Current Trends in Immunology
Vol. 25, 2025

Mini-Review

Staphylococcus aureus as a possible cause of diabetes mellitus type 2

Patrick M. Schlievert[1,*] and Donald Y. M. Leung[2]

[1]Department of Microbiology and Immunology, Carver College of Medicine, University of Iowa, 51 Newton Road, Iowa City, Iowa 52242, USA; [2]Department of Pediatrics, National Jewish Health, 1400 Jackson Street, Room K1016, Denver, Colorado 80206, USA.

ABSTRACT

Diabetes mellitus 2 (DM2), a serious, chronic condition, affects 40 million U.S. persons and one billion worldwide. The condition is characterized by unusually elevated blood glucose, insulin-resistance, and a pro-inflammatory state. We discuss data fulfilling the four Koch's postulates, demonstrating that *Staphylococcus aureus* may cause DM2. First, patients are chronically infected with high levels of skin *S. aureus*, producing pro-inflammatory superantigens, compared to 17% of healthy persons colonized on skin with small numbers. Second, *S. aureus* is easily cultured from patients and shown to produce the superantigens toxic shock syndrome toxin-1, enterotoxin B, or enterotoxin C. Superantigens traverse skin barriers after interaction with CD40 and gp130 receptors. Third, *S. aureus* superantigens cause elevated blood glucose and insulin-resistance in experimental rabbits. *S. aureus* is easily re-isolated, fulfilling the fourth of Koch's postulates. The data suggest that *S. aureus* superantigens cause DM2. Insights into this etiology may lead to cure or sustained remission.

KEYWORDS: *Staphylococcus aureus*, diabetes, superantigens, CD40, gp130.

INTRODUCTION

There are four categories of diabetes mellitus (DM), including DM1, DM2, gestational, and DM secondary to other causes. Approximately 38.4 million adults (11.3% of the U.S. population) have DM2, the subject of this article, with an estimated 8.5 million not knowing they have the disease [1]. There are as many as 1 billion persons with DM2 in the world. DM is the 8th leading cause of death in the U.S., with many patients succumbing to heart diseases and strokes [1]. The annual cost of DM to the U.S. healthcare system approaches $327 billion [1]. In the U.S., 35.7% of adults and 15% of children and adolescents are obese, with significant risk of hypertension and development of DM2 [1]. Once DM2 progresses, severe complications may occur, including development of diabetic foot ulcers, which ultimately may lead to chronic infections and amputations [1].

This mini-review is a discussion of the likelihood that microbes, particularly *Staphylococcus aureus* and its superantigen (SAg) toxins, are important causes of DM2. Insights into the causative etiology of DM2 may lead to its cure or sustained remission.

Microbial association with DM2

Interestingly, the gut microbiome is significantly altered in both DM2, pre-DM2 states, and obesity [2, 3]. There are overall decreases in intestinal *Bacteroidetes* and increases in *Firmicutes*. The dominant *Firmicutes* human pathogens are *S. aureus*. These organisms become very common in DM2 patients and obese persons, approaching 100% chronic colonization and/or infection on the

*Corresponding author: Patrick-schlievert@uiowa.edu

skin and nasal mucosa of obese and DM2 patients [4, 5], compared to 17% transient colonization/ infection of the skin [6] and up to 40% colonization of the anterior nares in otherwise healthy persons [7]. In a small study, we showed that DM2 patients may have up to 10^{13} *S. aureus* on their normal skin [4]. To put this in perspective, this amounts to about one-fourth of a stick of margarine spread around the body, usually in moist areas of the skin, for example antecubital fossa (front of elbow), axilla (underarms), and popliteal fossa (back of the knees). The *S. aureus* strains on these same individuals, both methicillin-resistant (MRSA) and methicillin-sensitive (MSSA), produced one or more of the major highly pro-inflammatory superantigens (SAgs), that is, toxic shock syndrome toxin-1 (TSST-1), enterotoxin B (SEB), and enterotoxin C (SEC) [4].

Role of SAgs in human diseases

SAgs are relatively low molecular weight (20K to 28K), exceptionally heat-, acid-, and protease-stable, secreted proteins [8, 9]. For example, TSST-1 and SEs can be boiled for one hour without loss of SAg activity. The SEs, the common causes of millions of cases of food poisoning each year in the U.S., are resistant to stomach acid and proteases, as is the non-enterotoxin SAg TSST-1, which allow SEs to cause vomiting and diarrhea in amounts as low as nanograms per person [10].

All human pathogenic *S. aureus* strains produce one or more SAgs [8, 9]. The large SAg family includes TSST-1, SE serotypes A-G (excluding F), and enterotoxin-like SAgs (serotypes I-X), as well as streptococcal pyrogenic exotoxins from Group A streptococci [8, 9]. SAgs can be produced *in vitro* in amounts as high as 10-20 mg/ml [11].

All of the SEs have the ability to cause staphylococcal food poisoning, but SEA is the predominant cause. TSST-1 is the cause of 100% of menstrual, tampon-associated TSS [12], and this SAg is highly associated with eczema herpeticum [13] and bullous pemphigoid [14]. Patients with menstrual TSS cannot produce neutralizing antibodies to TSST-1 [15, 16]. Thus, recurrences of menstrual TSS are common [17]. We know of women who have had six episodes of this serious disease. When menstrual TSS was at its peak, prior to removal of the highest absorbency tampons from the market, the actual incidence of menstrual TSS correlated well with the percentage of women lacking antibodies.

TSST-1 and SEs B and C are the causes of non-menstrual staphylococcal TSS, most often following influenza respiratory infections [8, 9, 18]. Rarely, SEA may be the cause of non-menstrual staphylococcal TSS. The reason for the causation of staphylococcal TSS most often by TSST-1, SEB, and SEC is presumed to be because of the high concentration produced on body surfaces compared to other SAgs [11, 19]. It is estimated that 1-10% of SAg applied to skin or mucosal surfaces gains access to the bloodstream in the course of a few days [10]. It is important to note that TSST-1 is better able to transit mucosal surfaces than SEB, SEC, and streptococcal pyrogenic exotoxins, and thus, TSST-1's unique association with menstrual TSS [10]. Additionally, it is noteworthy that the peak onset of menstrual TSS is 3-4 days after onset of menstruation [20], with TSS *S. aureus* vaginally peaking on day 2 of menstruation [21, 22]. These data are significant since it suggests that SAgs cause their major effects 3-4 days downstream of initial exposure, and that continuous exposure is much more toxic than bolus exposure [23-26]. SAgs accumulate in mucosal and skin tissues to serve as reservoirs for their continued chronic exposure [27, 28]. These same observations are seen in rabbit models where exposure over 3-4 days leads to TSS, but single bolus injections do not [23, 24]. Further, *in vitro* assays show that maximum T lymphocyte proliferation due to SAgs is on day 4 [29, 30]. These observations will be important in the DM2 discussion below.

Some SAgs, whether staphylococcal or streptococcal, are also capable of causing rheumatoid arthritis and experimental allergic encephalomyelitis in animal models of human rheumatoid arthritis [31] and multiple sclerosis [32, 33], respectively. Additionally, streptococcal pyrogenic exotoxins are associated with guttate psoriasis [34], acute rheumatic fever [35], and post-streptococcal acute glomerulonephritis [35]. Because of the commonness of *S. aureus* and

Group A streptococci, and the exceptional potency of SAgs, it is likely that *S. aureus* and Group A streptococci and their SAgs are important in many other human conditions.

Host receptors for SAgs

SAgs are a unique, large serotype family of highly pro-inflammatory proteins that cause massive T lymphocyte proliferation, $CD4^+$ and $CD8^+$, with the major effects requiring simultaneous engagement of antigen-presenting cells [36]. This suggests that the dominant interactions, at least initially are among antigen-presenting cells and $CD4^+$ T cells. T lymphocyte proliferation depends on SAgs binding to α- and/or β-chains of MHC II molecules and the variable part of the β-chain of T lymphocyte receptors (VβTCRs) [8, 9, 37-43]. No SAg activates all $CD4^+$ T lymphocytes. Rather, each SAg may activate up to 50% of $CD4^+$ T cells, dependent on the composition of the variable part of the TCR β-chain [36]. For example, the approximate percentage of Vβ2TCRs in humans is nearly 10%, but in active cases of menstrual TSS, TSST-1 causes proliferation of these Vβ2TCR-containing T cells to become 60-70% of all T cells; $V\beta2TCR^+$ T cells is the only T cell subpopulation that is stimulated by TSST-1 [44]. However, the consequence of this massive T cell stimulation is over activation of macrophages, with both T cell and macrophage production of cytokines, including interleukin-1β (causing fever), tumor necrosis factors α and β (causing hypotension due to capillary leak), and interleukin-2 and interferon gamma (minimally causing macular erythroderma) [8, 9]. TSS is the disease where the term cytokine storm was initially used. While the most obvious observation of SAg activities is dominated by Th1 lymphocyte and macrophage cytokines, chronic T cell activation or simply genetic differences among humans leads to dominance by Th2 cells and their cytokines, seen most often as an anaphylactic form of TSS or the presence of an atopic dermatitis rash as opposed to the standard scarlet fever-like rash [45].

For SAgs to gain access to the circulation to exert their pro-inflammatory effects, the proteins must first interact with epithelial cells [46] and keratinocytes [47]. Studies have shown that human vaginal epithelial cells have the immune co-stimulatory molecule CD40 as its receptor for both staphylococcal and streptococcal SAgs, with TSST-1 ten times better able to interact than other SAgs [46]. The interaction of human keratinocytes with SAgs is more complicated, requiring both CD40 and other receptor molecules, including gp130 [47, 48]. gp130 also constitutes a receptor on adipocytes for SAgs [49]. The downstream effect of the interaction of SAgs with epithelial and keratinocyte receptors is harmful chemokine production with loosening of the barrier function of these cells and facilitation of SAg access to the circulation [50]. We refer to this process as outside-in-signaling to cause disease [50]. The consequence of SAg interaction with adipocytes is harmful pro-inflammatory adipokine production [51].

An important question that commonly arises related to SAg effects on humans is: Why does not everyone develop TSS when so many folks are infected with TSS *S. aureus*? The answer to this question takes the form of the following parts:

1. Not all strains produce the three major *S. aureus* SAgs (TSST-1, SEB, SEC) that are made in high concentrations [11].
2. Those individuals infected with strains that produce the three major *S. aureus* SAgs develop TSS when body conditions facilitate production of the SAgs. For example, we have shown that the major reason for the association of the highest absorbency tampons with menstrual TSS is that they introduce oxygen into the normally anaerobic vagina [52]. TSST-1 production is absolutely dependent on oxygen for its production, despite *S. aureus* being able to grow both anaerobically and aerobically [53-55].
3. Not all SAgs are equal in their abilities to traverse mucosal and skin surfaces. TSST-1 is better able to cross the vaginal mucosa, as demonstrated in rabbit models, and this likely explains its unique association with menstrual TSS [10]. This may also depend on stronger interaction of TSST-1 with CD40 receptors on vaginal epithelial cells than the other major SAgs [46].
4. Many humans (20%) cannot produce neutralizing antibodies to any given SAg [15, 16].

This 20% varies depending on the SAg. Thus for example, it is not the same 20% lacking immunity to all three major staphylococcal SAgs (TSST-1, SEB, and SEC).

5. Finally, it appears that the epithelial cells and keratinocytes from small numbers of females, and thus likely also males, lack receptors to transport TSST-1 across barriers [19]. This phenomenon has been observed but remains understudied. This was shown in women who lack antibodies to TSST-1, use tampons, but do not develop TSS, despite TSST-1 being present in their used tampons.

Koch's postulates, SAgs, and DM2

There are four Koch's postulates, which were developed by Robert Koch, for demonstration of a microbial, and later adapted to show exotoxin, cause of disease. These are:

1. The microorganism and associated toxin must be found in diseased but to a much lower extent in healthy individuals.
2. The microorganism and toxin should be prepared in pure culture, or isolated in pure form, from diseased persons.
3. Inoculation of a non-diseased animal model with the cultured microorganism or associated toxin should duplicate the disease.
4. The microorganism or associated toxin should be re-isolated from the animal model and match up with the original microorganism.

These postulates are critical in establishing within biomedical sciences that the microorganism and its associated toxin, for example SAg, causes the disease. These postulates were modified by Koch in cases where an animal model does not exist, but the epidemiology says the microorganism causes the disease. For example, *Salmonella typhi* is a pathogen of humans only, causing typhoid fever. There is no useful animal model for studying the organism. However, epidemiologically the causative microorganism is uniquely associated with the disease entity we know as typhoid fever; the organism is usually not found in healthy persons unless they become carriers after having typhoid fever, but the organism is always associated with typhoid fever. Thus, Koch indicated typhoid fever was caused by *Salmonella typhi*.

Koch's postulates can be modified somewhat to include the ability of a toxin, such as a SAg (or tetanus and diphtheria toxins in the cases of tetanus and diphtheria, respectively), to be associated with a disease. For example, we know that *S. aureus* is associated with menstrual, tampon-associated TSS (and additionally post-influenza or other forms of TSS) [18, 56]. However, one third of women of menstrual age have *S. aureus* vaginally and one-third of all persons have the microorganism in the anterior nares [7]. It turns out that 100% of women with menstrual TSS, who have vaginal *S. aureus*, have the microorganism producing the SAg TSST-1 [56]. For persons with post-influenza TSS, >90% have TSST-1 producing *S. aureus* in the lungs, and up to 10% have *S. aureus* that produce the SAgs SEs B or C [18]. These three major SAgs are not present in the lungs of otherwise healthy persons. All three of these major SAgs can be used to cause TSS in appropriate rabbit animal models [23, 24]. Also, these three SAgs, TSST-1, SEB, and SEC can be produced in biofilms, as might be present in menstrual, tampon-associated or post-influenza TSS, in amounts as high as 10-20 mg/ml [11]. In a human trial with use of a SAg to attempt to treat cancer patients with SAg therapy, a dose of SAg in the range of 100 ng/ human was sufficient to cause TSS symptoms [57].

In the remainder of this mini-review, we will present evidence for the ability of SAgs, first, and then *S. aureus*, to cause cases of DM2. We will begin with the premise that DM2 patients are nearly 100% colonized on the skin and anterior nares with *S. aureus* that produce the major SAgs associated with TSS [4]. The obvious question again is: Why do these persons not develop TSS? In answer to this question, we know that the skin and anterior nares are not optimal sites for production of TSS SAgs, primarily due to sub-optimal temperatures and acidic pH. It has previously been shown that the conditions which favor high-level *S. aureus* SAg production are [52]:

1. Temperatures of 37-40 °C.
2. The presence of proteins.
3. The presence of oxygen.
4. pHs of 6.5-8.5.

Additionally, we have shown that only ~1% of SAg is likely to penetrate the surface barrier [10, 27].

The first of the four Koch's postulates states that a microbe, in this instance *S. aureus*, and its SAg should be associated with a disease state and less commonly isolated from healthy persons. The enormous difference in *S. aureus* percentages (100% on skin and anterior nares of DM2 persons versus 17% on skin and 40% in the anterior nares of healthy persons) counts up to 10^{13} on skin and nasal mucosa of DM2 patients versus approximately 100 on the skin and nasal mucosa of healthy persons fulfills the first of Koch's postulates for establishing the microbial cause of DM2 disease. In a small study, we showed that DM2 patients are consistently colonized or infected with *S. aureus* strains that produce the SAgs TSST-1, SEB, or SEC [4]. This compares to only 17% of healthy persons colonized on the skin with *S. aureus* and 40% in the anterior nares and 5% producing the same three SAgs [7-9, 56].

The second of Koch's postulates states that the microbe and SAg must be isolated in pure culture from patients. This is easily done in DM2 patients, with isolation of *S. aureus* from skin and mucosal surfaces. Additionally, we showed that *S. aureus* from DM2 patient skin produce at least one of the major SAgs, namely TSST-1, SEB, and SEC [4]. These SAgs are produced in the highest concentrations of all known SAg proteins, with production levels *in vitro* in biofilms as high as 10-20 mg/ml [11]. The total amounts of these SAgs on the skin of DM2 patients are unknown. However, we have shown significant production of TSST-1 on the vaginal mucosa of women [19], and all three proteins on the skin of atopic dermatitis patients [58].

The third and fourth of Koch's postulates include establishment of the disease in a model system and re-isolation of the same bacteria (SAgs) from the model. If such a model could be established with use of a TSS-associated SAg, this would allow completion of the final two of Koch's postulates for *S. aureus* as causes of DM2.

Previous research has shown that SAgs stimulate keratinocytes and adipocytes through CD40 and gp130 to cause harmful inflammation [47-49]. We have also shown that SAgs are highly toxic to humans and rabbits, but mice are highly resistant [59]. Interestingly, mouse adipocytes function similar to human preadipocytes, whereas mouse preadipocytes function similar to human adipocytes [51]. It has also been shown that patients with DM2 have gut-associated LPS in their circulations [60]. LPS itself is pro-inflammatory, but LPS synergizes up to 10^6-fold with SAgs [61]. Thus, the combination of gut-derived LPS in the presence of even small amounts of SAgs would be highly pro-inflammatory, a state that is associated with DM2.

Humans and rabbits share the presence of LPS-producing Gram-negative bacteria in their guts [59, 61]. Not all LPS is toxic to humans and rabbits, but *Enterobacteriaceae* LPS (as seen in humans) and *Pasteurellaceae* LPS (as seen in rabbits) are particularly toxic and synergize strongly with SAgs. Thus, we thought the most straightforward way to pursue setting up an animal model was to use outbred New Zealand white rabbits and subcutaneously-implanted miniosmotic pumps filled with TSST-1 or SEB [4, 23, 24]. These pumps deliver a constant amount of TSST-1 or SEB to the circulation of the animals over a two-week time period. A side note: SAgs cause significant delays in wound healing as shown in both humans and rabbits [62]; this finding is also observed in DM humans with diabetic foot ulcers which become infected with *S. aureus* producing SAgs [63].

In a first series of studies, it was shown that *in vitro*-cultured human adipocytes respond to TSST-1 and SEB with production of harmful cytokines and adipokines with synergistic production in the presence of Gram-negative *Enterobacteriaceae* LPS [51]. Primary human preadipocytes were immortalized by the reverse transcriptase component of telomerase (TERT) and the E6/E7 genes of human papillomavirus. The immortal cells were demonstrated to have all of the measurable properties of non-immortalized pre-adipocytes and could easily be differentiated into mature, functional adipocytes [51]. Differentiated adipocytes exposed to staphylococcal SAgs produced high levels of cytokines IL-6 and IL-8. Cytokine production was increased by co-incubation of adipocytes with

SAgs and LPS together. As a negative control, the staphylococcal cytotoxin, α-toxin alone, was cytotoxic to adipocytes at high concentrations, but, at sub-cytotoxic doses, did not stimulate production of IL-6 and IL-8. The data indicated that the staphylococcal SAgs TSST-1 and SEB alone and in combination with toxic bacterial LPS stimulate adipocytes to produce cytokines and thus may contribute to the pro-inflammatory response found in the systemic inflammation that is associated with the development and persistence of DM2, and additionally in diabetic foot ulcers [51]. As noted above, human adipocytes likely have at least two receptors that are engaged by SAgs (CD40 and gp130) with synergism with LPS acting on TLR4.

In an important follow-up study, it was shown that rabbits, which are exposed chronically to TSST-1, experience elevated blood glucose levels, systemic inflammation, and elevated levels of LPS in their bloodstreams, and insulin-resistance, all of which are common findings in DM2 [4]. Additionally, such DM2-associated findings were also seen through effects of TSST-1 on isolated rabbit adipocytes from treated animals [4]. Collectively, these findings show that chronic exposure to *S. aureus* SAgs leads to the development of DM2 in rabbits. The study also showed that the continuous low-level exposure to TSST-1 does not lead to TSS, even though lymphocyte proliferation and downstream-proinflammation is occurring.

In discussions with our clinical colleagues, they state that persons with significant *S. aureus* infections develop insulin-resistance and elevated blood glucose, thus taking on the symptoms of DM2. As noted above 100% of DM2 patients and nearly all obese persons are chronically infected or colonized with *S. aureus.*

It was thus evaluated whether or not rabbits with semi-chronic, serious *S. aureus* infections develop insulin-resistance in adipocytes as a result of the infections. The infection system was infective endocarditis for seven days with use of a typical USA200 (CC30) *S. aureus* which produces TSST-1 [53]. The aortic valves of the animals were damaged with the use of sterile hard-plastic catheters abutting the valves for two hours. The catheters were then removed, and the TSST-1$^+$ *S. aureus* were then injected intravenously; the dose of *S. aureus* was adjusted such that the animal developed serious infective endocarditis (as measured by the presence of large vegetations at the end of 7 days) but did not succumb to their infections. At the end of the experiment, adipocytes from animals with infective endocarditis showed insulin-resistance, whereas adipocytes from control, non-infective endocarditis animals did not show insulin-resistance. The study did not evaluate rabbits for longer than seven days; so it did not assess damage to other organs or effects on wound healing. However, it is clear that SAg exposure, for example exposure to TSST-1 in menstrual TSS, leads to kidney damage [20, 22] and failure of wounds to heal [45], as is seen with diabetic foot ulcers [63].

Collectively, the three sets of experiments discussed above show that intravenous TSS *S. aureus* and subcutaneous SAgs have the ability to produce DM2 in rabbits, thus fulfilling the third of Koch's postulates.

The final Koch's postulate states that the same microbes (and SAgs) need to be re-isolated from the experimental animals, as has been done.

Thus, it has been shown that *S. aureus* and its highly-produced SAgs have the ability to cause DM2. Since humans are easily chronically colonized or infected with large numbers of TSS *S. aureus* on skin and mucosal surfaces, particularly in association with obesity and DM2, it becomes easy to see how *S. aureus* could be a cause of the condition. Figure 1 summarizes a proposed pathway for *S. aureus* on the skin to cause the symptoms of DM2 and cause these symptoms to persist with chronic infection or colonization.

If pathogenic Gram-positive cocci can cause DM2, then it is possible that the use of agents to reduce skin and mucosal strains may help reverse the course of the condition. It has become commonplace to assume that *S. aureus* are only opportunistic pathogens. This thinking, in absence of antibiotic treatment, is possibly contributory to the high infection and colonization rate in humans by this organism. This may also contribute to humans falsely assuming that *S. aureus* is not a cause of DM2.

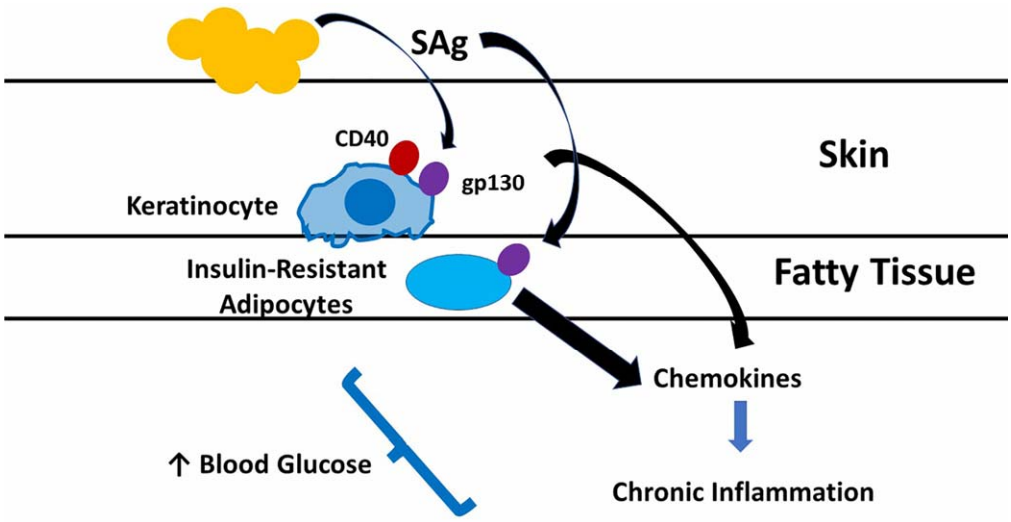

Figure 1. Proposed pathway for development of diabetes mellitus 2 as induced by chronic exposure to *Staphylococcus aureus* and more specifically its superantigens on normal skin. *S. aureus* colonizes the skin of large numbers of obese individuals, with numbers approaching 100% in pre-diabetic states. These *S. aureus*, both methicillin-resistant and methicillin-sensitive, produce superantigens in high concentrations. The highly pro-inflammatory superantigens penetrate into the skin, which then serves as a reservoir to transport small amounts of superantigens across the skin barrier. The receptors for superantigens on keratinocytes include the immune co-stimulatory molecule CD40 and gp130. The effect of the receptor interactions is chemokine production with weakening of the skin barrier. Superantigens that transit the skin bind to at least gp130 on adipocytes, cause adipokine production, and cause both insulin-resistance and elevated blood glucose, the major defining properties of diabetes mellitus 2. Not shown: Superantigens produced by *S. aureus* strains also prevent and delay wound healing. Wound healing is difficult to achieve in diabetic foot ulcers. These ulcers are very often infected with superantigen-producing *S. aureus.*

CONFLICT OF INTEREST STATEMENT

Both PMS and DYML contributed equally to the preparation of the manuscript. They declare no conflicts of interest.

REFERENCES

1. Centers for Disease Control and Prevention: https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html 2023.
2. Ley, R. E., Turnbaugh, P. J., Klein, S. and Gordon, J. I. 2006, Nature, 444, 1022.
3. Walters, W. A., Xu, Z. and Knight, R. 2014, FEBS Lett., 588, 4223.
4. Vu, B. G., Stach, C. S., Kulhankova, K., Salgado-Pabon, W., Klingelhutz, A. J. and Schlievert, P. M. 2015, mBio, 6, e02554.
5. Olsen, K., Danielsen, K., Wilsgaard, T., Sangvik, M., Sollid, J. U., Thune, I., Eggen, A. E., Simonsen, G. S. and Furberg, A. S. 2013, PLoS One, 8, e63716.
6. Otto M. 2010, Expert Rev. Dermatol., 5, 183.
7. Schlievert, P. M., Osterholm, M. T., Kelly, J. A. and Nishimura, R. D. 1982, Ann. Intern. Med., 96, 937.
8. Spaulding, A. R., Salgado-Pabón, W., Kohler, P. L., Horswill, A. R., Leung, D. Y. and Schlievert, P. M. 2013, Clin. Microbiol. Rev., 26, 422.
9. McCormick, J. K., Yarwood, J. M. and Schlievert, P. M. 2001, Annu. Rev. Microbiol., 55, 77.
10. Schlievert, P. M., Jablonski, L. M., Roggiani, M., Sadler, I., Callantine, S., Mitchell, D. T., Ohlendorf, D. H. and Bohach, G. A. 2000, Infect. Immun., 68, 3630.
11. Schlievert, P. M. and Peterson, M. L. 2012, PLoS One, 7, e40350.
12. Schlievert, P. M. and Davis, C. C. 2020, Clin. Microbiol. Rev., 33, e00032-19.

13. Schlievert, P. M., Roller, R. J., Kilgore, S. H., Villarreal, M., Klingelhutz, A. J. and Leung, D. Y. M. 2012, mSphere, 6, e00608-21.
14. Messingham, K. N., Cahill, M. P., Kilgore, S. H., Munjal, A., Schlievert, P. M. and Fairley, J. A. 2022, J. Invest. Dermatol., 142, 1032.
15. Parsonnet, J., Goering, R. V., Hansmann, M. A., Jones, M. B., Ohtagaki, K., Davis, C. C. and Totsuka, K. 2008, J. Clin. Microbiol., 46, 2731.
16. Parsonnet, J., Hansmann, M. A., Delaney, M. L., Modern, P. A., Dubois, A. M., Wieland-Alter, W., Wissemann, K. W., Wild, J. E., Jones, M. B., Seymour, J. L. and Onderdonk, A. B. 2005, J. Clin. Microbiol., 43, 4628.
17. Osterholm, M. T., Davis, J. P., Gibson, R. W., Mandel, J. S., Wintermeyer, L. A., Helms, C. M., Forfang, J. C., Rondeau, J. and Vergeront, J. M. 1982, J. Infect. Dis., 145, 431.
18. MacDonald, K. L., Osterholm, M. T., Hedberg, C. W., Schrock, C. G., Peterson, G. F., Jentzen, J. M., Leonard, S. A. and Schlievert, P. M. 1987, JAMA, 257, 1053.
19. Schlievert, P. M., Nemeth, K. A., Davis, C. C., Peterson, M. L. and Jones, B. E. 2010, Clin. Vaccine Immunol., 17, 722.
20. Shands, K. N., Schmid, G. P., Dan, B. B., Blum, D., Guidotti, R. J., Hargrett, N. T., Anderson, R. L., Hill, D. L., Broome, C. V., Band, J. D. and Fraser, D. W. 1980, N. Engl. J. Med., 303, 1436.
21. Schlievert, P. M., Case, L. C., Strandberg, K. L., Tripp, T. J., Lin, Y. C. and Peterson, M. L. 2007, J. Clin. Microbiol., 45, 2704.
22. Davis, J. P., Chesney, P. J., Wand, P. J. and LaVenture, M. 1980, N. Engl. J. Med., 303, 1429.
23. Lee, P. K., Deringer, J. R., Kreiswirth, B. N., Novick, R. P. and Schlievert, P. M. 1991, Infect. Immun., 59, 879.
24. Lee, P. K. and Schlievert, P. M. 1989, J. Clin. Microbiol., 27, 1890.
25. Schlievert, P. M., Bettin, K. M. and Watson, D. W. 1977, Infect. Immun., 16, 673.
26. Johnson, L. P. and Schlievert, P. M. 1984, Mol. Gen. Genet., 194, 52.
27. Davis, C. C., Kremer, M. J., Schlievert, P. M. and Squier, C. A. 2003, J. Obstet. Gynecol., 189, 1785.
28. Squier, C. A., Mantz, M. J., Schlievert, P. M. and Davis, C. C. 2008, J. Pharm. Sci., 97, 9.
29. Poindexter, N. J. and Schlievert, P. M. 1985, J. Infect. Dis., 151, 65.
30. Schlievert, P. M. 1983, J. Infect. Dis., 147, 391.
31. Schwab, J. H., Brown, R. R., Anderle, S. K. and Schlievert, P. M. 1993, J. Immunol., 150, 4151.
32. Schiffenbauer, J., Johnson, H. M., Butfiloski, E. J., Wegrzyn, L. and Soos, J. M. 1993, Proc. Natl. Acad. Sci. USA, 90, 8543.
33. Soos, J. M., Hobeika, A. C., Butfiloski, E. J., Schiffenbauer, J. and Johnson, H. M. 1995, Proc. Natl. Acad. Sci. USA, 92, 6082.
34. Leung, D. Y. M., Travers, J. B., Giorno, R., Norris, D. A., Skinner, R., Aelion, J., Kazemi, L. V., Kim, M. H., Trumble, A. E., Kotb, M. and Schlievert, P. M. 1995, J. Clin. Invest., 96, 2106.
35. Schlievert, P. M., Bettin, K. M. and Watson, D. W. 1979, J. Infect. Dis., 140, 676.
36. Kotzin, B. L., Leung, D. Y. M., Kappler, J. and Marrack, P. 1993, Adv. Immunol., 54, 99.
37. Li, H., Llera, A., Tsuchiya. D., Leder. L., Ysern, X., Schlievert, P. M., Karjalainen, K. and Mariuzza, R. A. 1998, Immunity, 9, 807.
38. Li, Y., Li, H., Dimasi, N., McCormick, J. K., Martin, R., Schuck, P., Schlievert, P. M. and Mariuzza, R. A. 2001, Immunity, 14, 93.
39. Li, H., Llera, A. and Mariuzza, R. A. 1998, Immunol. Rev., 163, 177.
40. Leder, L., Llera, A., Lavoie, P. M., Lebedeva, M. I., Li. H., Sekaly, R. P., Bohach, G. A., Gahr, P. J., Schlievert, P. M., Karjalainen, K. and Mariuzza, R. A. 1998, J. Exp. Med. 187, 823.
41. McCormick, J. K., Tripp, T. J., Llera, A. S., Sundberg, E. J., Dinges, M. M., Mariuzza, R. A. and Schlievert, P. M. 2003, J. Immunol., 171, 1385.

42. Fields, B. A., Malchiodi, E. L., Li, H., Ysern, X., Stauffacher, C. V., Schlievert, P. M., Karjalainen, K. and Mariuzza, R. A. 1996, Nature, 384, 188.
43. Sundberg, E. J., Li, H., Llera, A. S., McCormick, J. K., Tormo, J., Schlievert, P. M., Karjalainen, K. and Mariuzza, R. A. 2002, Structure, 10, 687.
44. Choi, Y., Lafferty. J. A., Clements, J. R., Todd, J. K., Gelfand, E. W., Kappler, J., Marrack, P. and Kotzin, B. L. 1990, J. Exp. Med., 172, 981.
45. Jacob, H. S., Vercellotti, G. M., Leung, D. Y. M. and Schlievert, P. M. 2020, Medicine (Baltimore), 99, e19746.
46. Schlievert, P. M., Cahill, M. P., Hostager, B. S., Brosnahan, A. J., Klingelhutz, A. J., Gourronc, F. A., Bishop, G. A. and Leung, D. Y. M. 2019, mBio, 10, e00214-19.
47. Schlievert, P. M., Gourronc, F. A., Leung, D. Y. M. and Klingelhutz, A. J. 2020. mSphere, 5, e00803-20.
48. Moran, M. C., Brewer, M. G., Schlievert, P. M. and Beck, L. A. 2023, Microbiol. Spectr., 11, e0168423.
49. Banke, E., Rodstrom, K., Ekelund, M., Dalla-Riva, J., Lagerstedt, J. O., Nilsson, S., Degerman, E., Lindkvist-Petersson, K. and Nilson, B. 2014, Metabolism, 63, 831.
50. Brosnahan, A. J. and Schlievert, P. M. 2011, FEBS J., 278, 4649.
51. Vu, B. G., Gourronc, F. A., Bernlohr, D. A., Schlievert, P. M. and Klingelhutz, A. J. 2013, PLoS One, 8, e77988.
52. Schlievert, P. M. and Blomster, D. A. 1983, J. Infect. Dis., 147, 236.
53. Pragman, A. A., Yarwood, J. M., Tripp, T. J. and Schlievert, P. M. 2004, J. Bacteriol., 186, 2430.
54. Yarwood, J. M., McCormick, J. K. and Schlievert, P. M. 2001, J. Bacteriol., 183, 1113.
55. Yarwood, J. M. and Schlievert, P. M. 2000, J. Clin. Microbiol., 38, 1797.
56. Schlievert, P. M., Shands, K. N., Dan, B. B., Schmid, G. P. and Nishimura, R. D. 1981, J. Infect. Dis., 143, 509.
57. Dohlsten, M., Lando, P. A., Bjork, P., Abrahmsen, L., Ohlsson, L., Lind, P. and Kalland, T. 1995, Cancer Immunol. Immunother., 41, 162.
58. Simpson, E. L., Schlievert, P. M., Yoshida, T., Lussier, S., Boguniewicz, M., Hata, T., Fuxench, Z., De Benedetto, A., Ong, P. Y., Ko, J., Calatroni, A., Rudman-Spurgel, A. K., Plaut, M., Quataert, S. A., Kilgore, S. H., Peterson, L., Gill, A. L., David, G., Mosmann, T., Gill, S. R. Leung, D. Y. M. and Beck, L. A 2023, J. Allergy Clin. Immunol., 152, 1179.
59. Salgado-Pabón, W. and Schlievert, P. M. 2014, Nat. Rev. Microbiol., 12, 585.
60. Piya, M. K., McTernan, P. G. and Kumar, S. 2013, J. Endocrinol., 216, T1.
61. Schlievert, P. M. 1982, Infect. Immun., 36, 123.
62. Merriman, J. A., Klingelhutz, A. J., Diekema, D. J., Leung, D. Y. M. and Schlievert, P. M. 2015, Biochemistry, 54, 4855.
63. Vu, B. G., Stach, C. S., Salgado-Pabón, W., Diekema, D. J., Gardner, S. E. and Schlievert, P. M. 2014, J. Infect. Dis., 210, 1920.