Evidence for Superantigen Involvement in Severe Group A Streptococcal Tissue Infections

Anna Norrby-Teglund,1 Pontus Thulin,1 Bing S. Gan,1,3 Malak Koth,4,5 Allison McGeer,2 Jan Andersson,1 and Donald E. Low2

Host-pathogen interactions were studied in tissue biopsy samples from patients with severe invasive group A streptococcus (GAS) infections. Skin, subcutaneous tissue, and fascia biopsy samples were divided into clinical grade 1 (no evidence of inflammation [n = 7]) or clinical grade 2 (inflamed tissue—erythema and edema including cellulitis, fasciitis, and necrotizing fasciitis [n = 24]). In situ imaging demonstrated significantly higher bacterial load in biopsy samples of higher clinical grade (P < .05), and the bacterial load correlated with the in vivo expression of the superantigen streptococcal pyrogenic exotoxin F (P < .02). Increased expression of the interleukin-1 cytokines and significantly higher expression of tumor necrosis factor–β, interferon-γ, and the homing receptors CC chemokine receptor 5, CD44, and cutaneous lymphocyte–associated antigen (P < .002–.05) were observed in biopsy samples of higher clinical grade. Thus, the cytokine profile at the local site of infection mimics that of a typical superantigen cytokine response. The findings of this study demonstrate a critical role for superantigens and Th1 cytokines in GAS tissue infections.

Group A streptococcus (GAS) is a common pathogen of the throat and skin. It causes infections of varying severity, ranging from uncomplicated superficial infections to severe invasive infections. The past decade has witnessed a worldwide increase in severe invasive GAS infections, including streptococcal toxic shock syndrome and necrotizing fasciitis [1]. These rapidly progressive infections are associated with high mortality rates, despite prompt antimicrobial therapy [1].

This resurgence of highly aggressive infections prompted intense research in the area of GAS pathogenesis. Epidemiologic studies revealed that most outbreaks, although reported from different countries and on different continents, were caused predominantly by GAS strains of M1 and M3 serotypes [1, 2]. Further characterization of the isolates by molecular techniques generated somewhat conflicting results: some reports suggested that a special clone of GAS was responsible for the more severe cases [3, 4], whereas other reports demonstrated clonal variation among strains of a given serotype and found no apparent correlation with a given clone and severity of disease [5–13]. Chatellier et al. [14] recently showed that clonal M1T1 strains could be isolated from patients with severe or nonsevere invasive infections, and the study emphasized the importance of host factors in determining the severity of infections.

GAS produces several exotoxins that exhibit superantigenic activity and can, as such, activate a large proportion of antigen-presenting and T cells, with subsequent high expression of cytokines [15]. To date, there are 11 distinct exotoxins produced by GAS, including the streptococcal pyrogenic exotoxins (Spe) A, B, C, F, G, H, and J; streptococcal mitogenic exotoxin Z (SmeZ), SmeZ-2, and SmeZ-3; and streptococcal superantigen (SSA) [15–17]. The distribution of these superantigens varies among streptococcal strains because some superantigens, such as SpeB and SpeF, are chromosomally encoded and are found in virtually all strains, whereas others are associated with mobile genetic elements and therefore are found at varying frequencies [15]. By virtue of their potent immunostimulatory capacity, superantigens have been implicated as central mediators...
of the systemic effects seen in severe invasive GAS infections. In vivo evidence for the involvement of superantigens in these diseases was obtained by analysis of the T cell receptor repertoire in patients with GAS infections, which revealed V8-specific alterations characteristic of superantigen effects in vivo [18, 19]. Furthermore, Sriskandan et al. [20] could detect circulating superantigen in the plasma of patients with streptococcal toxic shock syndrome.

It is well known that cytokines are central mediators of the systemic symptoms seen in sepsis and shock, and numerous studies have demonstrated a correlation between elevated cytokine levels in circulation and more-severe disease manifestations [21–32]. However, there are limited data on host-pathogen interactions at the local site of infection; we, therefore, undertook this study, in which bacterial load, superantigen expression, and inflammatory responses were studied in vivo and were related to severity of soft tissue infection caused by GAS.

Materials and Methods

Patient material. Five patients with various deep tissue infections, including necrotizing fasciitis and cellulitis, caused by GAS were included in the study. Three of the patients fulfilled the criteria for streptococcal toxic shock syndrome [33]. The patients were identified through active surveillance for all invasive GAS infections in Ontario during 1996–1997. Biopsy samples from the local infection site were taken at surgery, were snap-frozen, and were stored at−80°C. Biopsy samples were obtained at repeated surgical procedures during the acute phase of infection, 1–20 days after onset of infection, including biopsy samples from skin, subcutaneous tissue, and fascia (table 1). The tissue from which biopsy samples were taken was graded on the basis of a clinical assessment made by one of the investigators (D.E.L.) at the time of sampling. From each patient, biopsy samples were collected at surgical procedures done on different days, and from some patients, biopsy samples of different clinical grades were collected at the same time point (table 1).

The clinical characteristics of the tissue obtained from the patients were defined as follows. Clinical grade 1 was normal tissue, with no evidence of inflammation (n = 7). Clinical grade 2 was inflamed tissue—erythema and edema. Grade 2 was subdivided into grade 2a, cellulitis (inflammation of skin or soft tissue, but excluding fascia and muscle [n = 18]); grade 2b, fasciitis (inflammation of skin or soft tissue and fascia [n = 4]); and grade 2c, necrotizing fasciitis (inflammation of skin or soft tissue and nonviable fascia [n = 2]).

Clinical evaluation, classification of patients, and cytokine and cell marker analyses were done independently by different investigators and at different hospitals. Investigators who were unaware of the clinical grade of the biopsy samples did cytokine and cell marker analyses.

Characterization of GAS isolates. Isolates were identified and serotyped at the National Center for Streptococcus Research (Edmonton, Alberta, Canada) by standard methods [34]. Superantigens were genotyped by use of specific primer pairs and polymerase chain reaction amplification, as described elsewhere [14].

Antibodies used for immunostainings. The following human cytokine–specific monoclonal antibodies (MAbs) were used at concentrations of 2–5 μg/mL: anti–interleukin (IL)–1α (cocktail of 1277-89-7, 1277-82-29, and 1279-143-4), anti–IL-1β (cocktail of 2-D-8 and 1437-96-15), and anti–IL-1 receptor agonist (IL-1ra; cocktail of 1384-92-17-19 and 1398-93-9; all murine IgG1, from H. Towbin, Ciba-Geigy), anti–IL-2 (17H112, rat IgG2a; Pharmingen), anti–IL-4 (8D4-8, murine IgG1; 25.D.2, rat IgG1; Pharmingen), and anti–TNF-α (MAb 1 and MAb 11, murine IgG1; Pharmingen), anti–IL-12 (24932; R&D Systems), anti–IL-8 (NAP-1, murine

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NOTE. NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome.

* Days after onset of infection.

Based on clinical assessment made by surgeon at time of sampling. Clinical grade 1, normal tissue, no signs of inflammation; grade 2a, cellulitis; grade 2b, fasciitis; and grade 2c, necrotizing fasciitis.
IgG1, Sandoz), anti-\(\text{TNF-}\beta\) (LTX-22, murine IgG1; Bender Medsystem), and anti-\(\text{IFN-}\gamma\) (cocktail of 1-DIK and 7-B6-1, murine IgG1; MabTech).

The following antibodies specific for human cell markers were used at predetermined optimal dilutions ranging from 1:10 to 1:200: anti-CD68 (EBM11, murine IgG1; Dako), anti-CD3 (murine IgG1; Becton Dickinson), anti-CD4 (murine IgG1; Becton Dickinson), anti-CD8 (murine IgG1; Becton Dickinson), anti-\(\text{CC}\) chemokine receptor 5 (CCR5; cocktail of K45531.111 and M45549.111, murine IgG2b; R&D Systems), anti-\(\text{CXCl}\) chemokine receptor 4 (CXCR4; 44717, murine IgG2b; R&D Systems), and anti-\(\text{cutaneous lymphocyte antigen}\) (CLA; HECA-452, rat IgM; Pharmingen). GAS were identified by use of polyclonal rabbit antisera specific for the Lancefield group A carbohydrate (Difco), and the superantigen SpeF, by use of a polyclonal rabbit antiserum raised against recombinant SpeF; both sera were used at a dilution of 1:10,000. Irrelevant isotype–specific murine and rat antibodies (Vector Laboratories) and preimmune rabbit serum samples (diluted 1:10,000) were used to control for nonspecific staining reactions.

Secondary biotinylated antibodies, including goat anti-mouse IgG1, IgG2a, and IgG2b (diluted 1:300; Caltag), goat anti-rat IgG (diluted 1:500; Vector Laboratories), or goat anti–rabbit IgG (diluted 1:500; Vector Laboratories) were used.

**Immunohistochemical staining of tissue biopsy samples.** Biopsy samples were embedded in Tissue-Tek OCT compound (Sakura), were cryostat-sectioned to 8 \(\mu\)m, were mounted to heavy teflon coated glass slides (Novakemi), and were fixed with 2% freshly prepared formaldehyde in PBS. Intracellular cytokines, cell markers or receptors, GAS, or streptococcal superantigen were stained by permeabilization of the cell membranes with 0.1% saponin (Sigma) followed by immunohistochemical staining with antigen-specific antibodies, essentially as detailed elsewhere [35]. The method was modified to include an initial blocking step with 20% normal rabbit serum (diluted 1:10,000) and 5% normal goat serum. DAB peroxidase substrate was used (3,3-diaminobenzidine, Vector Laboratories) and were stained for CD3 expression with the avidin–alkaline phosphatase complex (ABC-AP kit; Vector Laboratories) and the alkaline phosphatase substrate kit 1 (Vector Laboratories).

**Statistical evaluation.** Data were entered into Statistica (version 5.1; Statsoft). Comparisons between groups were made with Mann-Whitney \(U\) rank sum test. Significant correlation between different parameters was determined with Spearman’s correlation test. Association between low or high bacterial load in tissue and clinical grade of biopsy samples was determined with Yates’s-corrected \(\chi^2\) test. \(P < .05\) was considered to be significant.

**Results**

The characteristics of the patients and their isolates are presented in tables 1 and 2. The isolate of 1 patient was missing. Biopsy samples of different clinical grades were collected at different time points, and there was no relationship between clinical grade of the biopsy samples and time of sampling or type of tissue collected (table 1; data not shown). For most purposes, biopsy samples of clinical grade 1 were compared with biopsy samples of clinical grades 2a–2c.

**Relationship of in vivo expression of superantigen to bacterial load at the site of infection.** Staining of the biopsy samples for GAS revealed that all biopsy samples contained GAS in varying amounts (figure 1). Image analysis showed that the bacterial load could be divided into high and low by use of a cutoff value of 5 (figure 1). Seventy-eight percent of the biopsy samples of clinical grades 2a–2c showed high bacterial load, whereas only 28% of the clinical grade 1 biopsy samples had high amounts of GAS (\(P < .05\); figure 1B). Thus, bacterial load was found to be significantly associated with severity of soft tissue inflammation.

In vivo expression of GAS superantigens at the site of infection was investigated. We chose to stain for the superantigen SpeF because this superantigen is chromosomally encoded and, therefore, is present in all GAS strains. As shown in figure 1A, SpeF was readily detectable in the tissue at varying levels. In situ imaging assessment revealed that the level of SpeF expression correlated with amount of GAS (\(P < .02\). Spearman’s correlation test). However, although there was a trend to higher

**Table 2.** Characteristics of isolates from patients with tissue infection due to group A streptococci: serotype and superantigen genotype.

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<th>Patient</th>
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<td>MIT1</td>
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**NOTE.** NA, not available; NF, necrotizing fasciitis; STSS, streptococcal toxic shock syndrome; +, positive for genotype; –, negative for genotype.
Figure 1. Bacterial load and in vivo expression of superantigens at the site of infection. Tissue biopsy samples obtained from patients with tissue infections caused by group A streptococci (GAS) were classified according to clinical grade, defined as grade 1 (no evidence of inflammation [n = 7]) or grade 2 (inflamed tissue—erythema and edema including cellulitis, fasciitis, and necrotizing fasciitis [n = 24]). Biopsy samples were immunostained for GAS and streptococcal pyrogenic exotoxin F (SpeF), and stainings were evaluated by acquired computerized image analysis (ACIA). Results are presented as ACIA values: area and intensity of positive stain (brown) in relationship to total cell area (blue). ACIA values >5 were used as cutoff to separate low or high bacterial load or SpeF expression. A, Tissue sections with high and low GAS and SpeF expression. B, Percentages of biopsy samples with high or low bacterial load. Statistical difference between biopsy samples of clinical grade 1 and grade 2 was analyzed by Yates’s-corrected \( \chi^2 \).

Figure 2. Characterization of cell infiltrates at the site of infection. Tissue biopsy samples of clinical grade 1 (no evidence of inflammation [n = 7]) or grade 2 (inflamed tissue—erythema and edema including cellulitis, fasciitis, and necrotizing fasciitis [n = 24]) obtained from patients with tissue infections caused by group A streptococci were immunostained for various cell markers, as indicated in panels A–E. F, Double staining for CD3\(^+\) (red) and CD4\(^+\) (brown) cells; double- and single-positive cells are indicated by arrows. G, Acquired computerized image analysis (ACIA) of CD4 and CD8 (see legend to figure 1 for details).
pressed levels of CD4 in biopsy samples of higher clinical grade, whereas no difference was noted in CD8 expression (figure 2G).

Relationship of proinflammatory and Th1-type cytokine responses to severity of tissue inflammation. Expression of several different cytokines, including IL-1α, IL-1β, IL-1ra, IL-2, IL-4, IL-8, IL-12, TNF-α, TNF-β, and IFN-γ, could be detected at varying levels in the biopsy samples, and they all, except the IL-1 family, demonstrated the typical intracellular staining pattern with a localized golgi staining, as described elsewhere in detail [36]. As expected, the IL-1 family showed a cytoplasmic staining pattern, because they lack the signal peptide directing secretion of the cytokines through the golgi organelle [36].

IL-1α, IL-1β, and IL-1ra were generally found at high levels, as reflected by the ACIA values, and image analysis indicated increased levels of these cytokines in biopsy samples of higher grade, compared with levels in samples of lower clinical grade (figure 3). An even more pronounced difference in expression of cytokines between different biopsy samples was seen for the Th1 cytokines. A significantly higher expression of TNF-β and IFN-γ (P = .03 and P = .002, respectively) was found in biopsy samples of clinical grades 2a–2c than in samples of clinical grade 1 (figure 4A). Furthermore, a strong correlation was noted between increased expression of TNF-β and IFN-γ and higher clinical grade of biopsy samples when 10 biopsy samples of varying clinical grade obtained from the same patient were compared (P = .01 and P = .003, respectively; figure 4B and 4C). Although IL-2, IL-4, IL-8, IL-12, and TNF-α were detected at varying levels in different biopsy samples, there was no correlation between expression level and clinical grade of the biopsy samples (data not shown).

Relationship of homing receptor expression at the local site to severity of tissue inflammation. Expression of the homing receptors CXCR4, CCR5, CD44, and CLA was determined in biopsy samples of clinical grade 1 (n = 5) or 2a–2b (n = 5). The analyses revealed a significantly higher expression of CCR5, CD44, and CLA (P = .05, P = .02, and P = .009, respectively) in biopsy samples of clinical grades 2a–2b than in samples of clinical grade 1, whereas CXCR4 expression was equally low in all 10 biopsy samples (figure 5). Interestingly, there was a significant correlation between the expression level of CCR5 (Spearman’s R = .68; P = .03), CD44 (Spearman’s R = .86; P = .001), and CLA (Spearman’s R = .89; P = .006) and the levels of Th1 cytokines (TNF-β plus IFN-γ) in biopsy samples of varying clinical grade obtained from the same patient were higher clinical grade of biopsy samples when 10 biopsy samples of clinical grade 1 or grades 2a–2b ( ). Biopsy samples were immunostained for tumor necrosis factor (TNF)-β and interferon (IFN)-γ, and stainings were evaluated by acquired computerized image analysis (ACIA; see legend to figure 1 for details). Horizontal bars indicate mean values.

Figure 3. Expression of interleukin (IL)-1 cytokines at the site of infection. Tissue biopsy samples of clinical grade 1 (no evidence of inflammation [n = 7]) or grade 2 (inflamed tissue [n = 24]) obtained from patients with tissue infections caused by group A streptococci were immunostained for IL-1α, IL-1β, and IL-1 receptor agonist (IL-1ra), and stainings were evaluated by acquired computerized image analysis (ACIA; see legend to figure 1 for details). Horizontal bars indicate mean values.

Figure 4. Correlation between severity of tissue infection and Th1 cytokine levels. Biopsy samples obtained from patients with tissue infections caused by group A streptococci were classified according to clinical grade, defined as grade 1 (no evidence of inflammation [n = 7]) or grade 2 (inflamed tissue [n = 24]), including 2a (cellulitis [n = 18]), 2b (fasciitis [n = 4]), and 2c (necrotizing fasciitis [n = 2]). Biopsy samples were immunostained for tumor necrosis factor (TNF)-β and interferon (IFN)-γ, and stainings were evaluated by acquired computerized image analysis (ACIA; see legend to figure 1 for details). Horizontal bars indicate mean values. Expression of TNF-β and IFN-γ in biopsy samples of clinical grade 1 or grades 2a–2c (A) and expression of TNF-β (B) and IFN-γ (C) in biopsy samples of varying clinical grade obtained from patient 5611. Statistical differences between biopsy samples of clinical grade 1 and grade 2 were analyzed by Mann-Whitney U test. Significant correlation between Th1 cytokine levels and clinical grade of biopsy samples from 1 patient was determined by Spearman’s correlation test.
Discussion

In this study, we demonstrate that the bacterial load and the magnitude and type of cytokine expression correlate with severity of GAS tissue infection. Furthermore, we show that there is high in vivo production of the GAS superantigen SpeF at the site of infection. Superantigens have previously been identified in the circulation of patients with invasive GAS infection [20], but, to our knowledge, this is the first time superantigens have been demonstrated at the local site of infection in patients’ tissue. It seems reasonable that several different GAS superantigens are involved in the pathogenesis of invasive GAS diseases and, most likely, that the bacteria during the infection produce >1 superantigen [37]. The expression of SpeF in tissue is particularly interesting because, aside from being a superantigen, SpeF also exhibits heat-resistant nuclease activity [38] and is immunologically and genetically identical to streptococcal DNase B [39, 40]. DNase B has often been suggested to be important for virulence, presumably aiding bacterial dissemination, although direct evidence for this effect is lacking. However, we cannot exclude that this additional DNase activity might be an important virulence trait in the tissue milieu. It will be of interest to analyze in vivo production of additional superantigens to elucidate their role in pathogenesis.

The tissue biopsies revealed massive mononuclear cell infiltrates that consisted predominantly of macrophages/monocytes and T cells, whereas no pronounced polymorphonuclear cell infiltration could be seen. A previous study by Cockerill et al. [41] demonstrated few or no inflammatory cells in superficial subcutaneous tissue from 4 patients with necrotizing fasciitis, but, in agreement with our study, high frequencies of inflammatory cells could be found in deeper subcutaneous tissue.

We recently demonstrated that patients with severe invasive GAS infections had significantly higher frequencies of proinflammatory cytokine–producing cells in their peripheral blood than did patients with nonsevere invasive infections [28]. A similar correlation between the severity of infection and the magnitude of cytokine response was noted in the current study, with increasing levels of IL-1 cytokines and significantly higher Th1 cytokines in more severely affected tissue. Several in vitro studies have reported that superantigens induce a cytokine response that is characterized by proinflammatory cytokines, most importantly by very high levels of Th1-type cytokines, in particular TNF-α and IFN-γ [36, 42–45]. Thus, our data on the cytokine profile at the local site of infection mimic that of a typical superantigen cytokine response and provide evidence for the direct actions of superantigens in GAS tissue infections.

Previous studies have failed to detect TNF-α and IFN-γ, measured by ELISA of plasma or intracellular immunostaining of peripheral blood mononuclear cells in circulation of patients with fulminant GAS diseases [27, 28, 46]. However, on the basis of other studies of cytokine responses at the local site of inflammation [35], we hypothesized that the Th1 cytokine–producing cells could not be found in the circulation because they had migrated to the site of inflammation. This study provides evidence supporting this hypothesis, because TNF-α and IFN-γ–producing cells were readily detectable in tissue biopsy samples. Furthermore, the significant correlation between levels of Th1-type cytokines and severity of tissue infection provided strong support for a critical role of these cytokines in the pathogenesis of invasive GAS diseases.

To elucidate the mechanism responsible for this migration of cells, we examined the expression of homing receptors. Chemokines are of major importance for leukocyte traffic and homing, as well as their maturation [47]. The chemokine receptors CXCR4 and CCR5 were analyzed because of their differential expression on Th1 and Th2 cells [48]. In agreement with the cytokine analysis showing a predominant Th1 cytokine response in the more-severe tissue infections, analysis of chemokine receptors showed an up-regulation of CCR5 in the more severe tissue biopsy samples that correlated with the level of Th1 expression, whereas CXCR4 was equally low in all analyzed biopsy samples. Thus, chemokine receptor expression reflects the type of cytokine response seen at the local site of infection.

The finding of a significant up-regulation of CD44 in the more severe tissue biopsy samples, which correlated with the magnitude of Th1 cytokines, provided further support for the action of superantigens. CD44 is a receptor that mediates extravasation of activated T cells into inflammatory sites by bind-
ing to its ligand, hyaluronic acid [49, 50]. However, binding to hyaluronic acid requires activation of CD44, which may be achieved via T cell receptor stimulation by superantigens [49]. Binding of CD44 to hyaluronic acid makes this receptor especially interesting, because GAS express a capsule consisting of hyaluronic acid, and it was shown recently that CD44 acts as a receptor for GAS, thereby increasing bacterial adherence and colonization [51, 52]. Thus, one can speculate that the very high expression of CD44 demonstrated at the local site of infection may benefit GAS adherence and further exacerbate disease progression.

Another interesting homing receptor is CLA, which is a tissue-specific homing receptor involved in directing effector and memory T cells to the skin [53]. In vitro studies have shown that bacterial superantigens can induce a marked up-regulation of CLA on human peripheral blood mononuclear cells [54]. Furthermore, it was demonstrated that superantigens were involved in skin homing of CLA-positive T cells in atopic dermatitis [55]. Thus, superantigen activation of circulating T cells may induce up-regulation of CLA and thereby promote migration of these activated T cells to the skin and subsequent increased pathologic inflammatory response at the site of infection. Our findings verify this theory, because we found a pronounced expression of CLA in the tissue and a highly significant correlation between CLA expression and Th1 cytokine expression as well as severity of tissue infection.

Together these findings have led us to propose a multifaceted role of superantigens in the pathogenesis of GAS tissue infections. We believe that GAS superantigens trigger a pathologic proinflammatory cytokine response not only by their direct actions at the site of infection but also by their induction of certain homing receptors that promote migration of T cells and antigen-presenting cells to the site of infection as well as improved adherence of bacteria to host cells. The study also provides support for a critical role of Th1 cytokines in the pathogenesis of severe invasive GAS disease. Our findings suggest that superantigens are pivotal players in the destructive tissue infections caused by GAS, and therapy directed towards superantigens may be an efficient therapeutic strategy in these diseases.

Acknowledgments

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References


