Natural killer cells and γ/δ T cells in synovial fluid and in peripheral blood of patients with psoriatic arthritis

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Abstract

Objective

NK surface markers and γ/δ TCR antigen are involved in non-MHC-restricted cytotoxicity, which represents a major effector mechanism of the cell-mediated immune response. We evaluated in PsA patients SF and PB lymphocytes expressing these cellular subsets in order to obtain information on the possible role played by them in the disease.

Methods

We studied 29 PsA and 27 RA patients, as well as 27 healthy controls. In 17 PsA and 16 RA patients with knee joint effusion, analysis of SF was performed. SF and PB lymphocyte analysis was performed by direct dual immunofluorescence flow cytometry using anti-CD3, anti-CD4, anti-CD8, anti-CD19, anti-TCR-γ/δ-1 and anti-CD16 and anti-CD56 monoclonal antibodies.

Results

PsA and RA patients had, with respect to controls, lower values (both as percentages and in absolute numbers) of PB T cells expressing γ/δ TCR. SF lymphocytes of PsA and RA patients were characterised, as compared to PB lymphocytes, by lower numbers (both in absolute numbers and in relative terms) of NK and NK-T cells. Considering the absolute numbers of the various lymphocyte subsets, a strong correlation was found in PsA SF between γ/δ T cells and NK ($p < 0.0007$) or NK-T cells ($p < 0.0003$), as well as between NK and NK-T cells ($p < 0.0019$). There was instead no statistically significant correlation among the different SF or PB lymphocytes and the most relevant clinical or serological parameters.

Conclusion

This study, analyzing the impairment of different subsets involved in non-MHC-restricted cytotoxicity, suggests that this component of the cell-mediated immune response seems to play a pivotal role in the development of PsA.

Key words

Psoriatic arthritis, natural killer cells, γ/δ T cells.

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Introduction

Natural killer (NK) cells are large granular cells expressing CD16 and CD56 surface markers that constitute up to 15% (1, 2) of peripheral blood (PB) lymphocytes in normal individuals. The continued presence and function of this CD3 negative lymphocyte subset is integral to the prevention of autoimmune diseases; NK cells appear in fact to play a most important role in immunological surveillance, being responsible for the cell-mediated, non-MHC-restricted destruction of a variety of target cells including neoplastic and virus infected cells (2, 3).

An NK-like non-MHC-restricted cytotoxic activity is also shared by a small proportion of CD3-positive T cells that express CD16 and CD56 surface markers and are therefore indicated as NK-T cells (4) and by the majority of a small (1-9%) subpopulation of circulating T lymphocytes characterised by the presence of γ and δ chains in their T cell receptor (5), which are therefore indicated as γ/δ T cells or γ/δ TCR positive lymphocytes (6). γ/δ T cells may be involved in two apparently polar situations: immunodeficiency and hyperimmune states such as autoimmunity and inflammatory conditions (7).

A reduction in NK cells has been described in many autoimmune diseases (8); moreover, experimental models show that the selective depletion of NK cells from the PB is capable of causing the early onset and exacerbation of autoimmune phenomena (9). In particular, NK and NK T cells have been demonstrated in the plaques of psoriasis (10) and circulating NK cells are reduced in psoriatic patients compared with normal controls (11, 12), observations which have led researchers to hypothesize a role of these cells in the pathogenesis of the disease, where they may modulate autoimmune inflammation and generate proinflammatory cytokines. Modulating effects on immunocompetent cells are also shown by γ/δ T cells (13, 14) which, in advance, have been demonstrated to proliferate in response to stimulation by streptococcal antigen in patients with psoriatic arthritis (PsA), as well as having been observed in rheumatoid arthritis (RA) (15).

Conversely, little and often conflicting data are available on the possible involvement of NK, NK-T and γ/δ T cells in PsA and on their distribution between the synovial fluid (SF) and PB compartments (16-19).

The present study was performed with the aim of evaluating, in PsA patients, the SF and PB lymphocytes that express either the NK surface markers or the γ/δ TCR antigen, in order to obtain more information on the possible role played in PsAby these cellular subsets, which are involved in non-MHC-restricted cytotoxicity, a major effector mechanism of the cell-mediated immune response.

Patients and methods

We studied 29 PsA patients diagnosed by the presence of psoriasis and seronegative peripheral arthritis (20), 27 RA patients classified according to Arnett's criteria (21), and 27 healthy controls matched for sex and age to the PSAgroup.

We evaluated in each patient the main clinical and laboratory parameters, including the number of painful and/or swollen joints, the Ritchie index, morning stiffness, the erythrocyte sedimentation rate (ESR), and serum concentrations of C-reactive protein (CRP) and rheumatoid factor (RF). In 17 PsA and 16 RA patients with knee joint effusions, analysis of SF by therapeutic arthrocentesis was performed.

SF and PB lymphocyte analysis of the patients and normal controls was performed by direct dual immunofluorescence flow cytometry (FACScan, Becton Dickinson, Mountain View, Ca). A Simultest Leucogate reagent was used to establish an optimal lymphocyte gate. Venous blood was taken and analyzed within 6 hours. Phenotypic characterisation of the lymphocytes was carried out, as described elsewhere (22), on whole blood samples using "Lysis-II®" software and the following fluorescein isothiocyanate (FITC) or phycoerythrin (PE) labelled monoclonal antibodies (purchased from Becton Dickinson): anti-CD3, anti-CD4, anti-CD8, anti-CD19, anti-TCR-γ/δ-1 (which reacts with all known γ/δ T cell clones and lines) and anti-CD16 and anti-

CD56 (specific for the NK-associated antigens). To identify NK and NK-like cells, double staining with FITC-labelled anti-CD3 and PE-labelled anti-CD16 and CD56 was used, since NK cells are anti-CD3 negative and anti-CD16 and CD56 positive while NK-like T cells have a double positivity. The percentages of lymphocyte subsets could be converted into absolute values by performing independent whole blood counts.

Statistical analysis

Categorical variables were analysed by the χ^2 test or by Fisher's exact test. The results were presented as the median (25th-75th percentile) and the significance of the differences was determined using the Mann Whitney test for unpaired samples and Wilcoxon's test for paired samples. The significance of any correlation was determined by the Spearman's rank correlation coefficient. P values < 0.05 were considered statistically significant.

Results

The main demographic, clinical and laboratory data of PsA and RApatients are shown in Table I. These features were not significantly different in patients with or without SF samples.

As shown in Table II, PsApatients had, with respect to controls, considerably lower values of PB T cells expressing γ/δ TCR (both as percentages and in absolute numbers), CD4 and CD8 (absolute numbers). A reduction of PB T cells expressing γ/δ TCR was also found in RApatients.

A comparison between the SF and PB lymphocytes subsets in PsA and RA is shown in Table III. SF lymphocytes of PsA patients were characterised, as compared to PB lymphocytes, by lower numbers (both in absolute and relative terms) of NK and NK-T cells (Figs. 1 and 2), while the occurrence of γ/δ, CD4 and CD8 on T cells was variably expressed regarding the absolute number and percentage. The CD4/CD8 ratio was significantly decreased in SF with respect to PB in RA, but not in PsA. Considering the absolute numbers of the various lymphocyte subsets, a strong correlation was found in PsASF between γ/δT cells and NK ($r_s = 0.849$, $p < 0.0007$) and NK-T cells ($r_s = 0.894$, $p < 0.0003$), as well as between NK and NK-T cells ($r_s = 0.792$, $p < 0.0019$). No correlation with other leucocyte subsets and the most relevant clinical or serological parameters was found in PsA patients.

Table I. Main demographic, clinical and laboratory features of patients with psoriatic arthritis (PSA) and rheumatoid arthritis (RA).

	PsA (n = 29)	RA (n = 27)
Mean age (years)	47 (range = 17-76)	53 (range = 19-70)
Sex (M/F)	22/7	5/22
Mean disease duration (months)	83 (range = 4-371)	109 (range = 4-424)
Corticosteroid treatment, no. (%)	7 (24)	17 (63)
DMARDs, no. (%)	14 (48)	14 (52)
ESR (mm/1st hour)*	29 (16-47)	43 (22-64)
CRP(mg/dl)*	1.2 (0.3-4.8)	2.4 (1.2-4.8)
RF+ve, no. (%)	0 (0)	18 (67)
Knee arthrocentesis, no. (%)	17 (59)	16 (59)
SF analysis		
Low viscosity, no. (%)	15 (88.2)	15 (93.7)
Mucin clot, no. (%)		
Good	2 (11.8)	2 (12.5)
Fair	11 (64.7)	9 (56.2)
Poor	4 (23.5)	5 (31.2)
WBC (cells/mL)*	7470 (4250-11300)	13416 (3410-17760)
PMN cells (%)*	70 (60-85)	70 (45-86.5)

DMARDs: Disease modifying antirheumatic drugs
* Median (25th-75th percentile)

Table II. Values (median/25th-75th percentile) of the main PB lymphocyte subsets in patients with PSA (n = 29), RA (n = 27) and in controls (n = 27).

	PsA		RA		Controls	
			Absolute number (n/μL)			
Lymphocytes	1907	(1570-2280)**	2110	(1650-3000)	2245	(1858-2680)
CD3+/CD19-	1319	(1052-1610)**	1534	(1073-2248)	1552	(1427-2005)
CD3-/CD19+	168	(117-230)	212	(120-333)	181	(152-256)
CD3+/CD4+	808	(633-1058)*	1017	(671-1579)	1008	(824-1127)
CD3+/CD8+	440	(333-600)***	440	(264-791)	566	(488-739)
NK cells	213	(153-284)	215	(116-296)	238	(152-392)
NK-Tcells	63	(41-123)	93	(39-181)	89	(46-138)
γ/δTcells	51	(24-76)****	53	(27-92)***	94	(57-120)
CD4/CD8 ratio	1.76	(1.38-2.65)	2.32	(1.44-3.32)***	1.77	(1.24-2.17)
			Relative abundance (%)			
Lymphocytes	24.4	(18.9-31.5)*****	24.8	(19.1-29.8)*****	35.8	(33.1-43.1)
CD3+/CD19-	73.2	(68-75)	75.5	(70.3-80.4)	73.5	(69.9-76.5)
CD3-/CD19+	9.0	(7.0-10.7)	9.1	(5.7-12.2)	8.2	(6.9-10.1)
CD3+/CD4+	45	8 (19-30.9)	21.3	(15.2-28.2)	26.5	(21.2-31)
NK cells	12.2	(7.4-16-1)	8.3	(6.4-13.4)	10.6	(6.8-17.6)
NK-Tcells	3.6	(2.4-5.7)	5.0	(2.0-6.3)	3.9	(2.3-6.9)
γ/δTcells	2.9	(1.6-4)*	2.3	(1.2-3.2)***	3.7	(2.6-5-9)

Versus controls *p < 0.05; **p < 0.025; ***p < 0.01; ****p < 0.005; *****p < 0.001.

Discussion

Non-MHC-restricted cytotoxicity is mediated by different types of cellular subsets, namely NK, NK-T and γ/δ T lymphocytes (1, 2, 6, 23). It has been proposed that, in RAand PsA, NK cells play a role in the immunoregulatory processes promoting chronic synovitis

Table III. Values (median/25th-75th percentile) of paired SF and PB lymphocyte subsets in patients with PSA(n = 17) and RA(n = 16).

	Absolute number (n/mL)							
	PsA				RA			
	SF		PB		SF		PB	
Lymphocytes	1181	(410-1733)**	1874	(1460-2280)	1665	(1201-2290) §	1895	(1605-2775)
CD3+/CD19-	942	(305-1388)	1172	(987-1610)	1363	(1030-2026) §	1315	(883-1967)
CD3-/CD19+	16	(4-27)*****	160	(103-208)	24	(11-41)*****	213	(103-309)
CD3+/CD4+	508	(167-752)**	784	(581-946)	811	(644-1175) §§	896	(641-1297)
CD3+/CD8+	327	(125-569)	403	(325-566)	486	(350-940)	377	(257-500)
NK cells	79	(27-196)***	207	(175-243)	99	(69-203)***	228	(116-405)
NK-Tcells	18	(10-42)*****	60	(40-123)	31	(18-54)*	70	(39-104)
γ/δTcells	28	(10-62)	56	(32-84)	65	(22-110)	46	(22-85)
CD4/CD8 ratio	1.17	(0.97-1.6)	1.75	(1.41-2.28)	1.51	(1.19-2.13)****	2.6	(2.21-3.51)
	Relative abundance (%)							
Lymphocytes	14.0	(5.0-27.2)	22.7	(16.3-30.7)	14.2	(7.6-50.5)	24.2	(15.3-26.5)
CD3+/CD19-	79.0	(77.4-84.1)*****	73.7	(68.1-75)	84.8	(82.2-88.1)***** §§	73.0	(68.2-78.2)
CD3-/CD19+	1.6	(1.1-3.0)*****	8.7	(6.7-10.7)	1.3	(0.9-2.1)*****	8.7	(5.6-11.5)
CD3+/CD4+	42.0	(36.0-48.8)	45.0	(39.0-48.8)	47.7	(43.6-54.9)	48.5	(42-55.8)
CD3+/CD8+	36.0	(30.5-40.7)****	25.7	(17.7-30.9)	32.4	(26.0-36.0)*****	19.0	(14.1-24.4)
NK cells	7.8	(6.6-12.3)***	12.7	(8.5-16.1)	6.6	(5.2-7.5)****	9.4	(7.5-15.9)
NK-Tcells	2.0	(1.1-2.6)****	3.2	(2.4-7.0)	1.6	(1.4-2.5)***	4.1	(1.8-5.9)
γ/δTcells	3.7	(2.3-4.4)	3.2	(1.9-4.5)	3.7	(2.8-7.7)***	2.3	(1.1-3.8)

versus PB *p < 0.05; **p < 0.025; ***p < 0.01; ****p < 0.005; *****p < 0.001
versus SF of PsApatients § p < 0.05; §§ p < 0.025;

both via direct cytotoxic effects on the cells of cartilage and bone (24) and by indirect effects such as the suppression of immunoglobulin production (25), while NK-T cells have never been investigated in PsA.

NK activity has been reported to be lower or unchanged in SF than in paired PB samples from PsA patients, even if it has to be stressed that NK activity failed to correlate with the percentage of NK cells in PB and SF (19). These results can be explained by the evidence that, although CD16 and CD56 are the characteristic markers of human NK cells, their relative expression varies among NK cells at different sites (26). In fact a $CD3^{neg}/CD56^{bright}$ subset of NK cells, predominantly CD16-negative, is preferentially recruited from the periphery and greatly expanded within inflamed joints, where it may be further activated by cytokines (27). The relative expression of CD56 and CD16 affects NK cytotoxicity, cells with higher levels of CD56 and lower levels of CD16 having a lesser capacity to express cytotoxicity (28). CD56 does not appear in fact to play an important role in cytotoxicity (29), although natural killing does not depend on the CD16 IgG receptor (26).

In our study we showed in PsAand RA patients a reduction of NK and NK-T cells in SF as compared to matched PB lymphocytes, but we could not discriminate whether this reduction was linked to CD56 or CD16 expression. The finding in PsA of a strong correlation between the absolute numbers of NK, NK-Tand γ/δ T lymphocytes, i.e of cell types that possess a common NK-like cytotoxic activity, is in agreement with the evidence of common markers and

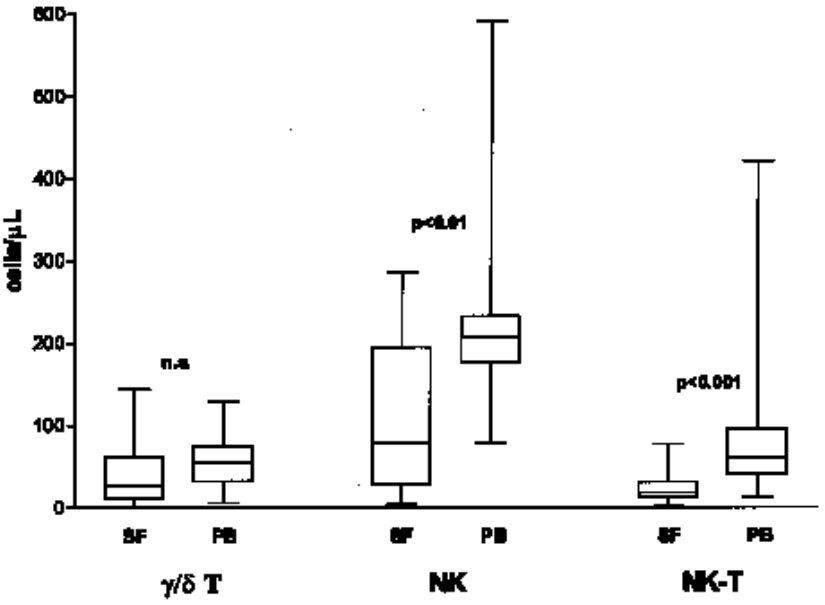

Fig. 1. Absolute values (box and whiskers plot: median/25th-75th percentile/range) of NK, NK-Tand γ/δTlymphocytes in synovial fluid (SF) and peripheral blood (PB) from 17 PsApatients.

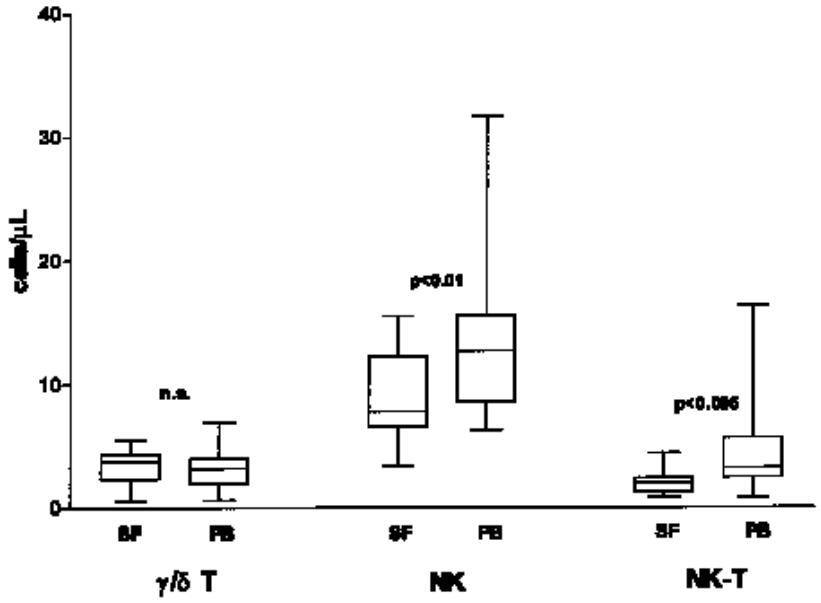

Fig. 2. Relative abundance values (box and whiskers plot: median/25th-75th percentile/range) of NK, NK-Tand γ/δTlymphocytes in synovial fluid (SF) and peripheral blood (PB) from 17 PsApatients.

similarly inhibitory receptor expression (30), perhaps under the influence of the same effector. This observation in any case suggests a possible role of non-MHC restricted cytotoxicity in this disease. The function of γ/δ T cells has so far not been investigated in detail in PsA, and then only in small patient series from which no uniform data have emerged (17,18). Our results show in PsApatients a small reduction (not significant) in the absolute number of this subset in the SF as compared to PB lymphocytes, but we must consider that the absolute number and relative abundance of γ/δ T cells in the PB of PsA patients were lower respect to PB of controls. These results do not agree with a proposed γ/δ T cell-dependent mechanism in RA pathogenesis, in which a continuous expansion of this subset has been hypothesised (7).

Our findings indicate that the low number of NK and NK-T cells in SF, together with the decrease in the number and relative abundance of γ/δ T cells in PB, could reflect a down-regulation of non-MHC-restricted cytotoxicity in PsA, as well as in RA. A possible explanation for this finding may be due to a perturbed homing that decreases the possibility of these cells reaching the joint. Nevertheless, PsAsynovial membrane is characterised by the presence of adhesion molecules (31), which suggests other possible mechanisms responsible for NK reduction, such as apoptosis. In fact, dysfunctional alterations in the NK cells of patients affected by chronic inflammatory conditions have been demonstrated to trigger an intrinsic cell death program (32).

The lack of correlation in RA could be due to the immune regulatory properties of these cell subsets. In fact, NK cells are able to either suppress or support antibody production by directly helping B cells differentiate into antibody-forming cells or by indirectly enhancing the suppressor activity of CD8+ T cells (23,33). Moreover γ/δ T cells appear to exert considerable action on autoimmune processes, either by developing modulatory effects on other T cell subsets or by exerting a regulatory role in the maturation of B cell autoreactivity (34).

Moreover, CD4- and CD8-positive T cell changes in our PsApatients, generally not in early arthritis, could not be easily interpreted (see Tables II and III), with the SF CD4/CD8 ratio being nearly 1:1, confirming that a large prevalence of CD4 T cells is not observed in chronic disease SF (35).

In conclusion, this study shows the impairment of different subsets involved in non-MHC-restricted cytotoxicity, even if the further assessment of the cytotoxic activity and the evaluation of a more complete phenotype may clarify whether this component of the cell-mediated immune response plays a pivotal role in the development of PsA.

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