REVIEW

Superantigens and their Association with Dermatological Inflammatory Diseases: Facts and Hypotheses

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Superantigens have been suggested to play an important role in the pathogenesis of several inflammatory skin diseases as well as systemic diseases such as atopic dermatitis, psoriasis, vasculitis, T-cell lymphoma and autoimmune diseases. Infections often precede the onset and relapse of these diseases, and antibiotic treatment with or without additional glucocorticosteroids and immunoglobulins is occasionally successful. Superantigens are microbial proteins that are able to stimulate up to 20% of the naïve T-cell population in a non-specific way. They are produced by Gram-positive and -negative bacteria as well as by viruses, parasites and yeasts. The importance of the pathogenic role of superantigens is determined by the potency to induce inflammation by extensive cytokine release after T-cell stimulation and/or T-cell-mediated cytotoxicity and, thereby, tissue damage. Furthermore, superantigens may be able to induce auto-immune processes by stimulation of autoreactive T-cells as well as autoantibody production by stimulation of B-cells. Among the diseases associated with superantigens, atopic dermatitis, guttate and chronic plaque psoriasis, as well as Kawasaki disease, are by far the best-characterized. Nevertheless, conflicting results have been obtained and formal proof of a pathogenic role of superantigens in these diseases is still lacking. The aim of this review is to summarize the data on superantigens in terms of their distribution in microorganisms, their interactions with the adaptive immune system and their contribution to skin pathology. *Key words: superantigens; skin disease; V*β *repertoire.*

Superantigens (SAgs) are potent virulence factors which stimulate several immunological processes and play a role in the maintenance of inflammation. The term "super-antigen" was coined in 1989 by White et al. (1) to describe a murine self-antigen which is not presented via the conventional pathway. This review considers the role of SAgs in clinical conditions. It will be necessary to give some basic information on the structure and effects of these molecules in order to illuminate their potential impact on the pathogenesis of dermatological inflammatory diseases.

MECHANISMS OF ACTION OF SUPERANTIGENS

Common and distinct features of different SAgs

A SAg binds as an unprocessed protein to non-polymorphic regions of major histocompatibility complex (MHC) class II molecules on the surface of antigen-presenting cells, which are regions different from the antigen binding groove (2). SAgs can interact with a large number of T-cells, which all share particular sequences within the variable region of the β-chain (Vβ) of the T-cell receptor (TCR) and, thereby, stimulate up to 20% of the naïve T-cell population. Although SAgs are mitogenic for T-cells, the term "mitogen" should not be used as a synonym. "Mitogens" induce polyclonal T-cell stimulation by using pathways different to those of SAgs; for example they act independently to Vβ-components of the TCR (3).

Most SAgs are of microbial origin (Table I). In order to understand SAg effects on the immune system, several investigations have concentrated on the characterization of their molecular structure and attempted to relate this to their function. Despite considerable differences in the primary sequence of SAgs there are remarkable similarities between their overall folded structures, suggesting a common ancestral origin. For example, staphylococcal enterotoxin (SE) B and toxic shock syndrome toxin 1 (TSST-1) show only 20–30% identity and yet have a similar conformational structure, which is of consequence for their binding to receptor molecules (4, 5).

MHC dependence and human leucocyte antigen preference of SAgs

MHC class II molecules serve as SAg receptors. SAgs are bifunctional molecules: the amino-terminal site has a high affinity for binding to the α-chain of the MHC class II molecule, whereas the carboxy-terminal site is responsible for a strong binding to the TCR. In cases of direct SAg–T-cell interactions of which, for example, SEC and SEE are capable, higher doses of SAgs are needed to activate T-cells independently of MHC (6). The fact that the MHC-independent pathway seems not to lead to apoptosis indicates that MHC involvement and MHC independence induce different immune reactions. In addition to differences in MHC restriction, differences in the binding affinity of SAgs to MHC class II molecules are also affected by allelic variations in these molecules as well as by cellular factors that profoundly modulate SAg responses. The majority of staphylococcal SAgs interact better with human leukocyte antigen (HLA)-DR than HLA-DQ or HLA-DP, and several streptococcal SAgs prefer HLA-DQ (7, 8). A given SAg has diverse effects in different individuals with distinct MHC class

Table I. *Microorganisms and their SAgs*

Gram-positive bacteria	Gram-negative bacteria	Viruses	Parasites	Fungi/yeasts
Toxic shock syndrome toxin-1	*Yersinia pseudotuberculosis*-derived mitogen types A and B	Mouse mammary tumour virus 1, 3, 6, 7, 9, 43	*Toxoplasma gondii* (superantigen in mice)	*Candida albicans* (some evidence)
Staphylococcal enterotoxin A–E; G–I	*Y. enterocolitica*	Mouse mammary tumour virus strain SW	*Heligmosomoides polygyrus*	*Cryptococcus neoformans*
Exfoliative toxin	*Mycoplasma arthritidis* mitogen	Rabies virus-associated superantigen	*Theileria annulata*	(some evidence)
Streptococcal mitogenic exotoxin Z	Mitogenic factors from group G streptococci	Cytomegalovirus-associated superantigen	Plasmodium (murine malaria)	
LMWS	*Pseudomonas aeruginosa*	HIV-1 gp 120 superantigen		
17 kD mitogen epsilon	*Clostridium perfringens*	HIV-1 Nef protein		
S. pyogenes mitogen-2	(some evidence)	Epstein–Barr virus		
S. pyogenes cytoplasmic membrane-associated protein (CAP)	*Mycobacteria tuberculosis* (some evidence)	(some evidence)		
S. pyogenes secretion-type CAP				
S. pyogenes exotoxin A–J				
Streptococcal superantigen A				
Streptococcal M protein 5, 6, 18, 19, 24				
Borrelia burgdorferi (some evidence)				

II haplotypes (9). It has been shown that expression of certain MHC class II haplotypes, which bind specific SAgs, is associated with the development of severe manifestations and toxic shock compared to individuals expressing haplotypes with lower affinity for the same SAgs (10).

Vβ preference of SAgs

There are ≈30 Vβ phenotypes in humans. Depending on the particular host, a given type of Vβ sequence may be expressed frequently or not at all on the T-cells. Individuals who have relatively higher frequencies of T-cells expressing Vβ elements that can interact with a particular SAg will be most likely to develop stronger responses to this SAg than individuals who have a lower frequency of these T-cells in their repertoire (11). Specific patterns of Vβ expansion or Vβ depletion serve as fingerprints for a particular SAg. Although, for example, SEA and SEE show >90% homology they have distinct patterns of human Vβ specificity.

Influences of other factors on SAg effects

The biological effects of SAgs also may be potentiated by environmental factors, for example other bacterial components, as has been shown for streptolysin and *Streptococcus pyogenes* exotoxin A. Simultaneous bacterial and viral infections have been documented to potentiate SAg effects, for example Varizella zoster and staphylococcal infections (12).

HOST EFFECTS OF SUPERANTIGENS

General effects

The toxicity of bacterial SAgs is mediated by their potent T-cell-stimulating activity, which leads to abnormally high levels of cytokines, for example tumour necrosis factor (TNF), interleukins (IL)-1, -2 and -6 and interferon (IFN)-ψ,

as well as nuclear factor χ B binding proteins (13). SAg reactions with T-cells may have a number of outcomes, leading to different clinical symptoms. They may induce anergy, inflammation, cytotoxicity, deletion of T-cells and autoimmunity (11, 14, 15).

SAgs and autoimmunity

SAgs seem to be involved in the development of autoimmune diseases by different mechanisms. T-cell clones that manifest cross-reactivity towards endogenous host and microbial epitopes, and that normally exist either anergized or in very low numbers in the blood of healthy individuals, may be amplified according to their Vβ type, and may migrate to the target tissue containing the autoantigen, a mechanism believed to play an important role for streptococcal M-proteins in the pathogenesis of rheumatic fever (16, 17). Certain individuals with autoimmune diseases show an increase in T-cells bearing selected Vβ elements in affected organs or peripheral blood (18).

SAgs have been shown to stimulate not only selective T-cell expansion but also autoantibody production by bridging the MHC class II molecule of B-cells with the TCR on T-cells (19). Whether deletion or autoimmunity occurs, however, will be dependent on the dose and persistence of the SAg in the host and is likely to be affected by the magnitude of the cytokine response (20).

SAgs and the conventional pathway of antigenic stimulation

TSST-1 is a SAg and can also be immunogenic, leading to the production of neutralizing anti-TSST-1-IgG antibodies (21). In patients with atopic dermatitis anti-toxin-IgE antibodies are detectable, which indicates: (i) that SAgs play a role in the pathogenesis of atopic dermatitis; and (ii) that they are also processed as antigens (22). It has been shown that SAgs stimulate B-cells to increase production of

allergen-specific IgE, e.g. against pollen. Furthermore, it was demonstrated that TSST-1 induces the expression of B7.2 on B-cells, a molecule known to be involved in Th 2 responses and IgE regulation, thereby aggravating primary allergic inflammation (23).

B-cell SAgs

Recently, bacterial proteins with unconventional immunoglobulin-binding capacities that parallel the properties of known T-cell SAgs have been described (24). The best characterized are the cell wall protein of *Staphylococcus aureus* protein A, the glycoprotein 120 envelope protein of certain isolates of HIV 1, an endogenous human gut-associated sialoprotein termed protein Fv and protein L from *Peptostreptococcus magnus*. SAg activity is defined by the fragment of antigen binding (Fab). The site at which *S. aureus* protein A binds Fab enables interactions with most immunoglobulins with heavy chains from the human variable element H (VH) 3 families, but not with immunoglobulins from other VH families. B-cell SAgs are thought to be involved in the pathogenesis of certain rheumatic and inflammatory diseases such as rheumatoid arthritis and lupus erythematosus via production of autoantibodies that arise preferentially (>85% and 98%, respectively) from the VH3 family (24).

SUPERANTIGENS AND THEIR RELEVANCE IN DERMATOLOGICAL DISEASES

Multiple risk factors are involved in susceptibility to certain inflammatory skin diseases. Inherited determinants are known to increase the risk but mostly are insufficient to induce the disease. Among the environmental factors that trigger the outbreak and relapse of inflammatory diseases, bacteria, especially bacterial SAgs, are thought to play an important role (Table II).

Psoriasis

T-lymphocyte activation and infiltration are believed to play a crucial role in the initiation and maintenance of psoriasis (25–27). Guttate psoriasis rather than chronic plaque psoriasis has been shown to be triggered, like a T-cell-mediated autoimmune disease, by bacterial SAgs. The association between guttate psoriasis and a preceding streptococcal infection was recognized as early as the 1960s (28).

Boehncke et al. (29) demonstrated in 1997 that intradermal injection of SAgs induced psoriasis in normal appearing human skin of psoriasis patients grafted onto severe combined immune deficiency (SCID)-hu mice. Additionally, when SAg-stimulated peripheral blood mononuclear cells (PBMC) of patients were administered intraperitonally to the graft-bearing mice homing of T-cells to the graft was observed (29). The fact that SAgs may upregulate the expression of cutaneous lymphoid antigen (CLA), the skin homing receptor on T-cells, is a possible explanation for the observation that pharyngeal infection with toxin-producing streptococci induces stimulation of Vβ2+ T-cells bearing CLA in local lymph nodes. This is followed by localization of these Vβ2+ / CLA+ T-cells to the skin, where psoriasis develops (25, 26).

Boehncke et al. (30) also reported recently that SAgs induce a psoriasiform dermatitis in psoriasis patients but not in healthy individuals, implying that the genetic status of the individual is important. They also observed a more severe form of atopic dermatitis and psoriasis in those patients colonized with SAg-producing *S. aureus* (27).

In vitro, T-cell clones from psoriatic skin lesions stimulate keratinocyte proliferation (31). Enrichment of particular Vβ element-bearing T-cells (Vβ2+) and a moderate increase in Vβ 5.1+ T-lymphocytes in the lesional and perilesional skin of psoriasis patients also indicated the involvement of bacterial SAgs (26, 32). Valdimarsson et al. (33) proposed that T-lymphocytes specific for streptococcal M-proteins cross-react with psoriatic keratins, thereby inducing and maintaining psoriasis (Fig. 1).

Another completely different approach to the investigation of T-cell-derived skin disease and autoimmunity was taken by Hales & Camp (34) in 1998. They attempted to define T-cell epitopes in inflammatory skin diseases, and psoriasis in particular, by stimulating PBMC of healthy donors and patients with aqueous extracts of normal facial and plantar stratum corneum. They found a potent stimulation of PBMC of both healthy donors and patients with autologous and allogenic extracts. The response was of T-cell nature and the activity was inhibited by an anti-HLA-DR monoclonal antibody, indicating the presence of antigen or SAg. This may be endogenously or exogenously derived and is normally sequestered from the cellular immune system in the epidermis (34).

The above-mentioned immunological investigations sup-

Table II. *Skin diseases associated with superantigens**

Strong association	Weak association
Toxic shock syndrome	Atopic dermatitis
Staphylococcal scalded skin syndrome	Psoriasis
Streptococcal toxic shock syndrome	Palmoplantar pustulosis
Scarlet fever	Cutaneous T-cell lymphoma
Necrotizing fasciitis	Kawasaki disease
Recalcitrant erythematous desquamating disorder	Wegener's granulomatosis
Toxin-mediated erythema	Microscopic polyangiitis
	Giant cell arteritis
	Takayasu's arteriitis
	Inflammatory acne?

*From refs. 48, 57, modified

Accumulation of superantigens on the skin	Streptococcal pharyngitis

Left column flowchart:

Activation of circulating T-cells by superantigens according to their V_β elements

↓

Selective expansion of particular V_β-specific T-cell subsets

↓

CLA-expression on T-cells

↓

Localization to the skin

↓

Additional activation of monocytes and macrophages by superantigens, release of cytokines that induce recruitment of inflammatory cells

↓

Secretion of TH1 cytokines

↓

HLA-DR-expression on keratinocytes and their proliferation

↓

Immunohistologically characteristic psoriasis lesion (guttate psoriasis)

Right column flowchart:

Persistence of superantigens in the skin

↓

Interaction with accessory cells in dermis and epidermis (Langerhans cells and keratinocytes) and cytokine release

↓

Influx of inflammatory cells and recruitment of V_β-specific (auto-) reactive T-cells

↓

Expression and presentation of epidermal antigens (type I keratins)

↓

Local recognition of specific antigens by superantigen-specific T-cells

↓

Cytokine release

↓

Proliferation of keratinocytes

↓

Immunohistologically characteristic psoriasis lesion
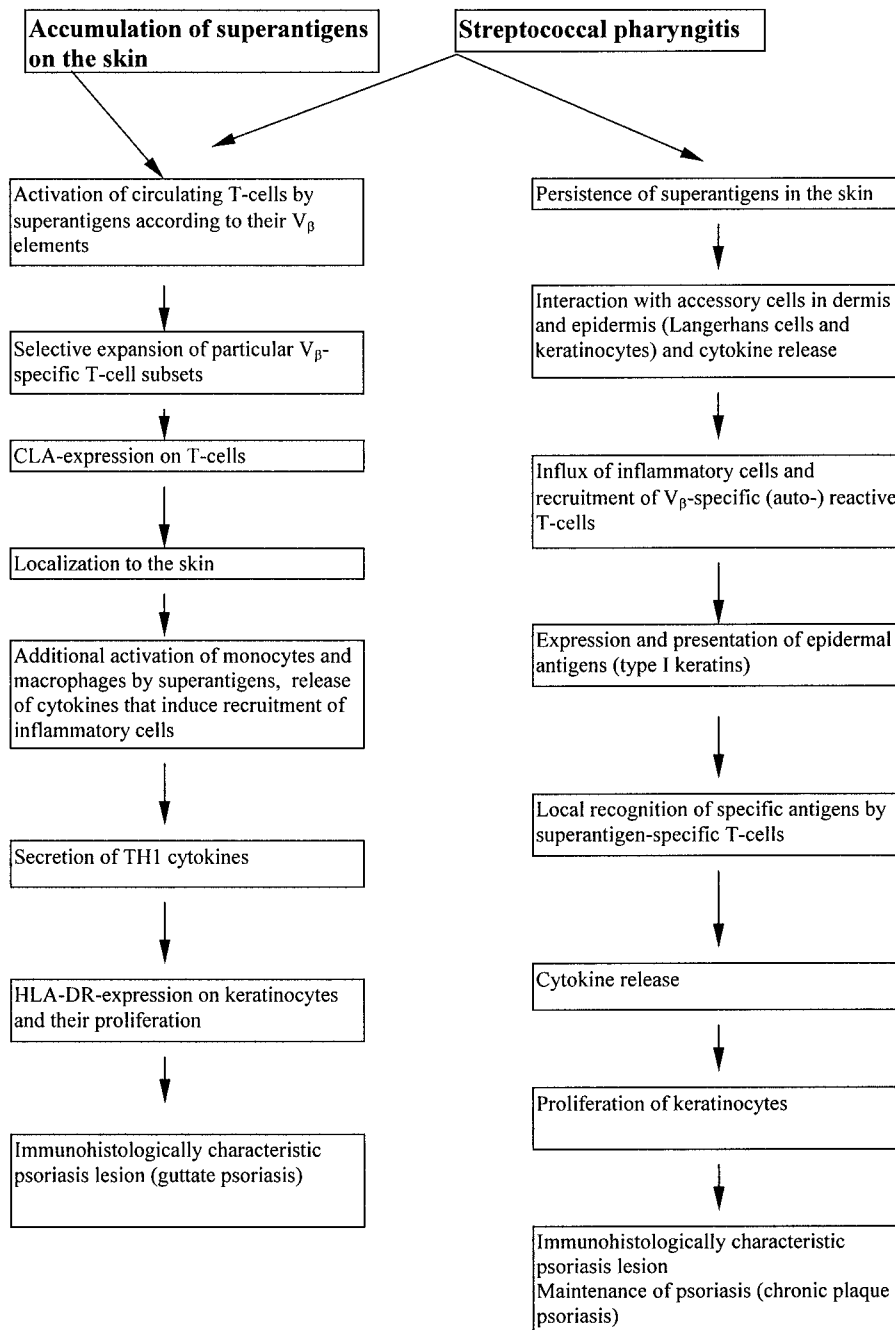Maintenance of psoriasis (chronic plaque psoriasis)

Fig. 1. Superantigens and their role in the pathogenesis of psoriasis: a model.

port the hypothesis that SAgs may induce the pathology of psoriasis. However, Sayama et al. (35) failed to detect SAg-producing *S. aureus* in lesional skin, non-lesional skin and throat sites of psoriasis patients in significant percentages. Therefore, they concluded that SAgs are not essential to maintain psoriasis, although they may be exacerbating factors or triggers for the disease.

Atopic dermatitis

A number of studies have found a relatively high prevalence of colonization (64–100%) with SAg-producing *S. aureus* strains in atopic dermatitis (AD) patients (36, 37). An association between SAg-producing *S. aureus* and the

aetiology of AD has been suggested (37–39). Strange et al. (40) showed that SEB applied to intact skin of both normal subjects and patients with AD induced an inflammatory reaction. In several patients with AD, toxin-specific IgE could be detected, and colonization with SAg-producing *S. aureus* was proposed also to be a stimulant for toxin-specific IgE production in *in vitro* experiments (22). It was demonstrated that the degree of disease severity correlated with a higher level of SEA/SEB-specific antibodies than with total serum IgE levels. Density of colonization with SAg-producing *S. aureus* strains was higher in the anti-SAg-IgE group (41). Also, it has been shown that SAgs stimulate B-cells to produce allergen-specific IgE, which were restricted to the allergen to which the patient was allergic, especially
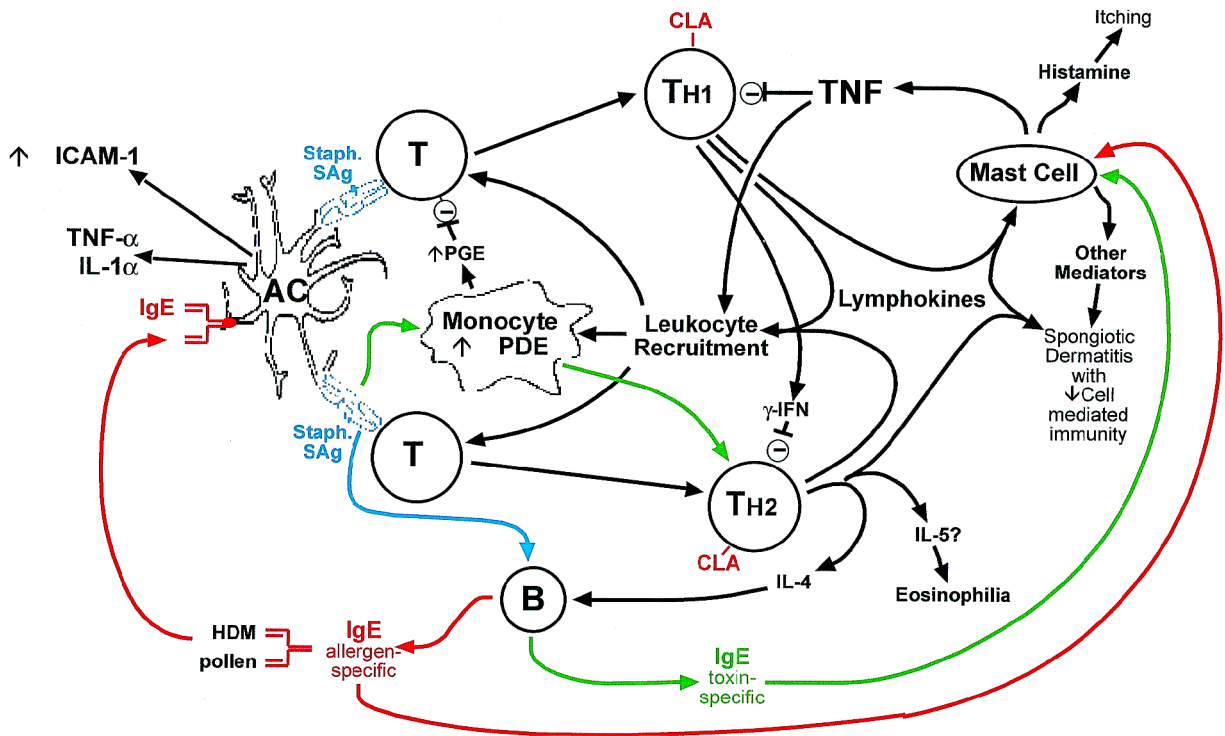
Fig. 2. Superantigens (SAg) and their relevance in atopic dermatitis [modified from Cooper (38)]. AC= accessory cell (Langerhans cell, dendritic cell, HLA-DR-expressing keratinocyte); CLA= cutaneous lymphoid antigen, skin homing factor.

during the pollen season (23). The same authors demonstrated that TSST-1 induced expression of B7.2 on B-cells, a molecule known to enhance Th 2 responses and to be involved in IgE regulation. This might be a mechanism for aggravating allergic inflammation (Fig. 2).

An association between AD and SAgs is, however, still debatable. The investigations of Jappe et al. (42) revealed that the frequency of colonization with SAg-producing *S. aureus* strains in patients with AD corresponded to the results for SAg secretion of *S. aureus* strains isolated from healthy carriers (45% vs. 44%). Molecular typing of *S. aureus* from AD patients by means of Sma1-macrorestriction and r-RNA gene spacer patterns revealed the same population structure as demonstrated for *S. aureus* from nasal colonization. Although this study, however, does not exclude a possible role of *S. aureus* SAgs in the acceleration of the individual clinical course of AD the results of Jappe et al. (42) contradict the hypothesis that skin colonization with *S. aureus* and, especially, SAg formation are essential prerequisites in the pathogenesis of AD.

Palmoplantar pustulosis

The pathogenesis of the sterile pustulosis of palms and soles still remains unclear. It has been shown to be associated with focal infections such as tonsillitis, dental caries, appendicitis and periodontal abscesses. In severe cases, bone and joint symptoms are involved. Antibiotic treatment occasionally improves the clinical course. Investigations of T-cells from tonsillar tissue of patients with palmoplantar pustulosis revealed a preferential expression of Vβ6+ and Vβ12+ . IL-6, IL-8 and TNFα release by these T-cells was shown, indicating the presence of SAgs (43).

Cutaneous T-cell lymphoma

Clinical experience often shows a decrease in erythema and tumour size in cutaneous T-cell lymphoma (CTCL) with systemic as well as topical antibiotic therapy, indicating microbial involvement. Tokura et al. (44) demonstrated that 90% of Vβ2.1+ sezary cells in the peripheral blood of patients could be activated *in vitro* by TSST-1 but not SEB, which showed specificity for both the Vβ sequence and the toxin. In a large prospective cohort of CTCL patients, 32 out of 42 showed *S. aureus* in either skin or blood samples and 78.6% of investigated patients had SAg-producing *S. aureus*. Instead of a monoclonal expansion of certain Vβ subsets, an oligoclonal expansion was found, although patients with TSST-1-producing strains revealed the expected expansion of the Vβ2 gene (45).

Vasculitis

Kawasaki disease, a multiorgan vasculitis, is associated in particular with dermatological symptoms which present in other SAg-mediated inflammatory skin diseases, i.e. erythema and desquamation. Leung et al. (46) detected, in most patients with Kawasaki disease, skin colonization with TSST-1-secreting *S. aureus* and, to a lesser extent, *S. pyogenes*, producing *S. pyogenes* exotoxins B and C. The corresponding Vβ-elements, Vβ 2+ and Vβ8.1+ T-cells, were elevated.

Terveart et al. (47) investigated patients with Wegener's granulomatosis. Nearly 70% of patients were chronic nasal carriers of *S. aureus* and these carriers relapsed nearly 8 times more frequently than the non-carriers. Furthermore, the risk of relapse was higher in patients carrying SAg-producing *S. aureus* compared to those with non-SAg strains. Further

vasculitis subtypes (Table II) have been investigated and support the hypothesis of SAg involvement (48). These findings imply that *S. aureus* may be important in this condition, SAg production being a crucial factor.

Inflammatory acne

Acne is a multifactorial disease, and the pathogenesis is still debatable. Proliferation of *Propionibacterium acnes* is strikingly elevated in microcomedones, with between 10^5 and 10^6 organisms having been recovered from individual preclinical lesions (49). The first use of antibiotics in acne and the clear-cut clinical improvement seen with those agents that reduce *P. acnes*, together with the emergence of antibiotic-resistant strains and a concomitant clinical failure further solidifies the importance of *P. acnes* in acne (50). Increased cellular as well as humoral immunity to *P. acnes* has been observed in severe acne. The initial infiltrate into the lesion is lymphocytic, with later progression to a general infiltrate of mixed cell types. There is evidence that *P. acnes* is involved in invoking the inflammatory response in acne. Langerhans' cells expressing HLA-DR have been observed in close association with perilesional CD4+ T-cells, which suggests local antigenic/superantigenic stimulation. HLA-DR is upregulated in the periductal and perivascular infiltrates of acne lesions. Basal keratinocyte expression of HLA-DR has been demonstrated and is indicative of a specific immune response (51). The cytokine content of comedones consists of IL-1α (52). Weak expression of TNFα has been identified in both normal skin and acne lesions. IL-1, IL-6 and IL-8 have been shown to be present in acne lesions (McGeown, unpublished work). Preliminary data suggest that both Th1 and Th2 cells play a role in the inflammatory events. Investigations on T-cell Vβ gene usage in acne lesions showed that most TCR Vβ families were represented in both PBMC and inflamed lesions (53). However, the CDR3 size diversity of the expressed Vβ genes was restricted in lesional T-cells. For each patient, between 3 and 11 Vβ families were associated with 1–3 CDR3 sizes only, reflecting mono- or oligoclonal expansions of T-cells, whereas multiple CDR3 sizes were found in the Vβ families expressed in PBMC, indicating polyclonal expansions. The oligoclonal T-cell response in the cellular infiltrate shown in this study suggests that inflammatory acne may be antigen-driven or SAg-associated.

Lymphocyte transformation assays with whole cell preparations of *P. acnes* collected from patients with inflammatory acne gave, in some cases, stimulation indices that were comparable to those induced by the mitogen phytohaemagglutinin, whereas no stimulation could be obtained with the corresponding cell culture supernatant fluids (54). *P. acnes* whole cell extract induced a strong immune response in cord blood lymphocytes, which are considered to be immunologically naïve, indicating a non-antigenic response. Lymphocyte activation by *P. acnes* could still be detected after blocking the function of MHC class II. These results show that there is strong evidence for both antigenic and T-cell mitogenic reactivity of naïve lymphocytes to *P. acnes* (55). Further investigations on the molecular immunological features of *P. acnes* may demonstrate whether superantigenicity is involved in inflammatory acne.

CONCLUSIONS

The association between SAgs and several inflammatory skin diseases with or without systemic involvement has been investigated and very interesting and elegant models have been developed to explain several steps in the inflammation of psoriasis, atopic eczema and endothelial damage in vasculitis. Staphylococcal SAgs have been shown to induce inflammation when applied to the intact skin of normal subjects and patients with AD. SAg production in psoriasis and AD affects T-cell activation, T-cell CLA expression, keratinocyte proliferation and IgE-production. Nevertheless, the detailed reactions involving SAgs in the inflammatory process are still not fully understood.

While immunological findings are highly suggestive of an association between SAgs and disease, molecular-epidemiological studies in AD, psoriasis and even vasculitis cast some doubts on this association. For instance, colonization with SAg-producing strains of patients and controls indicates that there are no differences (35, 42, 56). Numerous host and environmental factors influence the expression and effects of secreted SAgs and thereby their influence on pathology. Many questions still remain to be answered, for example:

1. How long does *S. aureus* have to colonize patients' skin before an inflammatory response occurs?
2. What conditions lead to SAg production of microorganisms on the skin of patients with AD, psoriasis and acne?
3. What host factors are involved in protection against microbial SAgs?

Greater detail on the mechanism of interaction of SAgs with human skin will lead to a greater understanding of some inflammatory skin diseases and open up new avenues of therapy.

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