the near future. However, many questions remain unanswered and a lot more work needs to be done before we can close the chapter on the staphylococcal scalded skin syndrome.

References


