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REVIEW ARTICLE

Understanding host's response to staphylococcal scalded skin syndrome

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Abstract

Aim: The aim of this review was to summarise the current knowledge on host-related factors that contribute to the development and severity of staphylococcal scalded skin syndrome (SSSS) in children.

Methods: A comprehensive assessment and analysis of the existing literature on SSSS clinical features, pathogenesis and susceptibility factors.

Results: SSSS is a blistering skin disease caused by circulating exfoliative toxins (ETs) of *Staphylococcus aureus* (*S. aureus*), almost exclusively affecting infants, young children and immunocompromised individuals. ETs possess serine protease activity and target desmoglein-1 (Dsg-1) in the superficial epidermis. While the role of *S. aureus* ETs and site of action are well-described, other host factors such as impaired immune responses to ETs, poor renal clearance and genetic factors are crucial for the onset of and/or the severity of SSSS in children.

Conclusion: The fate of desmosomal fractions after cleavage by ETs, as well as the role of dermal inflammatory cell infiltrates remain to be elucidated.

KEYWORDS
desmoglein-1, exfoliative toxins, staphylococcal scalded skin syndrome

1 | INTRODUCTION

Staphylococcal scalded skin syndrome (SSSS) is a generalised, exfoliating skin disease caused by circulating exfoliative toxins (ETs) of *Staphylococcus aureus* (*S. aureus*).[1] It mainly affects otherwise healthy infants and children up to 6 years old, but older individuals with underlying conditions can be also rarely affected.[1] SSSS has been previously reported to cause significant morbidity and mortality in children,[2] but nowadays mortality among treated children is less than 3%.[3]

Clinical manifestations of SSSS range from erythema and blisters that affect confined body areas to a more generalised presentation with extensive skin involvement.[4] The differential diagnosis includes other infections or inflammatory conditions presenting with extensive, cutaneous erythema or blistering, such as toxic epidermal necrolysis, epidermolysis bullosa, bullous erythema multiforme and thermal or chemical burns.[5]

SSSS is mostly a toxin-mediated disease, as exotoxins, produced by several *S. aureus* strains, exhibit serine protease activity and cleave desmoglein-1 (Dsg-1) in the superficial epidermis, causing skin exfoliation, blistering and erythema.[6] SSSS-related exotoxins have been associated with certain strains of *S. aureus*, most of which have been methicillin-susceptible *S. aureus* (MSSA).[7,8] Strains

Abbreviations: BI, bullous impetigo; Dsc-1, desmocollin-1; Dsg-1, desmoglein-1; ETs, exfoliative toxins; LCs, Langerhans cells; MLST, multilocus sequence typing; MSSA, methicillin susceptible *S. aureus*; PG, plakoglobin; PF, pemphigus foliaceus; SSSS, staphylococcal scalded skin syndrome; ST, sequence type.

causing SSSS were previously reported as belonging to phage group II,[9] but recent studies using multilocus sequence typing (MLST) have reported isolates belonging to sequence types (ST)-15, ST-121, ST-2126 and ST-299.[10] Of these, ST-121 is currently the most commonly reported.[2] Diagnosis is mostly clinical. While histopathologic examination of a lesional biopsy can be used in atypical cases, usually diagnosis can be facilitated by positive PCR for *S. aureus* exfoliative exotoxin-encoding genes.[11] Successful management includes local care and administration of antibiotics.

While ETs are produced by as many as approximately 5% of *S. aureus* strains among healthy individuals,[12] SSSS is only rarely developed in children, suggesting that other host-related factors may be important. In this review, we provide an overview on the current knowledge on host-related immune and genetic factors that contribute to the development and/or severity of SSSS in children.

Key notes

- Staphylococcal scalded skin syndrome (SSSS) affects only a small proportion of individuals exposed to exfoliative toxins (ETs) and mainly young children and immunocompromised adults.
- Antibody levels against ETs, renal function, host genetic factors and the presence of atopic dermatitis appear to contribute to SSSS development and severity.
- Novel research findings are needed regarding host's susceptibility factors, such as desmoglein-1 gene polymorphisms.

2 | SSSS CLINICAL FEATURES

SSSS in children usually begins with irritability and fatigue.[13] The most common initial sites of localised infection by *S. aureus* include the conjunctiva, nose, throat, diaper area and umbilical stump.[5,13] Within the first 24–48 h, tender erythematous patches develop mainly on the face and flexural regions, such as the axillae, groin and neck,[13] to be followed by fragile blisters with accumulated sterile liquid or frank pus within the erythematous areas.[1] These blisters grow in size to form bullae, which rupture easily and cause desquamation. Patients have a positive Nikolsky sign, which is exfoliation of the upper epidermis as gentle pressure is applied to the affected skin.[14] Histopathology shows minimal or no dermal inflammation. A second period of desquamation follows in the next 10 days, and in most cases, the skin heals without scarring within 2 weeks.[13,14]

3 | SSSS PATHOGENESIS

3.1 | *S. aureus* carriage and *S. aureus* exfoliative toxins

Nasal carriage of *S. aureus* is reported in approximately 30% of the healthy population.[15,16] Among carriers, 20% are persistent carriers, typically of a single strain.[15] Children have a high carriage rate within the first month of life, that quickly drops and then rises again by the second or third year of life.[17] Maternal colonisation, atopic dermatitis and presence of siblings increase carriage rates in infants.[18,19] Apart from the nasopharynx, other colonisation sites in neonates are perineum, eyes, axillae and umbilicus.[5]

S. aureus produces at least five antigenically distinct ETs, of which ETA and ETB are responsible for most human cases of SSSS.[6] ETC has been identified in equine infection but has not been associated with human disease.[12] ETD is similar to ETA and ETB and may also disrupt the skin epithelial barrier and allow the organism to spread or invade local tissues, but is not strongly associated with SSSS.[5] Recently, ETE was identified from a *S. aureus* strain isolated from ovine mastitis that was showed to hydrolyse directly human desmoglein-1 (Dsg-1), the target of action in SSSS.[20] ETA is encoded by the *eta* gene, which is chromosomally located, carried on the genome on a temperate phage, and ETB by the *etb* gene on a plasmid DNA.[21] The accessory gene regulator (*agr*) is one of the major known regulatory mechanisms coordinating the expression of both *eta* and *etb*.[22] Strains producing ETA and ETB show phylogenetic relatedness and mainly belong to the *agr* group IV.[22]

It has been hypothesised that staphylococcal ETs act as superantigens, inducing the atypical, polyclonal proliferation of T cells.[23] However, it is known that even if ETs are truly superantigens, their mitogenic effect is much milder than of other staphylococcal superantigenic toxins.[23] Overall, there is no evidence of T-cell recruitment in SSSS lesions, so the presumed superantigenicity of the ETs is probably not involved in the pathogenesis of SSSS.

3.2 | Desmogleins, the targets of *S. aureus* exfoliative toxins

SSSS is defined by acantholysis, a loss of cell-to-cell cohesion in the superficial epidermal layers.[5] The skin protein target in SSSS, Dsg-1, is a desmosomal cadherin of superficial epidermis responsible for intercellular adhesion[13] (Figure 1). Acantholysis is induced when ETs, acting as serine proteases, target and cleave Dsg-1 between the third and fourth extracellular domains after glutamic acid residue 381, resulting in dissociation of homophilic binding of Dsg-1 molecules.[5] Tissue destruction follows, allowing *S. aureus* to invade the epithelium.

Tissue distribution of desmosomal cadherins clarifies the location of ET-induced blister formation.[6] Desmogleins in humans are divided in four subclasses with different tissue distributions. Dsg-1 is found throughout the epidermis and mucous membranes, but in both SSSS and pemphigus foliaceus blisters are only formed in the superficial epidermis with no mucosal involvement.[5] This finding can be explained by the 'compensation hypothesis',[24] in which Dsg-3, found in the deep epidermis and in mucous membranes but not in the superficial epidermis, compensate for Dsg-1 and protect

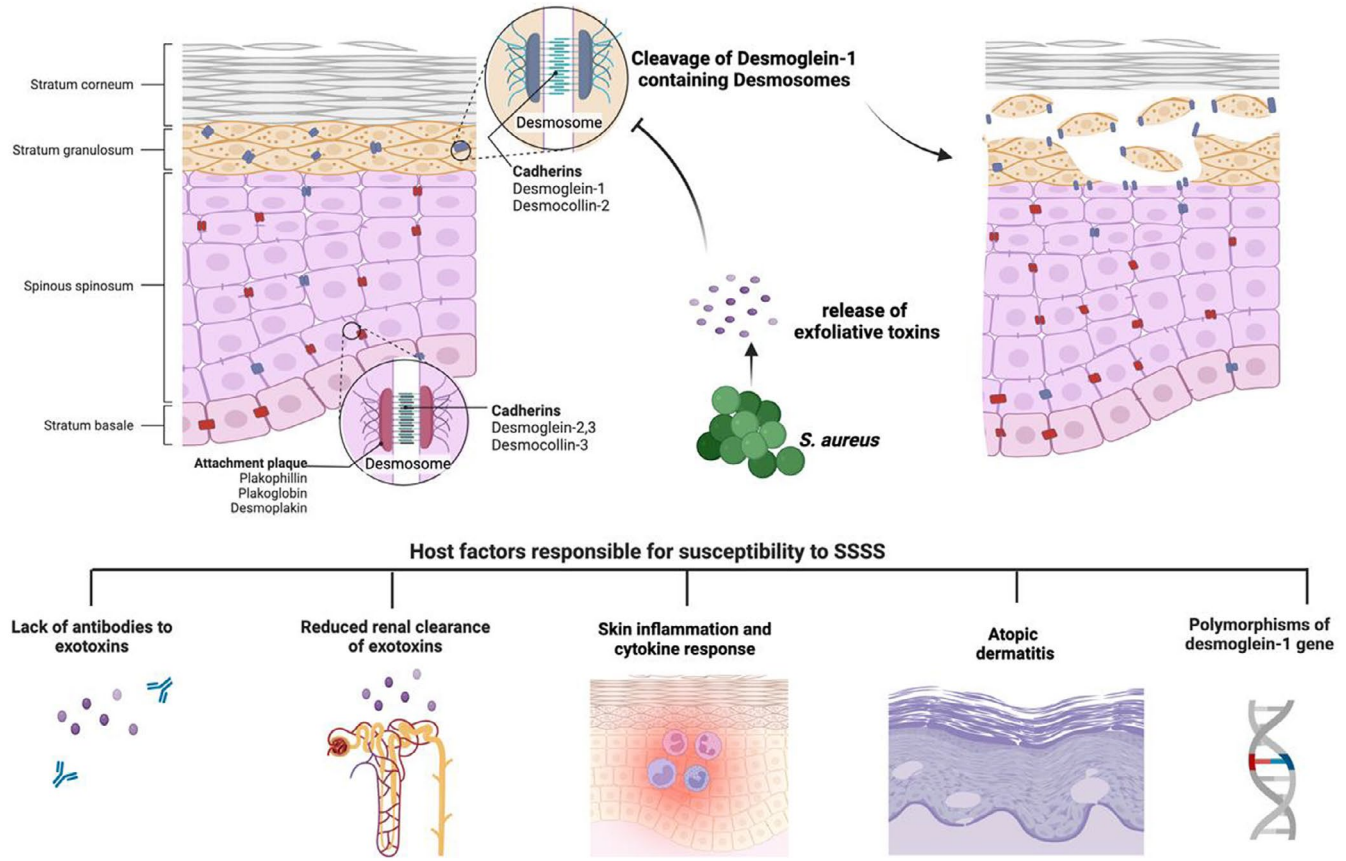

FIGURE 1 Host factors mediating susceptibility to staphylococcal scalded skin syndrome.

mucosal structure integrity. Dsg-2 and Dsg-4 are expressed weakly in basal and upper granular layers, respectively, and may have less ability to compensate the loss of Dsg-1 function.[6]

Other components of intercellular desmosome junctions expressed in superficial epidermis are desmocollin-1 (Dsc-1) and plakoglobin (PG). Dsg-1 and Dsc-1 may have combinational effects on maintenance of keratinocyte cell adhesion, while abolishment of either Dsg-1 by ETs or genetic ablation of Dsc-1 causes dissociation of keratinocytes in the superficial layer of mouse epidermis.[25] The removal of amino-terminal extracellular domains of Dsg-1 by ETs is sufficient to induce epidermal blister formation in SSSS, while the carboxy-terminal domain of Dsg-1 and amino-terminal domain of Dsc-1 remain on cell surfaces during the initial phase of blister formation.[26] In addition, after cleavage of the extracellular segment of Dsg-1 by ETs, the truncated Dsg-1 seems to cause sequestration of PG, which contributes to the expansion of intercellular spaces between keratinocytes.[6]

4 | SUSCEPTIBILITY TO SSSS

Despite the high prevalence of ET-producing *S. aureus* collected from clinical specimens,[27,28] the disease is rare in adults as opposed to infants and young children. This suggests that there may be host and/or pathogen factors that lead to the development and severity of SSSS (Figure 1). The host factors that have been implicated in the susceptibility to SSSS are summarised in Figure 1 and analysed as follows.

4.1 | Renal clearance of exotoxins in SSSS

Susceptibility to SSSS in young children may be due to the reduced renal clearance of toxins in early childhood.[5] A specific concentration of toxin is needed in the skin for exfoliation to occur, and neonatal kidneys are not able to clear the toxin rapidly enough to prevent their accumulation in the epidermis. Experimental data from mice have shown that healthy adult kidneys excrete the circulating toxins much more efficiently than those of neonates, where toxin levels reach a higher peak and decline more slowly.[29]

Regardless of age, patients with renal failure and immunocompromised individuals are also at higher risk of developing SSSS. On the contrary, toxin concentrations in serum of healthy adults do not reach the levels needed for significant exfoliation in the skin to take place. Nephrectomised adult mice develop generalised SSSS when ET is injected.[29] Similarly, when repeated injections of toxin are given to adult mice so that the maximal level of toxin is maintained for a sustained period of time, exfoliation does occur.[30] However, challenging adult mice with single administration of very high doses of ET does not result in exfoliation, therefore renal function alone cannot explain SSSS development.[29]

4.2 | Host's adaptive immune responses in SSSS

The presence of antibodies against ETs in individuals exposed to ET-producing *S. aureus* strains seem important for the development of the SSSS disease. Anti-ETs antibody levels are detectable in only 30% of infants aged 3–2 years, but then rise steadily to 42% at the age of 2–5 years and to 91% over the age of 40 years.[9] Anti-ET antibodies can be detected in healthy individuals with no history of SSSS and their presence or absence may affect disease severity.[9,29] Langerhans cells (LCs) are capable of capturing ETs from *S. aureus* through intact tight junctions (TJs) and subsequently prepare a repertoire of antibodies that confer protection from SSSS[31] (Table 1).

Occasionally, infectious agents trigger autoimmunity by causing antibodies that bind self-antigens, with typical example the streptococcal antigens in rheumatic heart disease. The observation that the SSSS-related infectious diseases, bullous impetigo (BI) and the autoimmune disease pemphigus foliaceus (PF) have the same target molecule Dsg-1, led to the hypothesis that partially degraded and modified Dsg-1 by *S. aureus* ETs may potentially trigger the immune response as a self-antigen.[32] The findings indicated that a small number of SSSS patients develop low titres of IgG antibodies specific for Dsg-1, but none of the patients with BI show any sign of anti-Dsg-1 antibody production, perhaps due to the fact that BI does not cause a major adaptive systemic immune response.[32] Although none of these patients developed PF after SSSS, this finding indicates that a bacterial toxin has the potential to modify a protein to a self-antigen to result in an autoantibody response.[32]

4.3 | Inflammatory cell infiltrate and cytokine release in SSSS

ETs' binding with Dsg-1 modifies the keratinocyte metabolism and induces an inflammatory reaction.[33] The infiltrate of inflammatory cells is composed of granulocytes (CD15+), macrophages (L1 protein+), memory T cells (CD45R0+) and expression of ICAM-3 (CD50) in the epidermis.[33] First, the binding of ETs with Dsg-1 activates keratinocytes, which release cytokines including IL-6.[34] The inflammatory cytokines IL-1α and IL-1β, as well as acute- phase reactants TNF and IL-12, were not found to be elevated upon Dsg-1 cleavage.[34] The absence of induction of other acute-phase pro-inflammatory cytokines other than IL-6 by ETA may favour the bacterial infection by suppressing the local immune response via limited recruitment of white blood cells into the skin lesion. Indeed, lesions caused by ETA-positive MSSA isolates have been shown to lack significant WBC infiltration.[34]

Following ETs' binding with Dsg-1, specific chemotactic factors and adhesion molecules are produced, such as ICAM-1.[33] This protein is not found in keratinocytes of normal skin, but lines the blisters on SSSS.[33] Additionally, ETs can also act on Langerhans cells in the epidermis and type I perivascular dendrocytes in the dermis, which are numerous in SSSS. Contrary to superficial pemphigus where the target molecule is also Dsg-1, the skin inflammatory reaction in SSSS is more intense than the one caused by autoantibodies in pemphigus.[33] Also, in BI, there is a lower number of type I dendrocytes, probably due to local production of ETs.[33] Thus, it seems that the released cytokines from keratinocyte activation by ETs play a critical role in the pathogenesis of ETs toxicity and the severity of the SSSS. Furthermore, host genetic factors regulating cytokine responses to ETs are probably crucial for SSSS disease severity. Factors such as host TCR repertoire, the type of MHC class II alleles expressed and the ability to upregulate cytokine gene expression can all affect the development of a more severe and complicated disease such as SSSS or a more localised and mild form, BI.[33]

TABLE 1 What is known on SSSS pathogenesis.

Antibodies: Antibodies against staphylococcal exotoxins may prevent the development of the disease
Cytokine response: Binding of staphylococcal exotoxins with desmoglein-1 induces a severe inflammatory reaction with potential modifications in the keratinocyte metabolism
Renal clearance: Defective renal clearance of the toxins increases the risk for developing SSSS
Local factors: Desmoglein-1 and desmocollin-1 may have combinational effects on maintenance of keratinocyte cell adhesion

4.4 | Atopic dermatitis and SSSS

SSSS often occurs in individuals with atopic dermatitis,[35] a condition with an increased rate of staphylococcal colonisation.[36] In these subjects, a reduction in the diversity of bacteria that comprise the skin microbiota is taking place, resulting in impaired inhibition of *S. aureus*.[19] Recently,[37] *S. aureus* strains isolated from AD patients revealed a high degree of genetic heterogeneity. Studies about the relationship between AD- and ET-producing strains are scarce. In Spain,[36] the *eta* gene was detected in 15.4% of cutaneous isolates from children with AD while a study in Italy[38] revealed a limited, but significant isolation rate of ETB-producing strains of *S. aureus* from AD patients. Furthermore, in Japan[39] the rates of ETA- and ETB-producing strains from patients with AD were 30.9% and 34.6% respectively. Further studies are needed to investigate the role of *S. aureus* in AD skin and the relationship with *eta* and *etb* genes.

4.5 | Desmoglein-1 gene polymorphisms

A single nucleotide polymorphism of Dsg-1 has been associated with pemphigus foliaceus in adults, an autoimmune skin disorder with similar lesions as SSSS.[40] By far, no association between Dsg-1 polymorphisms and SSSS has been described; however, Dsg-1 polymorphisms have not been extensively studied in SSSS. Since the 3D structure of Dsg-1 has been analysed, a further step in the research path would be the detection of Dsg-1 polymorphisms that may affect the amino acid sequence of Dsg-1 that is targeted by ETs and analysis of these

polymorphisms in patients with SSSS and exposed asymptomatic individuals; this might explain why only a small proportion of individuals who are exposed to ETs develops the disease.

5 | RECURRENT OR SEVERE SSSS AND IMMUNOLOGICAL INVESTIGATION

Recurrent SSSS in the paediatric population is rare and documented more often in the neonate population than in infants or older paediatric patients.[41] Specifically, there are five reported cases occurred in either healthy full-term, preterm, or low-birth-weight neonates.[41] It is well known, that in adults, the immune response against the staphylococcus is an important factor for the development of SSSS. In fact, in most adult cases, diabetes mellitus, or human immunodeficiency virus infection were identified as predisposing factors. In children, there are reports about hyper IgE[42] and Netherton syndrome[43] diagnosed in those children with severe or recurrent SSSS.

The immune response of children with SSSS is not usually explored. However, enhanced frequency or severity of *S. aureus* infections may constitute a clinical indicator of a specific underlying immunological impairment.[44] Basic immunological workup in patients with recurrent or severe SSSS should include a differential blood count and IgG, IgA, IgM, IgE.[44] Lastly, specific testing for chronic granulomatous disease, hyper-IgE syndrome, complement deficiency, leukocyte adhesion deficiency, Toll-like receptor deficiency, exclusion of secondary immunodeficiencies and assessment for phenocopies of inborn errors of immunity as well as genetic analysis may be warranted in severe cases.[44]

6 | CONCLUSIONS

Although the role of *S. aureus* exotoxins and their epidermal target has been elucidated, it appears that SSSS development and disease severity relies in several host factors are implicated such as antibody levels against ETs, renal function, host genetic factors regulating skin inflammation and cytokine responses to ETs as well as the presence of atopic dermatitis. The role of desmoglein-1 gene polymorphisms in SSSS require further investigation. However, the available data regarding host immune responses in SSSS are scarce, and further research will expand our understanding on SSSS immune regulation. In addition, further research on the role of truncated desmosomal components in ET-induced keratinocyte dissociation is needed (Table 2).

7 | FUTURE DIRECTIVES

Future applications in SSSS diagnosis and treatment include the investigation of rapid, specific and sensitive diagnostic tests using Dsg-1 as antigen to isolate the toxin in plasma or other biological fluids from suspected patients of SSSS.[5] Prevention of exfoliation by inhibiting toxins with analogues of the toxin-binding regions is also a promising prospect.[4] In addition to administration of antibiotics and fluids, another intriguing concept is the use of histone deacetylase inhibitors as an adjunctive therapy for SSSS, as they up-regulate desmosomal cadherins and prevent the loss of adhesion induced by Dsg1 truncation.[45]

Currently, there are no vaccines available against *S. aureus*, although efforts have been made to develop vaccines that would activate both humoral and cellular immunity.[46,47] The ETs of *S. aureus* could be a suitable and effective candidate antigen for vaccine development in order to eradicate SSSS.

TABLE 2 What needs further elucidation.

Role of the truncated desmosomal components in vivo during the keratinocyte dissociation induced by exotoxins
Role of autoimmune mechanisms possibly triggered by exotoxins
Role of host's susceptibility factors (antibody status against exotoxins, host genetic factors regulating cytokine responses and atopic dermatitis)
Role of desmoglein-1 gene polymorphisms and potential susceptibility or resistance to exotoxin cleavage

AUTHOR CONTRIBUTIONS

Glykeria Rouva: Writing – original draft; conceptualization; visualization; resources; investigation. **Eleni Vergadi:** Supervision; writing – review and editing. **Konstantinos Krasagakis:** Supervision; writing – review and editing. **Emmanouil Galanakis:** Supervision; writing – review and editing; conceptualization; visualization.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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