The T Cell Receptor Repertoire in Psoriatic Synovitis Is Restricted and T Lymphocytes Expressing the Same TCR Are Present in Joint and Skin Lesions

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ABSTRACT. ***Objective.*** To investigate the T cell receptor (TCR) repertoire in psoriatic synovitis and to determine whether T lymphocytes in joint and skin lesions show the same Vß CDR3 region.

Methods. The expression of Vα and Vß families was evaluated by reverse transcriptase-polymerase chain reaction. The CDR3 region of some Vß families was analyzed by cloning and sequencing.

Results. We found a diverse variable ß chain usage within psoriatic synovial fluid of 11 patients although some Vα and Vß families were more frequently expressed without evidence of clonality. Analysis of TCR in skin and synovial lesions of 3 patients showed identical CDR3 sequences, indicating that T cells bearing the same TCR are present at the 2 sites of chronic inflammation.

Conclusion. These data suggest that common or similar crossreactive antigens present in the 2 locations are responsible for the expansion of the same TCR-bearing T cells possibly already activated by a superantigen. This supports the hypothesis that both polyclonal and oligoclonal lymphocyte activation contribute to the initiation and persistence of psoriatic arthritis. (J Rheumatol 2002;29:1914–9)

Key Indexing Terms:
T CELL RECEPTOR   PSORIATIC ARTHRITIS   CDR3   SUPERANTIGEN

Psoriatic arthritis (PsA) is a seronegative spondyloarthropathy that occurs in 5 to 7% of patients with psoriasis[1]. Its prevalence in Northern Italian patients with psoriasis has been reported to be as high as 24%[2].

The etiopathogenesis of PsA is still poorly understood but genetic, immunologic, and environmental factors are believed to play a central role in the induction and perpetuation of the disease, for which new subgroup classifications have been proposed[3-6].

Genetic predisposition to PsA has been extensively studied and different associations with HLA class I and II genes have been reported[4,7-14].

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A large body of evidence suggests that psoriasis is a T cell mediated autoimmune disease induced and/or exacerbated by streptococcal superantigens (SAg)[15]. Analysis of the T cell receptor (TCR) repertoire of T cells infiltrating skin lesions has shown an overrepresentation of Vß2, Vß5.1, Vß8, and Vß12 families[16] known to be recognized by streptococcal SAg[17]. The sequence of the CDR3 region of the Vß families preferentially expressed has given conflicting results, showing either extensive junctional diversity[18,19] or highly conserved amino acid sequences[20,21], which would suggest the involvement of a conventional antigen rather than a SAg in the pathogenesis of psoriatic lesions.

T cells also play a central role in psoriatic synovitis, but only 2 studies have been reported on the TCR repertoire in psoriatic joints[21,22]. We studied the TCR repertoire expressed in psoriatic synovitis.

We previously reported the preferential expression of some TCR V genes in rheumatoid synovitis, using a semiquantitative polymerase chair reaction (PCR) based technique[23,24]. In this study we used the same method to compare the expression of Vα and Vß gene families in paired synovial fluid and peripheral blood T cells from 11 patients with PsA. The TCR repertoire was also evaluated in the skin of 3 patients, allowing comparison between the 2 sites of chronic inflammation. We then sequenced the CDR3 region of some Vß expressed more in the synovial fluid in order to analyze the presence of clonality. Finally, to evaluate whether clonally expanded T lymphocytes are involved in the pathogenesis of both the cutaneous lesions and the

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synovitis, we compared the CDR3 region of the same Vß family at both sites.

MATERIALS AND METHODS

Patients. Eleven patients (9 men, 2 women) with PsA were studied. Their HLA status and duration of disease are detailed in Table 1. In 3 of the 11 patients, the synovial fluid from both knees was analyzed; one patient was studied on 3 occasions, months apart. Two other patients were studied twice. Peripheral blood (PB) and synovial fluid (SF) samples were obtained at the same time and were used immediately to isolate mononuclear cells. In 3 cases (Patients 6, 9, and 11, Table 1) PB, SF, and skin lesions were analyzed.

Cell isolation and RNA extraction. Paired PB and SF samples were collected in preservative-free heparin (5 u/ml); SF samples were incubated with 3000 units of hyaluronidase (Sigma Pharmaceuticals, Milan, Italy) for 30 min at room temperature. Mononuclear cells were isolated by density gradient centrifugation on Ficoll (Lymphoprep, Nycomed, Oslo, Norway).

Table 1. HLA status and V genes found to be increased in the SF compared to PB of 11 patients.

Patient	Sex	Disease duration, yrs	HLA	Vα	Vβ
1	M	9	A: 26 (10), 29 (19) B: 7, 44 (12), Cw7 DR: 7, 15 (2), 51, 53 DQ: 1, 2	5, 13, 17	—*
2	M	10	A: 30 (19) B: 16, 53; Cw4 DR: 7, 13 (6), 52, 53 DQ: 2,3	2, 5, 7, 11	2, 3, 12, 13.1, 15
3	M	8	A: 1, 2 B: 15 (62); Cw3 DR: 2, w11, w5 DQ: w1 (w6), w3 (27)	R: 4, 5, 6, 9, 14 L: —	5.1, 8, 12, 13.1, 14, 15, 18, 20 2, 5.1, 12, 18, 20
4	M	14	A: 2, 24 (9) B: 35; Cw4 DR: 1, 11 (5), 52 DQ: 1, 7 (3)	R: — L: 6, 18	— 5.1, 11, 13.2
5	F	11	A: 1,3 B: 35, 39 (16) C: w4, s7 DR: 1, 14 (6), 52 DQ: 1	18	10
6	F	10	A: 1, 2 B: 8, 44 (12) C: w4, w6 DR: 4, 8, 53 DQ: 3	3, 5, 7, 15, 18	2, 5.1, 8, 12, 13.1, 14, 15
7	M	4	A: 3, 11 B: 35, 39 (16) C: w4, w7 DR: 4, 8, 52 DQ: 3, 4	—	13.1, 14
8	M	3	A: 2, 24 (9) B: 39 (16), 44 (12) C: w7 DR: 1, 13 (6), 52 DQ: 1	6, 9, 11, 17	3, 5.1, 8, 15, 21
9	M	9	ND	—	5.2, 14, 15, 18
10	M	1	A: 11, 32 (19) B: 44 (12); w4; C— DR: 7, 11 (5), 52, 53 DQ: 2, 7 (3)	R: 14, 15, 16, 17 L:—	13.1, 20 —
11	M	1	A: 1, 2 B: 8, 40;w6 C: w2, w7 DR: 3, 6, 52 DQ: 1, 2	ND	2, 12, 13.1, 21

R: right knee; L: left knee; ND: not done; * —: no V families were found to be increased in the SF.

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Skin biopsy was immediately frozen in liquid nitrogen and then homogenized with a small grinder. RNA was obtained from mononuclear cells and from skin following the cesium chloride-guanidinium thiocyanate method.

PCR analysis of TCR Vα and Vß expression. Reverse transcriptase (RT) PCR analysis was carried out as described[23]. Briefly, 4 μg total RNA was used in each RT reaction, with 50 units of avian myeloblastoma virus reverse transcriptase (Life Technologies, Milan, Italy) and 100 ng of Cß or Cα-specific oligonucleotide (Cß: 5'-CTCTTGACCATGGCCATAAC-3'; Cα: 5'-CAAGCTTTTCTCGACCAGC-3'). The reaction products were added to a master mix for PCR amplification of 22 Vß and 18 Vα families and of the C region. The sequences of the primers used and their relative positions in the TCRß and α cDNA have been described[23]. After a 5 min denaturation step at 95°C, PCR amplification was performed at 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min for a total of 30 cycles on a Perkin-Elmer thermal cycler (Perkin-Elmer, Milan, Italy). Negative controls (without cDNA added) were included for each set of experiments. Five microliters of the 50 μl PCR amplified product were visualized as a single band on ethidium bromide stained 1% agarose gel under UV light.

Quantification of Vα and Vß expression. PCR products were transferred onto a nylon membrane (Hybond N+; Amersham, Buckinghamshire, UK) using a slot blot apparatus (Hybri-slot manifold; BRL, Gaithersburg, MD, USA) and hybridized with a ^{32}P-CTP radiolabeled cDNA. The hybridization signal was analyzed using both a beta counter (Beckman LS 1801) and a densitometer (LKB Bromma Ultrascan xL Laser Densitometer, Sweden).

The level of expression of individual Vß and Vα families was calculated as an expression index, which compares the expression of paired SF and PB T cells from each patient, corrected for differences in the total amount of TCR α and ß mRNA between the 2 locations:

$$(Vsf/Csf)\ (Vpb/Cpb) = \text{expression index}$$

Assay reproducibility and validation of the expression index using pairs of samples of cell lines with known TCR and known number of cells have been reported[23]. Since an expression index > 2 indicates a difference in cell ratio between 100:1 and 1000:1, we used an expression index > 2 as the threshold to indicate a significant increase of a particular V gene family in one compartment over the other.

Cloning and sequencing of NDJ (CDR3) region. DNA obtained from PCR amplification of Vß gene families was blunt-end ligated into double stranded M13mp18 DNA and transformed into *Escherichia coli* TG2 strain. Recombinant phages were identified by screening of filter lifts that were transferred onto Hybond N membranes with a radiolabeled Cß probe. Sequencing was carried out using the dideoxy chain termination method using modified T7 DNA polymerase (Sequenase; US Biochem, Cleveland, OH, USA) and run on a 6% polyacrylamide gel. Nucleotide sequences were translated to obtain the amino acid sequence of the CDR3 region in order to identify the clonotype of the TCR transcript.

RESULTS

HLA status. Table 1 shows the HLA status of the patients analyzed: DR7 was present in 3 patients; one of them (Patient 1) had multiple erosions. DR1 was present in 3 patients, all with severe arthritis, one (Patient 5) with erosions. DR4 was present in 2 patients, one (Patient 6) with an RA-like disease, and finally, DR3 was present in one patient (Patient 11, 22 yrs old), who already had erosions one year after disease onset.

TCR Vα and Vß genes in SF. The Vα and Vß families that were preferentially expressed in patients' SF are shown in Table 1: many different Vα and Vß families were overexpressed in the SF compared to PB. In particular, some Vß were more frequently increased than others: Vß13.1 was increased in the SF of 6 of 11 patients; Vß15 in 5 of 11 patients; Vß2, Vß5.1, Vß12, and Vß14 in 4 of 11 patients; and Vß8 and Vß21 in 3 of 11 patients.

Table 2. Vα and Vß found to be increased in the SF compared to PB of the 3 patients analyzed in different occasions.

Patient	Time Points (mo)	Vα	Vβ
1	0	5, 13, 17	—*
	10	2, 5, 7	—
4	0	R: —	—
		L: 6, 18	5.1, 11, 13.2
	4	R: 5, 9	3, 6, 8, 9, 13.1, 14, 15, 18, 21
		L: 11	13.1, 14, 18, 21
	12	R: —	1, 5.1, 14
		L: 7, 9, 13, 14, 16	2, 5.1, 6, 14, 16, 17
7	0	—	13.1, 14, 17
	19	—	14

* — no V families were found to be increased in the SF compared to PB.

When 2 joints were analyzed simultaneously (Patients 3, 4, 10, Table 1), different patterns of TCR expression were found in different joints (right vs left knee); however, in Patient 3 some Vß were the same. Patient 4 was analyzed 3 times and 2 other patients (Patients 1 and 7) were studied twice; as shown in Table 2, the pattern of the V families increased in SF changes during the course of the disease.

Taken together, these data indicate that different Vα and Vß families are expressed more in the SF of patients with PsA, and that some of the Vß preferentially expressed in the SF are those reported to be recognized by streptococcal SAg (Vß2, 5.1, 8, 12, and 14). These results also imply that psoriatic synovial inflammation is a dynamic process, since the pattern of TCR repertoire may vary at different stages of the disease.

Vß expression in SF and cutaneous lesions. To study the TCR repertoire expressed in cutaneous and synovial lesions, we compared the Vß gene families preferentially expressed in the SF and skin lesions of 3 patients. The pattern of the TCR repertoire in perilesional skin was not different from the pattern found in matched PB samples (data not shown). On the contrary, in the lesional skin, some Vß gene families were more expressed than in PB (Table 3). These findings may be related to a selective recruitment of some T lymphocytes at the site of skin and articular inflammation.

Analysis of Vß CDR3 region. To determine whether the increased expression of certain V gene families in the synovial compartment is due to polyclonal activation or to expansion of a clonal subset bearing a particular TCR, we sequenced the CDR3 region of Vß2 that was more expressed in the SF and skin lesion of Patient 11, and the CDR3 region of Vß14 from SF and skin lesion of Patients 6 and 9 (Table 4). These Vß families were chosen because they were pref-

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Table 3. Vβ families found to be increased in the SF and in skin lesion of the 3 patients studied.

Patient	SF vs PB	Skin vs PB
6	2, 5.1, 8, 12, 13.1, 14, 15	2, 12, 14
9	5.2, 14, 15, 18	2, 3, 14
11	2, 12, 13.1, 21	2, 3

erentially expressed in SF and cutaneous lesions and because they are recognized by streptococcal SAg.

We did not find a conserved amino acid sequence in the SF, thus excluding the presence of clonality. On the contrary, different clonotypes were found more than once in the cutaneous lesion. Surprisingly, some sequences were present in both locations, indicating that the same T lymphocytes may infiltrate different sites of inflammation.

DISCUSSION

We show that in psoriatic synovitis, there is a restricted TCR repertoire without evidence of clonal expansion, and that lymphocytes expressing the same TCR are present in joint and skin.

We found that different Vα and Vß genes are increased in different patients, and that the pattern of preferentially expressed V families changes during the disease course, as in rheumatoid arthritis[25] and in psoriatic skin lesions[26], implying that the process of psoriatic skin and synovium inflammation is dynamic. Many reasons may account for the findings of a different preferential V gene usage in different patients: (1) the genetic background, (2) previous systemic and local treatment, (3) the stage of the lesion due to the release of additional self-antigens and/or to epitope spreading[27], and (4) the low number of pathogenic T cells at the site of chronic autoaggression.

Some of the Vß genes found preferentially expressed in the SF, such as Vß13.1, 2, 5.1, 8, 12, and 14, have been reported to be increased in skin lesions and are recognized by SAg. A consequence of SAg stimulation would be an extensive ß chain junctional diversity, and indeed, analysis of the CDR3 region of different Vß that were increased in the SF showed no conserved sequence. These findings support the hypothesis proposed by Valdimarsson, *et al*[15] and by others[19] for the guttate psoriasis skin lesions, that psoriasis may be initiated or exacerbated by ß-hemolytic streptococci and/or to a lesser extent by other possible pathogenic organisms such as *Staphylococcus aureus* and *Candida albicans*. Staphylococcal SAg seem to exacerbate PsA[28], whereas streptococci reactive T lymphocytes seem unlikely to play a role in the pathogenesis of PsA[29]. Both host factors and immunologic triggers probably differ in the different forms of cutaneous psoriasis and in the onset of PsA.

Our findings on the TCR repertoire in psoriatic synovitis differ from previous reports[21,22] that describe the presence of an oligoclonal population in SF. Different reasons may account for this discrepancy, such as different duration of the disease in the patients analyzed, variances in the patient population (e.g., HLA status), and methodologic differences. Also, analysis of the TCR repertoire in skin lesions has given conflicting results[18-21].

The patients whose repertoire has been studied in SF and skin lesions showed the presence of multiple clonotypes in the cutaneous lesion analyzed, but not in the perilesional skin. The significance of these different T cell clones present at very low frequency (< 10%) is uncertain, although activation in an oligoclonal manner following antigen recognition is the only possible explanation. Remarkably, when the CDR3 sequences of different Vß in the SF and skin were compared, we found that some clonotypes were the same in both locations. The evidence that T cells bearing the same receptor are present at 2 different sites of inflammation are not in contrast with a report by Pitzalis, *et al*[30], who described the lack of the adhesion molecule cutaneous lymphocyte antigen (CLA) in synovium-infiltrating lymphocytes. The clonotypes identified in skin and

Table 4. Frequency and CDR3 sequence of the Vβ clonotypes found in the SF and skin lesions of Patients 6, 9, and 11. The amino acid sequence is shown in a single letter code. The last 4 amino acids of the Vβ segment are shown, followed by the NDN region sequence and the first 3 amino acids of the J region.

Patient	Frequency SF	Frequency Skin	Vβ	NDN	J
6	1/21	3/35	Vβ14 CASS	LSSGG	YGY 1.2
	1/21	4/35	Vβ14 CASS	GE	QET 2.5
	1/21	1/35	Vβ14 CASS	DRASYDE	YF 2.3
9	1/15	1/28	Vβ14 CASS	LISY	NEQ 2.1
	1/15	3/28	Vβ14 CASS	TLGGVP	NYG 1.2
	1/15	2/28	Vβ14 CAS	RNVAGGA	YEQ 2.7
	1/15	1/28	Vβ14 CASS	LGC	NYG 1.2
11	1/35	1/44	Vβ2 CSA	RQGD	TEA 1.1
	1/35	2/44	Vβ2 CS	EGSGRSK	YNE 2.1
	0/35	3/44	Vβ2 CSA	EGGK	NEO 2.1
	0/35	2/44	Vβ2 CS	YEPGLK	QET 2.5
	0/35	2/44	Vβ2 CSA	ETGKD	EQF 2.1
	0/35	2/44	Vβ2 CSA	PGQQK	QET 2.5

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synovium may be either CLA negative, since a high percentage of skin-infiltrating lymphocytes lack the CLA antigen, or may be divergent with regard to this marker, the acquisition of which seems to be necessary for homing to skin but not synovium. Similarly, the finding by the same group of a preferential localization of CD1 positive antigen-presenting cells to the skin but not to the joint seems to be a general property of these cells rather than a disease-specific phenomenon for PsA[31].

Molecular mimicry is a possible mechanism that helps explain autoaggression following infection, and indeed extensive sequence homology between streptococcal M proteins and human 50 kDa type I keratin has been reported[32]. Moreover, monoclonal antibodies that crossreact with group A streptococci and normal and psoriatic human skin[33], as well as circulating T cells from patients with psoriasis responsive to streptococcal M peptides sharing homology with human epidermal keratins, have been described[32,34]. The pathological significance of such cross-reactivity between bacterial antigens and autoantigens is not fully understood. However, autoimmune responses can be triggered by exogenous protein epitopes with crucial amino acids homologous to self-proteins. Indeed, we and others have recently reported that IgG from sera of patients with PsA recognize a philogenetically highly conserved glycine-rich cell wall protein (GRP) that shares homology with autoantigens such as keratin, collagen II, and a viral antigen such as EBNA-I[35]. Moreover anti-GRP-specific T cell clones have been derived from PB of patients with PsA.

Our findings of conserved sequences of the TCR Vß hypervariable region CDR3 in SF and skin lesions of the same patient suggest an immune response towards crossreactive antigens in the 2 sites possibly triggered by exogenous agents via a molecular mimicry mechanism[35,36]. Another possibility is that, depending on the genetic background and the nature of the triggering agent, SAg may activate particular Vß-expressing autoreactive T cells subsequently expanded by a local antigen driven process, as proposed for rheumatoid arthritis[37,38].

Our results are in accord with evidence that both polyclonal and oligoclonal lymphocyte activation contribute to the initiation and persistence of psoriasis[39], and suggest that similar or identical autoantigens are recognized at the 2 sites of chronic inflammation.

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