MiniReview

Evidence for the involvement of bacterial superantigens in psoriasis, atopic dermatitis, and Kawasaki syndrome

Jeremy M. Yarwood a, Donald Y.M. Leung b, Patrick M. Schlievert a, *

a Department of Microbiology, University of Minnesota Medical School, Box 196 FUMC, 420 Delaware St. SE, Minneapolis, MN 55455, USA
b Department of Pediatrics, National Jewish Medical and Research Center, Denver, CO 80206, USA

Received 31 July 2000; received in revised form 30 August 2000; accepted 30 August 2000

Abstract

A growing body of evidence implicates streptococcal and staphylococcal superantigens in the development of psoriasis, atopic dermatitis and Kawasaki syndrome. In each of these illnesses, an abnormal state of immunologic activity is observed. Superantigens, which have a unique ability to activate large numbers of lymphocytes, are likely to contribute to these disorders in a number of ways. The demonstrated activities of bacterial superantigens include increasing the number of circulating lymphocytes, with activation of autoreactive subsets, upregulation of tissue homing receptors on circulating lymphocytes, and local activation of immune cells within affected tissues. Through these and other mechanisms, superantigens have a proven ability to induce high levels of inflammatory cytokines and/or initiate autoimmune responses that contribute to the development of skin and vascular disorders. Though development of the illnesses discussed in this review are highly complex processes, superantigens may well play a critical role in their onset or maintenance. Understanding superantigen function may elucidate potential therapeutic strategies for these disorders. © 2000 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

Keywords: Superantigen; Psoriasis; Atopic dermatitis; Kawasaki syndrome; Streptococcus pyogenes; Staphylococcus aureus

1. Introduction

Streptococcal and staphylococcal superantigens (SAgs) are a unique family of bacterial toxins that activate large populations of both CD4+ and CD8+ T-cells and can induce polyclonal B-cell activation, as well. Unlike nominal peptide antigens, superantigens bind the T-cell receptor (TCR) outside the peptide binding groove on the Vβ region of the TCR, together with the major histocompatibility complex (MHC) class II molecule of the antigen-presenting cell (APC) (Fig. 1). Normally, less than one T-cell per 10,000 responds to a conventional, processed antigen. In contrast, as many as 20% of circulating T-lymphocytes may be activated by superantigens recognizing a particular Vβ region. This activation of large numbers of lymphocytes leads to the massive release of cytokines that mediate disease processes.

The roles of bacterial superantigens in the development of psoriasis, atopic dermatitis and Kawasaki syndrome, discussed in detail in this review, are summarized in Fig. 2. Several properties of superantigens suggest a key role for these unique proteins in the initiation and/or propagation of various skin and vascular diseases in human patients. Treatment of peripheral blood mononuclear cells (PBMC) with staphylococcal enterotoxin B (SEB), toxic shock syndrome toxin-1 (TSST-1) and streptococcal pyrogenic exotoxins A (SPEA) and C (SPEC) significantly upregulates the expression of cutaneous lymphocyte-associated antigen (CLA) [1]. CLA is a homing receptor involved in selective migration of memory and effector T-cells to the skin. Furthermore, superantigens that are present in the epidermis bind directly to constitutively expressed HLA-DR molecules on professional APC, such as macrophages and dendritic cells, as well as on non-professional APC, such as keratinocytes. Both the migration of activated lymphocytes into the dermal layers and local actions of superantigens lead to the release of cytokines such as interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α), either systemically or locally. These factors induce leukocyte migration into the skin through vascular dilation, induction of adhesion molecules on vascular endothelium and upregulation of adhesion molecules and...
homing receptors on leukocytes. These events contribute to the inflammation common to the skin disorders discussed in this review. Superantigens may also contribute to skin disorders by the activation and expansion of autoreactive T- and B-cells that express particular Vβ regions. These T-cells may migrate to the skin (due to CLA upregulation) and mediate damage via secretion of proinflammatory cytokines or cytotoxicity directed toward cells expressing the autoantigen. Superantigens also have the capability to damage epidermal layers via mechanisms that do not involve the immune system. Staphylococcal exfoliative toxin A, for instance, can induce separation of the superficial epidermis, perhaps mediated by its proteolytic activity.

2. Psoriasis

Superantigens likely function in the initiation and/or propagation of psoriasis, a common inflammatory autoimmune hyperproliferative disease characterized by the eruption of reddish, silvery-scaled maculopapules, usually on the trunk, knees, elbows and scalp of the patient. The disease has a strong genetic component, based on population studies and familial clustering, and affects 2–3% of the world population [2]. Major features of psoriasis include immune, keratinocyte and vascular activation. The observation that immunsuppressive drugs that inhibit T-cell activation and cytokine release, such as anti-CD3, corticosteroids and cyclosporin A, are effective treatments for psoriasis, strongly implicates T-cell activation in this disease (reviewed in [3]). Wrone-Smith and Nickoloff confirmed the importance of T-cell activation by stimulating autologous PBMCs from psoriasis patients with IL-2 and SEB [4]. Intradermal injection of these stimulated PBMCs into clinically uninvolved skin of psoriatic patients grafted onto severe combined immunodeficient (SCID) mice resulted in the development of plaques with scaling of the skin and histologic features reminiscent of psoriasis. It was then shown by immunoperoxidase staining that the epidermis and dermis of the skin graft became enriched for CD4+ and CD8+ T-cells. The grafts were also diffusely positive for HLA-DR, β1 integrin and keratin 16, characteristic of psoriasis. The ability of SAgs to induce the formation of skin inflammation in psoriasis was recently demonstrated by Travers et al. who topically applied purified TSST-1, SEB, SPEA and SPEC to tape-abraded skin [5]. Application of the toxin-induced inflammatory reactions in the clinically uninvolved skin of psoriatic patients to a much greater extent than in normal control subjects. However, T-cells isolated from skin biopsies of these patients did not exhibit expansion of specific Vβ populations that might be expected to respond to these superantigens. Instead, it was shown that keratinocytes from the psoriatic patients expressed HLA-DR at levels significantly higher than in normal patients. When a mutant TSST-1 protein that failed to bind HLA-DR was used, no inflammatory skin reaction was observed. This suggested that the inflammatory response to epicutaneous application of superantigens on psoriatic skin may depend on human keratinocytes expressing HLA-DR rather than direct activation of T-cells by superantigens. This model is supported by the observation that keratinocytes expressing MHC class II proteins acquire the ability in vitro to activate T-cells in the presence of superantigen when treated with interferon γ (IFN-γ) (a cytokine characteristic of a Th1-type response). This interaction can be blocked by antibodies to MHC class II proteins, intercellular adhesion molecule-1 (ICAM-1) or to lymphocyte function-associated antigen (LFA-1). In contrast, MHC class II+ keratinocytes cannot present peptide antigens to naive T-cells.

Selective expansion of superantigen reactive T-cell populations can be demonstrated in guttate psoriasis, however. Guttate psoriasis is often preceded by streptococcal pharyngitis. It was shown that streptococcal isolates from these patients consistently produced SPEC, although there was no consistent M protein type [6]. Leung et al. demonstrated a selective expansion and accumulation of Vβ2+ T-cells in the perilesional and lesional skin of psoriatic patients, as might be expected by superantigen activation of
T-cell populations [7]. Coupled with the observation that superantigens upregulate the expression of CLA on T-cells, these findings support the idea that, following streptococcal pharyngitis, streptococcal superantigens (in particular, SPEC) selectively drive expansion and cutaneous localization of Vβ2+ T-cells. These activated T-cells can then initiate the cytokine-driven inflammation characteristic of psoriasis as well as defective differentiation of keratinocytes that results in formation of the psoriatic plaque. Some of these activated T-cell populations may remain...
persistently activated due to abnormal recognition of skin antigens, such as keratins or carbohydrates, which have cross-reactive determinants with bacterial antigens. Indeed, psoriasis may be both induced and exacerbated by M-protein specific Th1-type cells that cross-react with human epidermal keratin [8]. These persistently activated T-cells may also contribute to the development of chronic plaque psoriasis, which 70% of patients with guttate psoriasis eventually develop.

Interestingly, the presence of autoreactive antibodies recognizing antigens present in keratinocytes was demonstrated in psoriatic, but not healthy, patients [9]. In addition, mouse anti-streptococcal sera recognized epidermal antigens present in lesional psoriatic skin, but not in healthy skin from psoriatic patients or healthy controls. Superantigens may contribute to this autoantibody production by cross-linking the MHC class II molecule on B-cells with the TCR on T-cells, thus activating B-cells in a non-antigen specific manner [10,11]. Clearly, there exists a genetic component to the disease, as well, as patients with family members that suffer from psoriasis are much more likely to develop the disease. This may reflect the differential ability of various MHC class II haplotypes to present superantigens, as well as autoimmun epidermal peptide antigens.

Finally, it has been demonstrated that staphylococcal protein A, α-toxin and superantigen toxins found on patients with psoriasis can induce the release of TNF-α from the keratinocyte cell line HaCaT [12]. TNF-α is thought to be a principal trigger in the induction of psoriasis, and may also contribute to lesion formation and maintenance in atopic dermatitis, discussed in Section 3. Superantigens, as well as other bacterial products commonly found in Staphylococcus aureus isolates from the skin of psoriatic patients may locally trigger the development of lesions by release of TNF-α from epidermal keratinocytes. Indeed, colonization and infection with S. aureus, as well as streptococci, has been reported to exacerbate psoriasis.

3. Atopic dermatitis

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease characterized by local infiltration of monocytes and T-cells, mast cell degranulation and immediate and cellular immune responses [13]. Consistent with the development of Type I immediate hypersensitivity, serum IgE levels are elevated in nearly 80% of AD patients. It has been demonstrated that up to 10^7 colony forming units of S. aureus can be isolated from the skin of nearly 90% of AD patients [14]. Most AD patients are colonized with S. aureus secreting identifiable superantigens, primarily SEA, SEB and TSST-1 [15–17]. The application of SEB to normal skin and the uninvolved skin of patients with AD resulted in significant erythema and induration in both skin types [18]. These studies suggest that superantigens can initiate, exacerbate and sustain inflammation associated with AD.

Interestingly, the majority of AD patients examined by Leung et al. had IgE specific for one or more of the bacterial toxins TSST-1, SEA and SEB [19]. Basophils from the patients with IgE anti-toxin degranulated when incubated in vitro with the toxin recognized by the IgE. Basophils from normal controls or from AD patients without IgE anti-toxin did not show degranulation when incubated with the staphylococcal toxins. Based on these observations, it is likely that the toxins penetrate the defective epidermal layer in atopic skin [20], induce specific IgE in AD patients, mast cell degranulation and the subsequent IgE triggered histamine release that promotes the scratch–itch cycle in AD patients. As mentioned earlier, superantigen-mediated induction of IgE may occur via cross-linking of the B-cell MHC class II molecule and the TCR [11]. Recently, Hofer et al. showed that TSST-1 stimulation of PBMCs from inhalant allergic patients was followed by an increased production of allergen-specific IgE that was restricted to the allergen to which the patient was allergic and recently exposed [21]. These authors also showed that TSST-1 induced the expression of B7.2 on B-cells; this molecule is thought to enhance Th2 responses. (This effect appeared to be T-cell dependent, as TSST-1 did not induce IgE synthesis by purified B-cells.) Th2 responses in acute AD skin lesions are characterized by secretion of IL-4, IL-5 and IL-13, which induce IgE production [22]. Langerhans cells infiltrating into AD skin lesions bear IgE on their cell surface, present cutaneous allergens to Th2 cells, and thus may contribute to atopic skin inflammation [23].

Other studies describe an important role played by T-cells in the skin inflammation present in AD patients. Epicutaneous application and intracutaneous injection of SEB elicited a strong inflammatory response in the skin of BALB/c mice, but not T-cell-deficient SCID mice [24]. In addition, mouse Th2 cells expanded by treatment with superantigen in vitro can induce cutaneous inflammation when injected into the skin of mice [25]. More recently it was demonstrated that in six of 12 AD patients from whom a superantigen-secreting S. aureus could be isolated, superantigen appropriate Vβ skewing occurred within the CLA^+ subsets of both CD4^+ and CD8^+ T-cells [21]. This skewing was not detectable among the overall CD4^+ or CD8^+ T-cell subsets of these patients. Therefore, staphylococcal superantigens likely contribute to AD by increasing the frequency of memory T-cells able to migrate to and be activated within AD lesions. Interestingly, it has recently been shown that PBMC from patients with severe AD contained significantly higher levels of apoptotic cells than PBMC from patients with mild AD [26]. In addition, significantly more T-cells from severe AD patients expressed APO2.7 antigen, an early apoptosis marker, after treatment with SEB than did T-cells from less severe AD patients. Thus, superantigens may also contribute to aggravation of AD by inducing apoptosis in T-cells.
4. Kawasaki syndrome

Kawasaki syndrome (KS) is an acute febrile illness that occurs primarily in infants and young children [27]. In addition to fever, the syndrome is characterized by four or more of the following: extremity changes, including erythema, induration or desquamation; polymorphous rash, nonexudative bulbar conjunctivitis, oral cavity changes, including hyperemia, lip changes or strawberry tongue; and cervical lymphadenopathy. Though an etiologic agent has yet to be consistently isolated from KS patients, several aspects of the disease suggest an infectious agent. Outbreaks of KS are geographically clustered, often with seasonal predominance, and the disease is self-limiting. The susceptibility of infants and young children, but not adults, to KS also suggests a widely circulating infectious agent to which most individuals gain immunity asymptomatically.

The evidence also suggests a role for superantigens in the development of KS. An unusual level of immune activation is achieved in the acute phase of KS [28], with both polyclonal B-cell activation and increased numbers of activated macrophages and CD4+ T-cells. KS is also characterized by increased cytokine production as well as the presence of autoantibodies. Several laboratories have reported TCR Vβ skewing in patients with KS, while other groups have been unable to detect Vβ skewing (reviewed in [28]). Inability to detect skewing may be a function of the timing of the blood sample. Increased percentages of specific Vβ2+ T-cells may be most consistently detected during the second week of illness [29] and, subsequently, Vβ2+ T-cell distributions begin to normalize. In fact, Vβ2+ T-cell expansion or depletion is not a consistent finding in toxic shock syndrome (TSS), a prototypic superantigen-induced disease [30]. Interestingly, *S. aureus* isolates from KS patients were found to produce significantly higher levels of protein A than did clinical isolates from normal controls [31]. A possible interpretation of these data is that protein A, which binds non-specifically to the Fc-component of IgG, may act as a B-cell mitogen in cases of KS. Finally, the clinical features of KS are similar to those seen in patients with staphylococcal- and streptococcal-mediated disease. Indeed, two case reports describe children who were initially diagnosed with TSS whose illness progressed to satisfy the clinical criteria of KS [32,33].

In a study involving one institution, superantigen-producing bacteria were isolated from 13 of 16 consecutive Kawasaki patients and only one of 15 febrile control patients (*P < 0.001*) [34]. Eleven of the 13 superantigen-positive cultures from KS patients contained TSST-1-secreting *S. aureus* and two of 13 cultures contained streptococci producing SPEB or SPEC. A subsequent study also found superantigen-secreting *S. aureus* in patients with KS complicated by coronary artery disease [35]. However, other investigators have been unable to isolate *S. aureus* on a consistent basis from patients with KS. This may be due to the fact that superantigen-producing *S. aureus* isolated from KS patients have an unusual phenotype in that they are white in color and only weakly hemolytic. Alternatively, the disease may be induced by other superantigen-producing bacteria or viruses, including streptococci and Epstein-Barr virus, both of which are common infectious agents known to produce SAgs.

Meissner et al. [36] proposed the following hypothesis to explain the pathogenesis of KS. An organism producing a superantigen colonizes the mucous membranes of a genetically susceptible host. Superantigen is absorbed through the inflamed mucosal surface and stimulates production of proinflammatory cytokines by mononuclear cells, resulting in fever and development of symptoms associated with KS. In response to cytokine stimulation, vascular endothelial cells present antigens on their surface that render them susceptible to attack by cytotoxic antibodies and activated T-cells.

Recent reports, however, have described clonal expansion of CD8+ T-cells in acute KS as well as clonal relation among IgA-producing B-cells from the vascular tissue of patients who died with KS [37,38]. Both of these reports support the contention that KS is incited by a conventional antigen rather than a superantigen. However, a mechanism by which both superantigen-activated T-cells and clonally related T- and B-cells are necessary to produce the autoimmune vasculitis of KS deserves investigation. Initially, a superantigen induces polyclonal expansion and activation of circulating CD4+ Vβ-restricted T-cell subsets. A subset of these activated T-cells that are autoreactive and bear homing receptors for target organs then enter vascular and myocardial tissue [28]. These T-cells, recognizing an autoantigen, or conventional antigen, within vascular or myocardial tissue, then initiate the cascade of cellular and molecular events that produce vasculitis and myocarditis. In addition, autoantibodies recognizing human cardiac myosin as well as vascular endothelial antigens are present in a significant number of KS cases [39–41].

In conclusion, the experimental data obtained thus far implicate bacterial superantigens in the development and maintenance of human skin diseases. However, while superantigens clearly are able to induce development of skin lesions, a great deal of controversy exists as to whether bacterial superantigens are necessary for disease development. This is particularly true for cases of psoriasis and KS, as toxin-producing bacteria are not always isolated from these patients. Improved methods for organism culturing may help to resolve this controversy. In addition, as novel superantigens continue to be identified in staphylococci and streptococci, it may well be that toxin production by clinical isolates will be detected at higher frequencies than previously described. Furthermore, other superantigen-producing organisms may be shown to be associated with development of these diseases, particularly...
in the case of KS. Future areas of investigation include the identification of mechanisms by which superantigens induce autoimmune responses and therapeutic strategies for control of superantigen-induced inflammatory responses.

Acknowledgements

The authors thank Douglas H. Ohlendorf and Gregory A. Vath for providing Fig. 1. This work was supported by USPHS research grants AI22159 and HL36611 to P.M.S. and NIH grants HL36577, AR41256, and HL37260 to D.Y.M.L. J.M.Y. was supported by a Howard Hughes Medical Institute Predoctoral Fellowship in the Biological Sciences. We thank John K. McCormick for his thoughtful review of the manuscript.

References


**coccus aureus** isolates from patients with Kawasaki disease express high levels of protein A. Infect. Immun. 67, 4737–4743.


