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ORIGINAL PAPER

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Hyporesponsiveness of peripheral blood lymphocytes to streptococcal superantigens in patients with guttate psoriasis: evidence for systemic stimulation of T cells with superantigens released from focally infecting *Streptococcus pyogenes*

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Abstract **Throat infection with *Streptococcus pyogenes* is the most important trigger for acute guttate psoriasis. We examined the in vitro responses of peripheral blood mononuclear cells (PBMC) to streptococcal superantigens, SPEA and SPEC, and staphylococcal superantigens, SEB and TSST-1, in patients with guttate psoriasis, in patients with chronic plaque psoriasis, and in healthy subjects. PBMC from patients with guttate psoriasis responded poorly to SPEA and SPEC at concentrations of 0.1 and 1 ng/ml as compared with those from patients with plaque psoriasis, but showed high responses to SEB and TSST-1. The hyporesponsiveness recovered after improvement of the skin eruption. There was no significant difference between guttate and chronic types of psoriasis in the percentage of circulating T-cell receptor BV2 or BV8-bearing T cells, responsive to streptococcal superantigens, indicating that T-cell clonal anergy was a mechanism underlying the hyporesponsiveness. Our results suggest that superantigens released from focally infecting *S. pyogenes* induce a transient activation of relevant T cells, leading to the development of skin eruption and, subsequently, temporary T-cell anergy to these toxins.**

Key words Psoriasis · Streptococcus · Superantigens · T cell

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Introduction

Psoriasis is a complex, inflammatory skin disorder characterized by epidermal keratinocyte hyperproliferation in association with a cellular infiltrate. Several studies have suggested that T lymphocytes, whose activation may precede epidermal proliferation [1–3], play a critical role in the pathogenesis of psoriasis [4, 5]. Superantigenic exotoxins produced by *Streptococcus pyogenes* (group A-*Streptococcus*) and *Staphylococcus aureus* have been reported to precipitate or to cause a deterioration in several skin disorders. For example, release of superantigens by skin-colonizing *S. aureus* potentially exacerbate skin lesions of atopic dermatitis [6] and cutaneous T-cell lymphoma [7] by stimulating skin-infiltrating, normal or malignant T cells. Stimulation of T cells under restriction of the T-cell receptor Vβ (BV) usage with superantigens [8] is also a pathogenic event in psoriasis. Throat infection with *S. pyogenes* [9] and possibly *S. aureus* [10] can trigger the disease by releasing the superantigenic toxins that these organisms produce [11, 12].

In the case of cutaneous bacterial colonization, released superantigens may stimulate infiltrating T cells locally in the skin milieu, where Langerhans cells and major histocompatibility complex class II-bearing keratinocytes are capable of functioning as superantigen-presenting cells [13–15]. On the other hand, tonsillar or pharyngeal infection with bacteria is considered to trigger or aggravate skin lesions by systemically stimulating T cells with superantigens because of the location of the infected site distant from the skin. Therefore, it is possible that peripheral T cells are already exposed to superantigens in psoriatic patients with throat infection and respond abnormally to superantigens. Various responses of peripheral blood mononuclear cells (PBMC) to superantigens have been reported in psoriatic patients [16–20], presumably because of differences in methodology and assessment of data and in the type and severity of psoriasis among patients. We [19] and another group [20] have shown that when the magnitude of responses is analyzed in terms of a

stimulation index (SI), PBMC from patients with chronic plaque psoriasis respond to staphylococcal enterotoxin (SE) B and toxic shock syndrome-1 (TSST-1) more vigorously than those from healthy subjects. However, we found three patients with severe, erythrodermic or, arthropathic psoriasis whose PBMC responded poorly to TSST-1 while maintaining a high responsiveness to SEB [21]. Since one of these patients had throat infection with TSST-1 producing *S. aureus* and the percentage of circulating $BV2^+$ T cells responsive to TSST-1 was not decreased in the blood, we considered that the mechanism of the low responsiveness was T-cell clonal anergy induced by exposure to TSST-1. Such hyporesponsiveness of PBMC has been reported by another group in patients with chronic plaque psoriasis in response to streptococcal superantigens, cytoplasmic membrane-associated protein (CAP) and secretion-type CAP (SCAP) [18]. These observations suggest that circulating T cells in a certain group of psoriatic patients are rather hyporesponsive to causative superantigens.

Acute guttate psoriasis is a well-defined form of psoriasis closely associated with streptococcal throat infection [22]. Moreover, it is strongly suggested that T cells in the lesions of guttate psoriasis skin are activated by streptococcal superantigens [12]. Therefore, guttate psoriasis is thought to be the most comprehensive type of psoriasis to clarify the responsiveness of psoriatic peripheral T cells to superantigens. We thus examined PBMC responses to streptococcal and staphylococcal superantigens in patients with guttate psoriasis as well as in patients with chronic plaque psoriasis. Our results suggest that peripheral T cells are hyporesponsive to streptococcal superantigens but not to staphylococcal superantigens during active guttate psoriasis.

Materials and methods

Patients and controls

The patients and controls enrolled in this study were: (1) four patients with guttate psoriasis (aged 27–42 years, two males and two females), (2) eight patients with chronic plaque psoriasis (aged 25–65 years, five males and three females, psoriasis area and severity index score [23] 18.5 ± 9.6), (3) three atopic patients with streptococcal impetigo (aged 20–24 years, one male and two females), and (4) eight healthy normal subjects (aged 28–47 years, five males and three females). Acute guttate psoriasis was defined as the sudden onset of small erythematous macules which evolved into parakeratotic maculopapules. In all patients, the onset of rash was preceded by a sore throat associated with a positive swab for *S. pyogenes* (three out of four patients) and/or elevated titres of serum antistreptolysin O and antistreptokinase (three out of four patients). Venous blood samples were taken on presentation with active guttate psoriasis, and again after 6 to 8 weeks when the guttate psoriasis had been improved by oral antibiotic therapy. All patients with chronic plaque psoriasis had been treated with topical corticosteroids and/or psoralen/ultraviolet A therapy before blood samples were tested. A diagnosis of streptococcal impetigo was made on the basis of clinical appearance and positive cultures for *S. pyogenes* identified as described previously [24], and blood was taken during the active stage.

PBMC response

RPMI-1640 supplemented with 10% heat-inactivated fetal calf serum, 25 m*M* HEPES, 2×10^{-5} *M* L-glutamine, 10^{-5} *M* sodium pyruvate, and 5×10^{-5} *M* 2-mercaptoethanol was used for the T-cell proliferation assay. PBMC were isolated from patients and normal subjects by the standard Ficoll-Paque (Pharmacia, Uppsala, Sweden) method. Cells (2×10^5/well)were cultured in triplicate in a final volume of 150 µl culture medium in 96-well, flat-bottomed microtiter plates (Corning Glass Works, Corning, N.Y.) for 72 h at 37 °C in 5% CO_2 in air and pulsed with methyl ^{3}H-thymidine (^{3}H-TdR; 1 µCi/well) 16 h before harvest. The cells were collected on glass fiber filters using a cell harvester (Cambridge Technologies, Watertown, Mass.). Staphylococcal exotoxins, SEB and TSST-1, and streptococcal toxins, streptococcal pyrogenic exotoxin (SPE) A and SPEC (all from Toxin Technology, Sarasota, Fl.) were used as superantigens and were added to wells at the beginning of culture. No endotoxin activity was detected in SPEA, SPEC, SEB, or TSST-1 at 100 ng/ml, as assessed by Endospec SP (Seikagaku Ko., Tokyo, Japan). As a control, concanavalin A (Con A, 5 µg/ml; Sigma Chemical, Saint Louis, Mo.) was added to PBMC culture.

Flow cytometric analysis

PBMC were suspended in Hank's balanced salt solution containing 1% heat-inactivated fetal calf serum and 0.1% sodium azide. They were single- or double-stained with phycoerythrin-labelled anti-CD3, -CD4, or -CD8 monoclonal antibodies (Becton Dickinson, San Jose, Calif.) and/or fluorescein isothiocyanate-labelled anti-BV2 or -BV8 monoclonal antibodies (Immunotech, Marseille, France). After washing, cells were analyzed in a FACScan (Becton Dickinson). The percentages of positive cells were obtained by counting 10 000 cells.

Statistical analysis

Student's *t*-test was employed to determine the significance of differences between means, and $P < 0.05$ was considered to indicate a significant difference.

Results

PBMC from patients with active guttate psoriasis were cultured in the presence or absence of SEB, TSST-1, SPEA or SPEC at concentrations ranging from 0.1 to 100 ng/ml, or Con A at 5 µg/ml. For comparison the responsiveness of PBMC from chronic plaque psoriasis and streptococcal impetigo patients, and normal controls were also examined. In PBMC from healthy subjects, as shown in Fig. 1A, all four superantigens induced T-cell proliferation at the lowest concentration 0.1 ng/ml, although the response levels to streptococcal superantigens were lower than those to staphylococcal toxins. PBMC from a representative patient with guttate psoriasis, responded normally to SEB and TSST-1, but poorly to SPEA and SPEC, as proliferative responses to these toxins were not substantial at 0.1 ng/ml but became apparent at 1 ng/ml (Fig. 1B).

To evaluate the reactivities of PBMC from all subjects, we first analyzed the data in terms of a SI. As shown in Fig. 2, the degree of proliferation was greater in guttate and chronic plaque psoriasis PBMC than in normal control PBMC in response to all four superantigens at concentrations of 1, 10, and 100 ng/ml, confirming the results

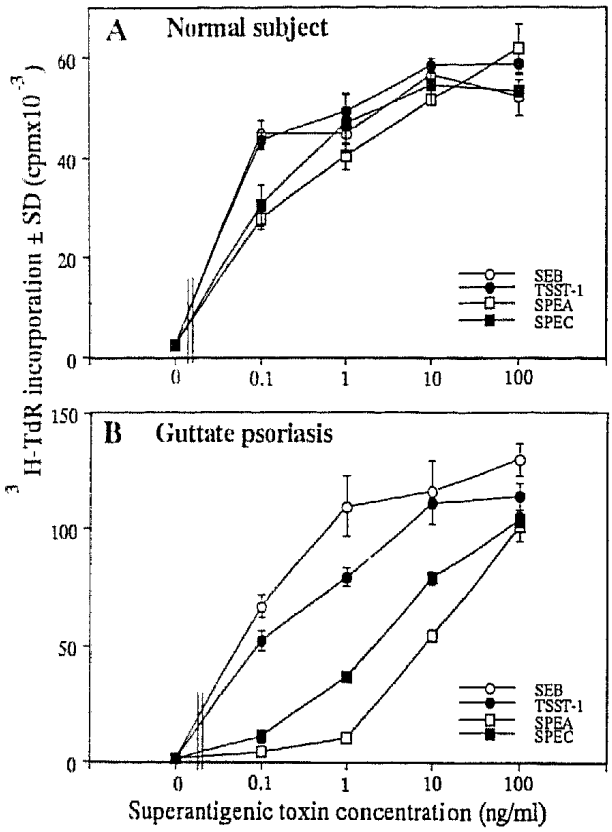

Fig. 1 A, B Poor responses to SPEA and SPEC of PBMC from patients with active guttate psoriasis. PBMC from a normal subject (**A**) and PBMC from a representative patient with guttate psoriasis on presentation of active eruption (**B**) were cultured for 3 days in the presence of SEB, TSST-1, SPEA, or SPEC at the indicated concentrations. The proliferative responses were measured by incorporation of ^{3}H-TdR. Vertical bars represent SD

of our previous studies [18] and those of another group [20]. At 0.1 ng/ml, however, PBMC of guttate psoriasis were significantly less reactive to SPEA and tended to be less reactive to SPEC than those of plaque psoriasis, whereas responsiveness to SEB and TSST-1 at this concentration was comparable between the PBMC from these two types of psoriasis. The SI of Con A stimulation were: guttate psoriasis PBMC, 30.8 ± 15.8; plaque psoriasis PBMC 30.6 ± 13.1; and normal PBMC 36.8 ± 9.9, indicating no significant difference in responsiveness to this polyclonal mitogen among the three PBMC groups.

The SI analysis was able to detect low responsiveness to SPEA and SPEC in PBMC from guttate psoriatics when these toxins were used in culture at low concentrations. However, evaluation of T-cell reactivity by means of SI is generally biased by the background count, as low background levels give rise to high SI. The mean ± SD background counts per minute of the three groups in this study were: guttate psoriasis PBMC 2060 ± 1136; chronic plaque psoriasis PBMC 1481 ± 1377; and normal PBMC 2988 ± 1796. Moreover, in all three groups, there were significant inverse correlations ($P < 0.05$) between the SI and the background count under stimulation with SEB and TSST-1. Therefore, it is necessary to evaluate the PBMC responsiveness by another index that is not influenced by the background. We therefore used the percentage proliferation to each toxin relative to SEB calculated as (cpm of the culture stimulated with the particular toxin)/(cpm of the culture stimulated with SEB) × 100. Figure 3 summarizes these values at toxin concentrations of 10, 1, and 0.1 ng/ml from cultures of PBMC from patients with guttate psoriasis, chronic plaque psoriasis and streptococcal impetigo, and from normal subjects. When

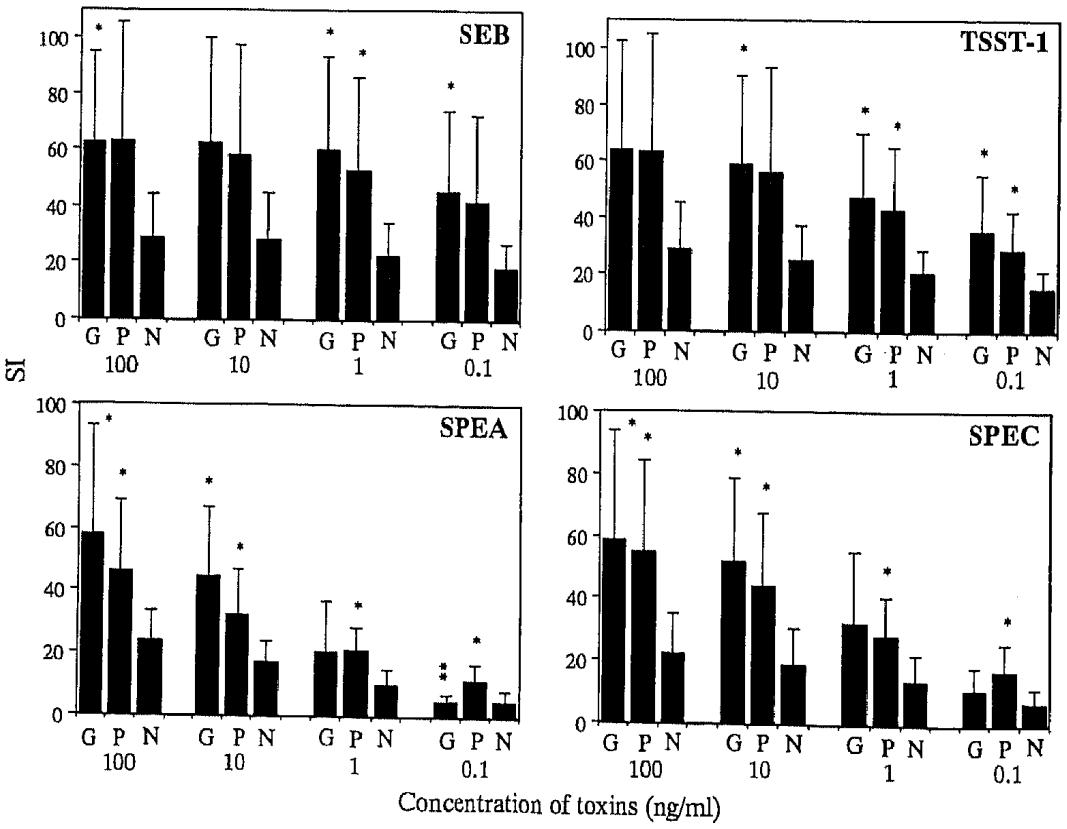

Fig. 2 SI of the responses to superantigenic exotoxins of PBMC from patients with acute guttate psoriasis and chronic plaque psoriasis, and normal subjects. PBMC from patients with guttate psoriasis (*G*) and plaque psoriasis (*P*) and from normal subjects (*N*) were cultured with SEB, TSST-1, SPEA, or SPEC at the indicated concentrations. The response of PBMC to each toxin is expressed as the mean ± SD of the SIs of each PBMC group (*$P < 0.05$, compared with the corresponding normal PBMC)

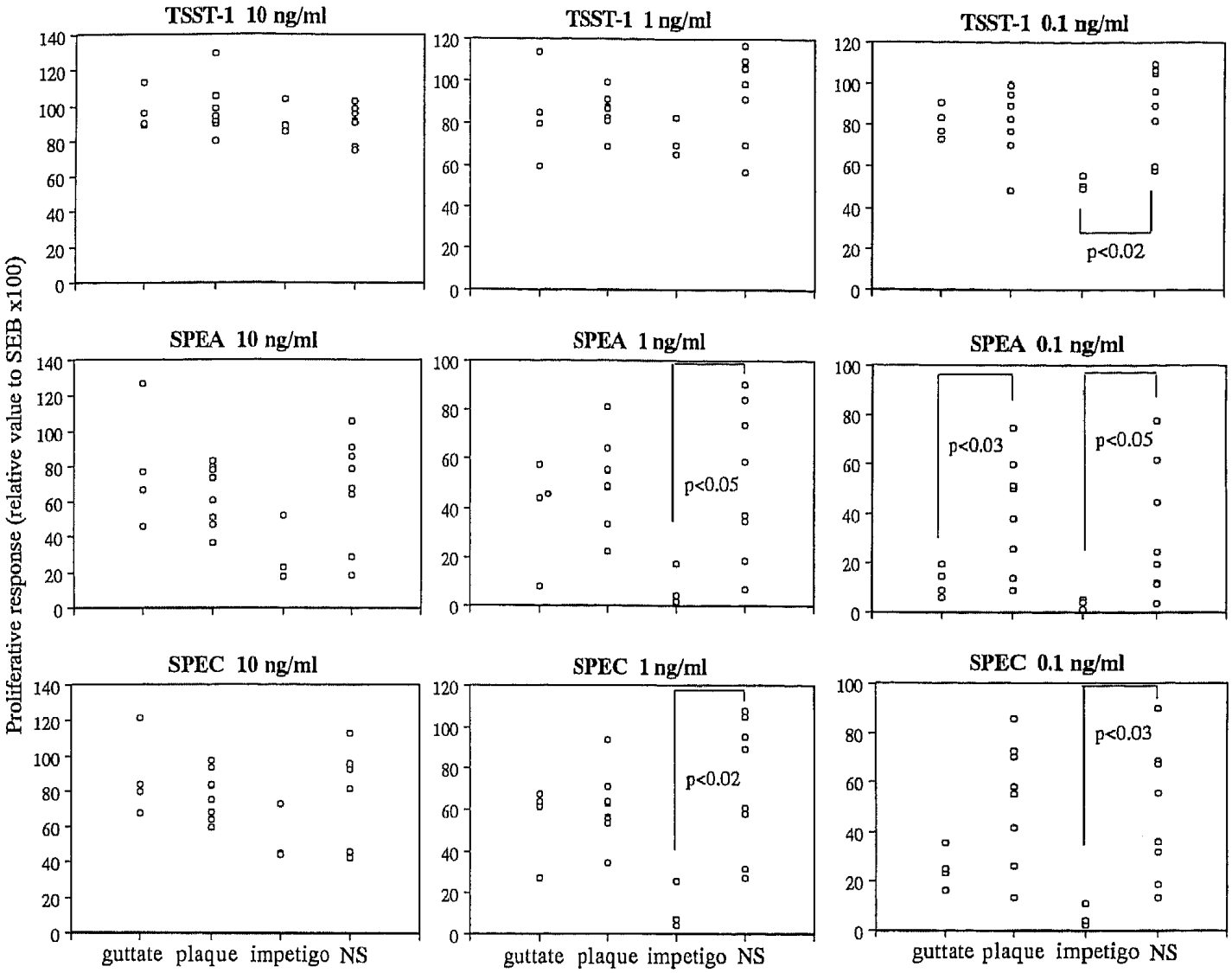

Fig. 3 Percentage proliferation of PBMC in response to TSST-1, SPEA, and SPEC relative to SEB. PBMC from patients with guttate or plaque psoriasis, atopic patients with streptococcal impetigo, and normal subjects were cultured with SEB, TSST-1, SPEA, or SPEC at the indicated concentrations. Data are expressed as the percentage proliferation in response to each toxin relative to SEB calculated as (cpm of the culture stimulated with the particular toxin)/(cpm of the culture stimulated with SEB at the same concentration) × 100

PBMC were stimulated with 10 (Fig. 3) or 100 ng/ml (data not shown) of the toxins, there was no significant difference among the groups. At 1 and 0.1 ng/ml, streptococcal impetigo PBMC exhibited significantly lower responses to SPEA and SPEC than normal PBMC, a known hyporesponsiveness presumably due to clonal anergy of T cells reactive to streptococcal superantigens [24]. At 0.1 ng/ml, guttate psoriasis PBMC, although less marked than impetigo PBMC, also showed a tendency to low responsiveness to SPEA and SPEC. A statistically significant difference was observed in SPEA reactivity between guttate and plaque psoriasis PBMC. Whereas PBMC from impetigo patients responded poorly to TSST-1 at this concentration, those from guttate psoriasis patients showed comparable levels of TSST-1 reactivity to normal PBMC. Thus, PBMC from guttate psoriasis hyporesponded to streptococcal superantigens when cultured with low concentrations of the toxins.

The reactivities of PBMC from three guttate psoriasis patients were tested again 6 to 8 weeks after the first examination, when the skin eruption had been improved by oral administration of antibiotics. The percentage proliferation in response to SPEA and SPEC relative to the response to SEB was substantially increased in PBMC from patients 1 and 2, respectively, while the proliferative response to TSST-1 was decreased (Fig. 4). In PBMC from patient 3, the levels of response to SPEA and SPEC were dramatically elevated with a slight increase in TSST-1 reactivity. This suggests that the hyporesponsiveness of peripheral T cells to streptococcal superantigens occurs mainly during the active stage of guttate psoriasis and recovers gradually thereafter.

In parallel with the T-cell proliferation assay, PBMC from all four patients with guttate psoriasis, seven out of eight patients with plaque psoriasis, and six out of eight normal subjects were phenotypically examined in terms of their expression of BVs as well as CD3, CD4 and CD8. T cells reactive to each superantigen bear the following BVs: SEB, BV3, 12, (13.2), 14, 15, 17 and 20 [8, 25];

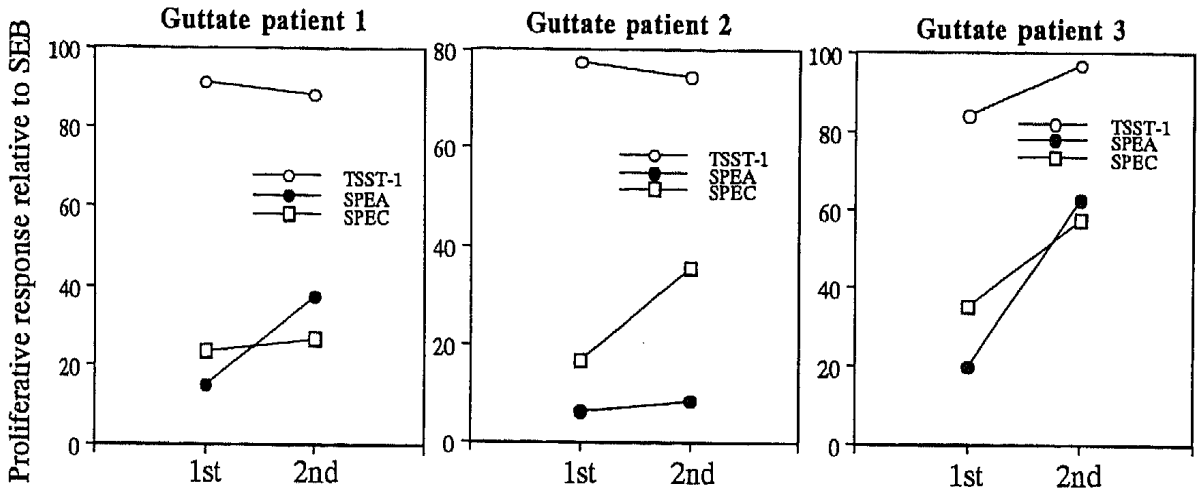

Fig. 4 Changes in PBMC responses to superantigenic toxins after improvement of skin eruption. The responses of PBMC from three patients with guttate psoriasis were re-examined after improvement of their psoriatic lesions. The interval between the first and second examinations was 6 to 8 weeks. Data are expressed as the percentage responses relative to SEB as described in Fig. 2

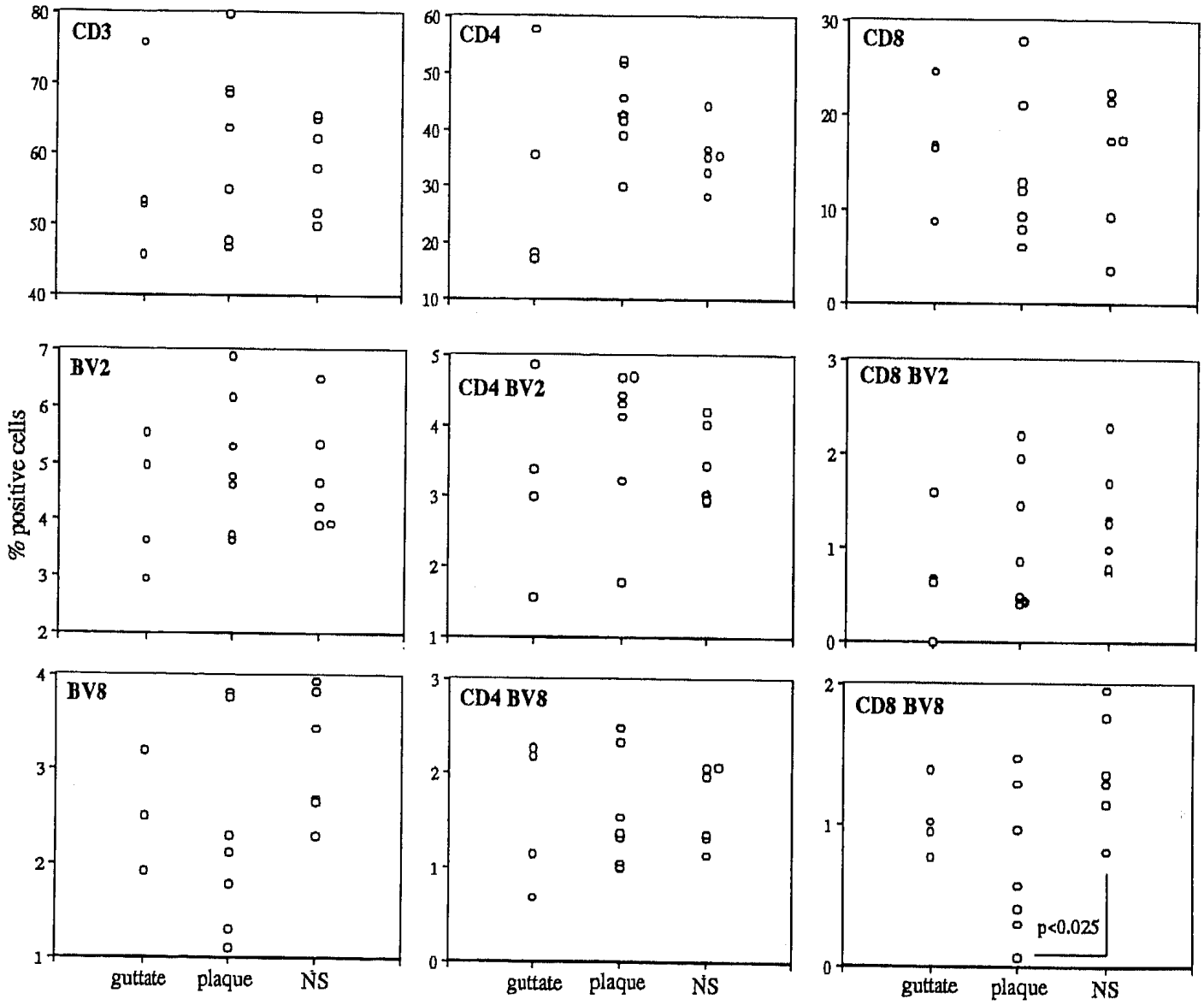

Fig. 5 Immunophenotype of PBMC from patients with acute guttate psoriasis, chronic plaque psoriasis, and normal subjects. PBMC from patients with acute guttate psoriasis (all four patients), chronic plaque psoriasis (seven out of eight patients), and normal subjects (six out of eight patients) were phenotypically analyzed by flow cytometry with single or double staining

TSST-1, BV2 [8, 25]; SPEA, BV2, (8), 12, 14 and 15 [25, 26]; and SPEC, BV1, 2, 5.1, (8) and 10 [25, 26]. In addition, other *S. pyogenes*-derived superantigens include: SPEB (activating T cells bearing BV8) [25, 26]; CAP (BV8) and SCAP (BV4, 7 and 8) [27]; pepM5 (BV2, 4 and 8) [26]; and mitogenic factor (BV2, 4, 8, 15 and 19) [26]. We chose BV2 and BV8 for monitoring because T cells possessing these BVs are reactive with SPEA, SPEC, and other streptococcal superantigens, but not with SEB. As shown in Fig. 5, the percentage of T cells positive for CD3, CD4, CD8, BV2, or BV8 was not significantly different between guttate psoriasis PBMC, chronic plaque psoriasis PBMC, and normal PBMC. The degree of T-cell proliferation, in response to streptococcal toxins did not correlate with the percentage of T cells bearing the relevant BV. In addition, in the PBMC from three patients with guttate psoriasis monitored, there was no substantial change in the percentage of BV2 or BV8 before and after improvement of the skin eruption (data not shown). These findings suggest that the hyporesponsiveness of PBMC to streptococcal toxins is not caused by numerical changes in toxin-reactive T cells, and hence T-cell clonal anergy [28, 29], but not clonal deletion [30], may be a mechanism of hyporesponsiveness. Additionally, $CD8^+BV8^+$ T cells in plaque psoriasis were significantly decreased compared with normal levels, while $CD4^+$ T cells bearing this BV were not decreased.

Discussion

This study showed that PBMC from patients with active guttate psoriasis are hyporesponsive to streptococcal superantigens. Since this low responsiveness was not found under stimulation with staphylococcal superantigens and recovered after improvement of the skin eruption, the hyporesponsiveness is specific for streptococcal toxins and disease course. A similar but more pronounced phenomenon has been observed in patients with streptococcal impetigo [24]. Therefore, throat and skin surface infections with *S. pyogenes* seem to result in virtually the same immunologic consequences for T cells.

The hyporesponsiveness to SPEA and SPEC was not associated with reductions in the percentage of T cells bearing the relevant T-cell receptor BV2 or BV8. This suggests that T-cell anergy is a mechanism of the hyporesponsiveness, as has been observed in streptococcal impetigo [24] and toxic shock syndrome [31]. The cascade of events leading to the T-cell hyporesponsiveness in guttate psoriasis seems to be as follows: superantigens released from *S. pyogenes* infecting tonsils and/or pharynx induce a transient activation of T cells which leads to the development of skin eruption, followed by temporary T-cell anergy to these toxins. In this suggested change of events, the anergic hyporesponsiveness of relevant T cells does not induce the development of psoriatic lesions, but is a sequela of preceding T-cell activation with streptococcal superantigens. Circulating superantigen can be detected in patients with streptococcal toxic shock syndrome [32]. Such systemic diffusion of exotoxins, although small in amount, may also occur in throat infections with *S. pyogenes*. Alternatively, locally stimulated T cells might emigrate to the blood after expansion in regional lymph nodes.

Streptococcal superantigens reportedly include SPEA, SPEB, SPEC, CAP, SCAP, pepM5, and mitogenic factor [25–27]. Although superantigenicity of some of these toxins remains controversial [26], hyporesponsiveness of certain T-cell populations is potentially inducible by any of these toxins. Horiuchi et al. [18] have reported that psoriatic PBMC show significantly lower responses to CAP and SCAP, but not staphylococcal superantigen SEA or SEE, than PBMC from healthy controls. They have suggested the existence of anergy of a population of peripheral lymphocytes to the superantigens and the presence of serum inhibitors specific for T-cell response to the superantigens in psoriatic patients. The phenomenon of hyporesponsiveness that they observed appears to be virtually identical to ours. However, there was no significant difference in the response of PBMC of guttate and plaque psoriasis in their study. It is possible that CAP and SCAP are more profoundly involved in the pathogenesis of chronic plaque psoriasis than SPEs, while SPEs are more pathogenic in guttate psoriasis, which might account for the difference between their and our observations.

In this study, we found that $CD8^+$ T cells bearing BV8 were significantly decreased in percentage in chronic plaque psoriasis (mean, 0.73%) compared with the percentage in normal subjects (1.39%), while the percentage of $CD4^+BV8^+$ cells (1.58%) was comparable to that in normal subjects (1.66%). In guttate psoriasis, although not statistically significant, a similar reduction in $CD8^+BV8^+$ T cells (0.99%) with a normal percentage of $CD4^+BV^+$ cells (1.57%) was observed (see Fig. 5). In addition, the percentage of $CD8^+BV2^+$ T cells was also reduced in average in guttate (0.73%) and plaque (1.11%) psoriasis compared with the percentage in normal subjects (1.30%) with comparable numbers of $CD4^+BV2^+$ cells (3.21%, 3.89%, and 3.43%, respectively). It has been reported that $CD8^+$ T cells predominate in epidermal lesions of psoriasis [33, 34], suggesting an important role for this type of T cell in triggering skin eruption. Leung et al. [12] have reported that when compared with peripheral blood repertoire, $V\beta2^+$ T cells markedly accumulate in the perilesional skin and acute skin lesions of guttate psoriasis and a high number of $BV8^+$ cells also occasionally infiltrate the skin. This is consistent with the observation by Lewis et al. [35] of a marked over-representation of $BV2^+$ T cells in skin lesions of guttate psoriasis. In addition, our previous observations have shown that the numbers of skin-infiltrating $BV2^+$ and $BV8^+$ cells are higher in plaque psoriasis than in other skin diseases such as atopic dermatitis [36]. Taken collectively, the results indicate that $CD8^+$ T cells bearing BV2 or BV8 become positive for cutaneous lymphocyte-associated antigen following stimulation with streptococcal superantigen(s) [37] and enter the epidermis to trigger psoriatic lesions. Massive migration of those T cells might result in their reduced numbers

in the peripheral blood. Furthermore, it is possible that when these CD8+ cells become anergic, they play a down-regulatory role or lead to a termination of the disease process.

The extent to which chronic plaque psoriasis is also evoked by superantigens remains to be elucidated. The numerical assessment of BV2+ and BV8+ T cells in the blood and skin lesions shows similarities between plaque and guttate types of psoriasis [36]. However, it should be noted that the results of studies of βV usage by skin-infiltrating CD4+ or CD8+ T cells in plaque psoriasis using polymerase chain reaction-based molecular techniques are not consistent [16, 38–42]. This indicates that immunologic triggers, e.g. superantigens, conventional antigens, and autoantigens [43], are more various in plaque psoriasis than the guttate type. In this respect, it is likely that the superantigenic contribution is more apparent in guttate psoriasis, as evidenced by the clearly observed hyporesponsiveness of peripheral lymphocytes to streptococcal superantigens.

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