Predominance of activated, clonally expanded T helper type 17 cells within the CD4+ T cell population in psoriatic lesions

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Summary

Recent evidence points to the T helper type 17 (Th17) subset as key in the pathogenesis of psoriasis, but cells of this type in lesions remain to be fully characterized. Here we isolated, enumerated, functionally tested and clonotyped the CD4+ Th cell population *ex vivo* from lesional biopsies and paired peripheral blood samples from psoriasis patients. Th17 cells were overrepresented dramatically in lesions from all patients, representing 49–93% of CD4+ Th cells compared with 3–18% in blood. Most lesional Th17 cells produced interleukin (IL)-17A *ex vivo* without further stimulation and expressed the CD45RO+ phenotype characteristic of activated or memory cells. There was no increase in 'natural' [CD25^{hi}forkhead box protein 3 (FoxP3+)] regulatory T cells in lesions *versus* peripheral blood, but there was enrichment of 'induced' IL-10+ regulatory T cell numbers in biopsies from some patients. The lesional Th17 cells exhibited a bias in T cell receptor Vβ chain usage, suggestive of specific expansion by antigen. The therapeutic challenge is to overcome the dominance of overwhelming numbers of such antigen-specific Th17 cells in psoriatic lesions.

Keywords: clonal expansion, IL-10, psoriasis, regulatory T cell subsets, T helper type 17 cell

Introduction

Psoriasis is a common and distressing chronic skin disease. It is widely accepted that the condition is T lymphocyte-driven and autoimmune in origin, with genetic, immunological and therapeutic evidence converging to highlight a central pathogenic role for the T helper type 17 (Th17) CD4+ subset [1,2]. Although central to current models of the disease, Th17 cells have yet to be enumerated and characterized directly in lesions.

Th17 cells are characterized by predominant secretion of the inflammatory cytokine interleukin (IL)-17A, and can also produce other mediators such as IL-17F, IL-6, IL-22 and tumour necrosis factor (TNF)-α [3] and express a characteristic combination of chemokine receptors, CCR4 and CCR6 [4]. Factors that promote human Th17 differentiation from uncommitted CD4+ T cells continue to be identified, but include IL-1β and IL-6, with subsequent expansion enhanced by IL-23 [5]. It has become apparent that this subset is responsible for inflammation attributed previously to Th1 cells in a number of autoimmune diseases [3], and

evidence has accumulated linking Th17 effector pathways with psoriasis [6].

Early clinical observations in psoriasis first suggested a role played by Th17 cells. For example, Ustekinumab and Briakinumab, biologics targeting the p40 subunit shared by IL-12 and IL-23 [7–9], have elicited marked clinical improvements in the disease. Th17 cells are equipped to migrate efficiently to the skin, via their chemokine receptors, CCR4 and CCR6, which mediate chemotaxis specifically to CCL17 and CCL20 expressed on cutaneous endothelium and dermal fibroblasts [10,11]. Cells capable of producing IL-17 have now been detected in psoriatic lesions [12,13] and may correspond to the Th17 phenotype .

In addition to effector subsets, the CD4+ helper population includes at least two regulatory T (T$_{reg}$) cell types, defined as 'natural' and 'antigen-induced' (also known sometimes as 'adaptive'), which are important in the maintenance of self-tolerance and resolution of immune pathology [14–17]. Natural T$_{regs}$ are committed to a regulatory phenotype in the thymus, constitutively express activation

markers such as CD25hi, are characterized by the transcription factor forkhead box protein 3 (FoxP3) and suppress via cell–contact-dependent mechanisms, at least *in vitro*. In contrast, antigen-induced T_{regs} differentiate from naive T cells in the periphery and regulate by secreting inhibitory cytokines such as IL-10 and transforming growth factor (TGF)-β1. Antigen-induced T_{reg} can be divided further into subtypes on the basis of cytokine secretion, with T regulatory 1 (Tr1) cells producing IL-10 and little IL-2, IL-4 or TGF-β1, while Th3 cells make high levels of TGF-β1, but only small amounts of IL-10 or IL-4 [18]. Natural, but not induced, T_{regs} have been studied in psoriasis, and although present in lesions appear to have a reduced capacity to inhibit effector responses [19]. Recently, natural T_{regs} have been shown to have the capacity to differentiate into IL-17-producing Th17 cells in psoriasis under inflammatory conditions [20].

Despite the evidence accumulating to implicate the Th17 subset in psoriatic pathology [21,22], a number of important questions remain unanswered. These include the numbers of lesional Th17 cells within the CD4+ helper population, their ability to mediate inflammatory functions and their state of activation. Previous studies have relied primarily on assays of IL-17A protein or message to detect Th17 cells, but such approaches can be confounded by the ability of other cell types, including γδT cells, CD8 memory T cells, eosinophils, neutrophils and monocytes to also produce the cytokine [4,23]. Moreover, IL-17 release by mast cells and neutrophils may contribute to the pathology of the disease [24]. Another limitation has been the dependence on techniques to expand and extract cells from lesions, which preclude the direct enumeration of Th17 cells *ex vivo*. Furthermore, not all the Th17 in lesions would be detected by IL-17A assays if the cells were inactive or suppressed by the T_{reg} cells that are also reported to be present [19]. It is therefore necessary to identify the exact nature of the IL-17A-producing cells in psoriatic lesions. The balances locally between Th17 cells and both natural and induced T_{reg} cells are important potential determinants of whether or not the inflammation perpetuates or resolves. What drives any Th17 expansion in lesions also remains to be established and, in particular, whether this is the result of an antigen-specific response, which would be predicted if the Th17 cells are the primary effectors of an autoimmune pathology.

The current study addressed directly the questions outlined above by characterizing CD4+ lymphocytes isolated directly *ex vivo* from untreated lesional psoriasis and from paired samples of peripheral blood. The first aims were to enumerate Th17 cells with a panel of characteristic surface markers that are independent of activation state, and then determine their ability to mount IL-17A and other cytokine responses. Any relative expansion of Th17 and natural or induced T_{reg} cells in lesions *versus* peripheral blood was also established. Finally, it was ascertained whether the Th17

lesional population had undergone clonal expansion as evidenced by biased T cell receptor (TCR) Vβ chain usage.

Materials and methods

Patients

Twenty-two patients aged 20–65 years (median age 50 years, 16 male, six female) were recruited with lesions that had been untreated with systemic agents or phototherapy for 1 month, or with topical therapy for 2 weeks, prior to investigation. Lesional skin was biopsied using a 6-mm punch. Two patients attending clinic for nevus excision were recruited as healthy donors, with the distal portions of the ellipse and peripheral blood collected. Skin samples were disaggregated physically immediately *ex vivo* for 1 min using 50 μM medicons in the Medimachine (BD Biosciences, San Diego, CA, USA), allowing efficient collection of viable lymphocytes [25]. The cell suspension was then prepared for culture or flow cytometry [26]. In addition, paired donations of blood from the patient group were collected by venepuncture into heparin. Peripheral blood mononuclear cells (PBMC) were obtained by density gradient centrifugation (Ficoll-Paque; Amersham Biosciences, Piscataway, NJ, USA).

The study was approved by the North of Scotland Research Ethics Committee, and followed the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients gave written informed consent.

Flow cytometry

The numbers of cells of each Th subset were determined by flow cytometry. Cell suspensions were analysed after staining with combinations of the following antibodies: anti-CD3-fluorescein isothiocyanate (FITC) (Beckman Coulter, Fullerton, CA, USA), anti-CD4-FITC or anti-CD4-allophycocyanin-cyanine 7 (APC-Cy7), anti-CCR4-phycoerythrin (PE)-Cy7, anti-CCR6-AlexaFluor 647 or anti-CCR6-PE (BD Pharmingen, San Diego, CA, USA), anti-IL-23R-APC or anti-IL-23R-PE (R&D Systems, Abingdon, UK) for Th17 cells [4]. Anti-CD45RO-FITC (clone UCHL1, a generous gift from Diaclone, Besançon, France) was used to identify activated or memory T cells [27]. Anti-CD25-AlexaFluor 700 (BioLegend, San Diego, CA, USA) or anti-CD25-PE-Cy5 (Beckman Coulter) plus anti-FoxP3-AlexaFluor 647 (BD Pharmingen) and anti-IL-10-Pacific blue (eBioscience, San Diego, CA, USA) allowed respective identification of the natural and induced T_{reg} populations. The production of IL-17A was measured by intracellular staining using anti-IL-17A-AlexaFluor 647 (eBioscience). For intracellular protein staining, cells were fixed and permeabilized using the Cytofix/Cytoperm kit (BD Biosciences), as per the manufacturer's protocol. IFN-γ pro-

duction was assessed using an anti-IFN-γ-PE antibody (Beckman Coulter). Compensation beads (BD Pharmingen) were used for each sample, providing single positive controls for voltage adjustments and compensation calculations.

Unless stated otherwise, the cytoplasmic staining of cytokines was enhanced by 12 h cell culture with 10 μg/ml Brefeldin A (Sigma-Aldrich, St Louis, MO, USA). In some experiments, cells were activated with 25 ng/ml phorbol 12-myristate 13-acetate (PMA) and 2 μg/ml ionomycin (Sigma-Aldrich) and cultured with Brefeldin A.

The clonality of CD4+ populations was assessed using a commercially available flow cytometry array kit (Beckman Coulter) containing antibodies specific for a panel of human TCR Vβ chains.

Data from each patient were acquired independently on different days using the LSR II (BD Biosciences) and analysed using FCS Express version 3 software (DeNovo Software, London, ON, Canada) and FlowJo version 7 (Tree Star Inc., Ashland, OR, USA). Cell populations were consistently gated and subgated on isotype controls.

Immunohistochemistry

Tissue samples were fresh-frozen, sectioned and fixed with acetone. Sections were incubated with a panel of primary antibodies detailed in the flow cytometry section, followed by a biotinylated anti-mouse secondary antibody (Vector Laboratories, Peterborough, UK). Positive staining was visualized using the avidin–biotin–horseradish peroxidase complex (the Vectastain Elite ABC Kit) (Vector Laboratories). Sections were counterstained with haematoxylin and Scot's tap water, as detailed by the manufacturer. A no-primary antibody (NPA) section was used as a negative control.

Statistics

Statistical analyses were conducted by the non-parametric Kruskal–Wallis test using Minitab® Statistical Software (Minitab Ltd, Coventry, UK). The level of significance was taken as $P < 0.05$.

Results

Expansion of the Th17 subset in psoriatic lesions

The main purpose of the work was to identify, enumerate and characterize precisely Th17 cells in psoriatic lesions. Initial flow cytometric analyses focused on combinations of surface markers, in particular CCR4+CCR6+ and IL-23R, which can be used to identify human Th17 cells [4] independent of their activation state or current ability to secrete cytokines. IL-23R can also be expressed on γδ T cells and natural killer (NK) cell lines, and at low levels on mono-

cytes, macrophages and dendritic cells [28], but staining in combination with the other markers supports the identification of the Th17 phenotype. Representative data from two psoriatic individuals are illustrated in Fig. 1a,b and one healthy control in Fig. 1c, with the results from the patient group summarized in Fig. 1d. It can be seen that, typically, cells with this Th17 phenotype make up more than 50% of the CD4+ population in lesions (mean 57·6%, $n = 6$), compared with fewer than 15% in peripheral blood (mean 11·2%, $n = 6$). The consistent over-representation of the Th17 cells in lesions *versus* peripheral blood is highly significant ($P < 0.001$, Kruskal–Wallis test) and striking, in some cases with, for example, the vast majority (> 90%) of lesional CD4+ cells expressing the Th17 phenotype in one individual (Fig. 1b). To corroborate these results, expression the receptor for the Th17 growth factor IL-23 [29] was also determined. Figure 1 demonstrates a significantly increased proportion of CD4+ cells with this marker in lesions *versus* peripheral blood, comparable to that observed for the CCR4+CCR6+ phenotype. Healthy control skin, as expected, contains lower Th cell numbers. The large lesional CD4+ population, including IL-23R+ cells, can be visualized in both the dermis and the epidermis by immunohistochemistry (Fig. 4b).

Functional and activation state of Th17 cells in psoriatic lesions

The next experiments were designed to determine the proportions of Th17 cells that are functionally active in producing the signature cytokine IL-17A. Peripheral blood and lesional cells were permeabilized and stained for IL-17A, either directly *ex vivo* or after brief culture with Brefeldin A, which increases the sensitivity of intracellular cytokine detection by blocking secretion and promoting cytoplasmic accumulation (Fig. 2). The results of flow cytometric analysis demonstrate that only rare peripheral blood CD4+ cells with either the CCR4+CCR6+ or IL-23R+ Th17 phenotypes also stained for IL-17A but by contrast, after brief incubation, 20–42% of lesional Th17 cells were active in producing this cytokine. IL-17A production by lesional cells was strongest after incubation with the potent polyclonal activator PMA/ionomycin and Brefeldin A, but in many cases there was spontaneous production sufficiently robust to be detectable even in the absence of these treatments (Fig. 2b).

The functionality of the lesional CD4+ population was dissected further by asking whether it also includes cells producing inflammatory cytokines of the Th1 rather than the Th17 type. Peripheral blood and lesional CD4+ T cells were co-stained for intracellular IL-17A and IFN-γ after incubation with Brefeldin A and analysed by flow cytometry. Figure 3a demonstrates that, as expected, few peripheral blood CD4+ cells produced either effector cytokine in the absence of any *ex-vivo* stimulation, while a large fraction (> 29%) of the lesional population stained for IL-17A only,
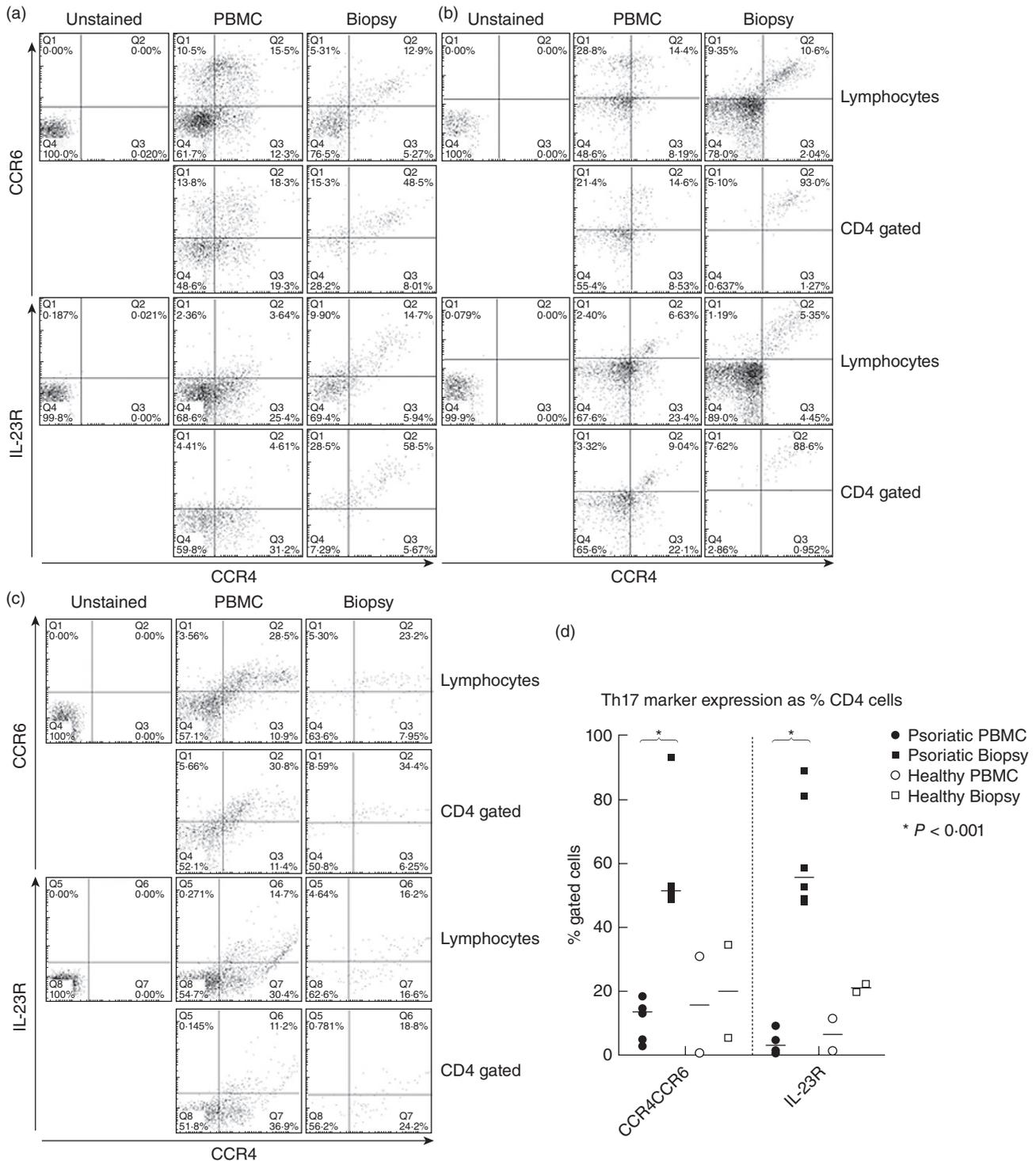
Fig. 1. CD4+ lymphocytes expressing T helper type 17 (Th17) markers CCR4 and CCR6 or interleukin (IL)-23R are greatly enriched in psoriatic lesions compared with peripheral blood. (a,b) Representative flow cytometric analyses from two patients and (c) from a healthy control. For each set, the expression of CCR4 and CCR6 (upper set) or CCR4 and IL-23R (lower set) are illustrated for paired samples of peripheral blood mononuclear cells (PBMC) (middle) and lesional cells (left), gated on the lymphocyte population (upper pairs), or CD4+CD3+ cells (lower pairs). Th17 cells stain CCR4+CCR6+ or CCR4+IL-23R+, (upper right quadrants). (d) Summarizes data from analyses of CD4+ cells from lesional biopsies and blood of psoriatic patients (n = 6) and healthy controls (n = 2), demonstrating the percentages of CD4+ cells that express Th17 markers (bar indicates median value; *P < 0·001, Kruskal–Wallis test).
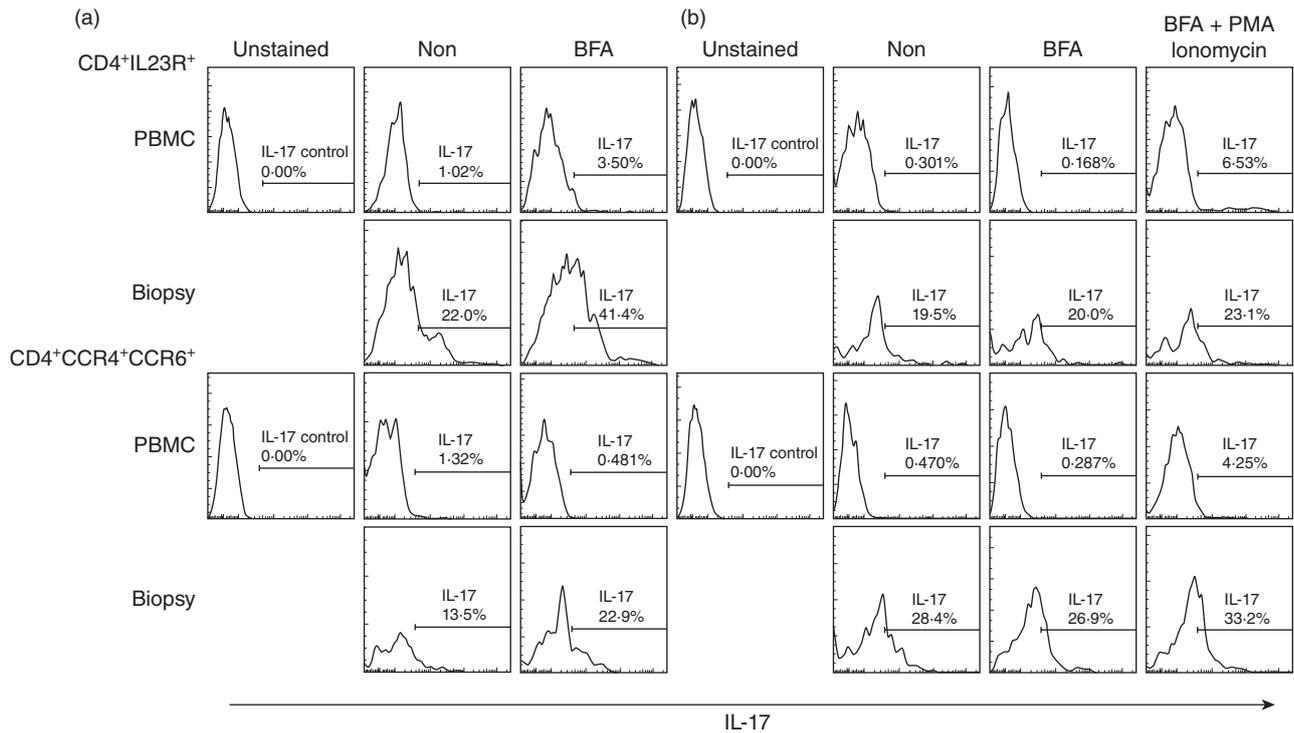
Fig. 2. Abundant production of interleukin (IL)-17A by CD4+ T cells expressing the T helper type 17 (Th17) markers CCR4 plus CCR6 or IL-23R from psoriatic lesions but not peripheral blood. (a,b) Representative flow cytometric analyses of peripheral blood mononuclear cells (PBMC) and paired lesional biopsies from two patients demonstrating the percentages of CD4+IL23R+ (upper sets of panels) or CD4+CCR4+CCR6+ (lower sets of panels) T cells that stain for intracellular IL-17A. Cells were stained for spontaneous IL-17A production *ex vivo* (Non), or after 12 h culture in Brefeldin A (BFA) to enhance cytokine accumulation, or after stimulation with phorbol 12-myristate 13-acetate (PMA)/ionomycin and culture with BFA. The marked spontaneous production of IL-17A by lesional Th17 phenotype cells indicates that they have been activated to produce cytokine *in vivo*.

up to 9% for both IL-17 and IFN-γ and up to 6% for IFN-γ alone, consistent with the mixed phenotypes elicited typically in human Th cells, even in highly polarized responses [30].

The *ex-vivo* flow cytometric assays for spontaneous cytokine production are consistent with the lesional Th17 cells having been activated *in vivo*. To confirm this activation status, peripheral blood and lesional CD4+ cells were analysed for co-expression of the Th17 marker IL-23R and CD45RO, which stains recently activated or memory human Th cells [27] (Fig. 3b). Approximately 40–45% of peripheral blood IL-23R+ cells were CD45RO+, consistent with previous studies of CD4+ populations in healthy adults [27] but, by contrast, more than 79% of lesional Th17 cells were of the activated or memory phenotype.

Natural and induced T$_{reg}$ cells in psoriatic lesions

The dramatic expansion of Th17 cells in psoriasis lesions leads to the question of whether or not there is any comparable increase in local T$_{reg}$ cells that might balance their activity. FoxP3 cells can be seen in the dermis and the epidermis by immunohistochemistry (Fig. 4a), and the
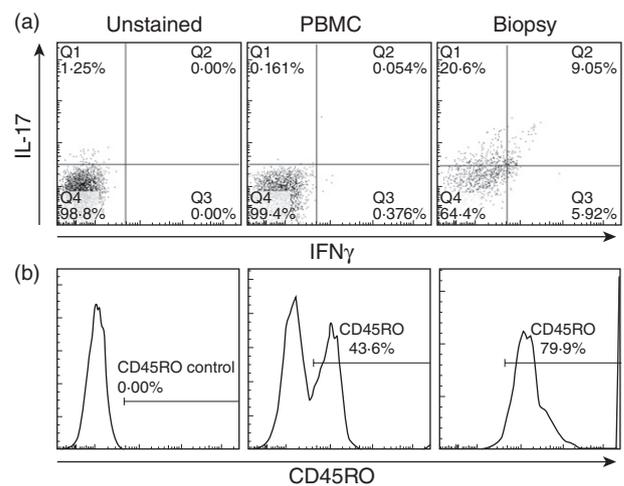

Fig. 3. T helper type 17 (Th17) cells from psoriatic lesions can produce the Th1 cytokine interferon (IFN)-γ and are all of the activated CD45RO phenotype. Representative flow cytometric plots of paired peripheral blood mononuclear cells (PBMC) and lesional CD4+ T cells showing staining for interleukin (IL)-17A and IFN-γ (a) after 12-h culture with Brefeldin A, or expression of the activation or memory marker CD45RO by IL-23R+ gated Th17 phenotype cells (b).
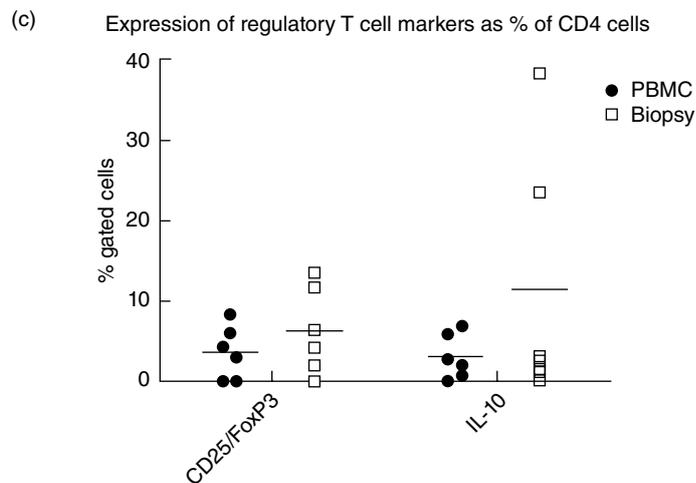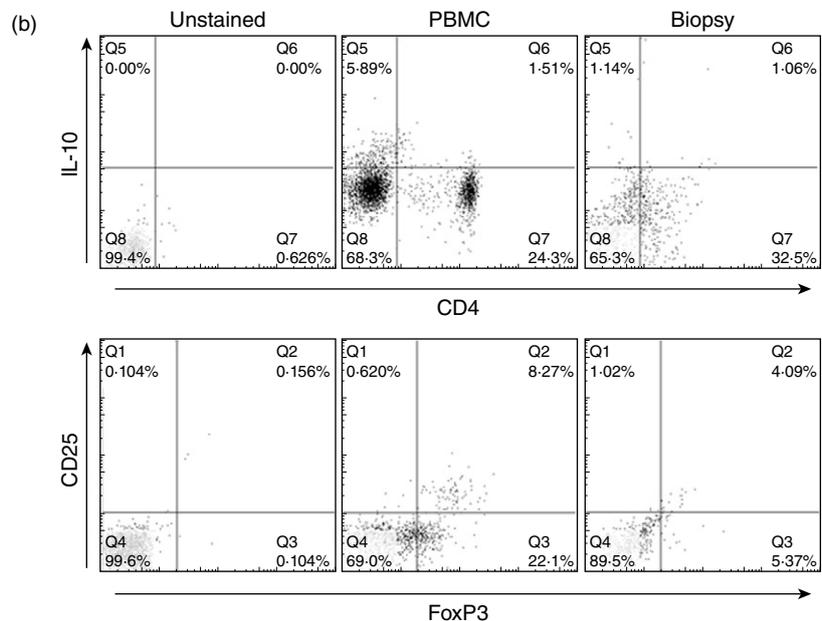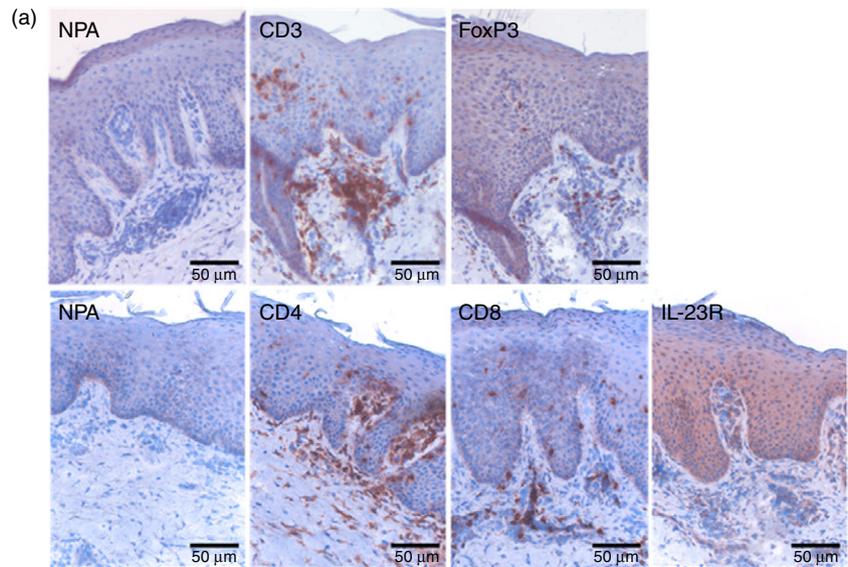
Fig. 4. Natural and induced regulatory T cells (T$_{regs}$) are present in psoriatic plaques, but while the frequency of the natural type is similar to that in peripheral blood, induced T$_{regs}$ can be enriched in lesions from some patients. (a) Immunohistochemistry slides showing that CD4+ lymphocytes, forkhead box protein 3 (FoxP3+) cells and interleukin (IL)-23R+ cells are all found in both the dermis and epidermis of psoriatic lesions. (b) A set of representative flow cytometric data from psoriatic patients are shown, demonstrating the numbers of IL-10+-induced T regulatory 1(Tr1) phenotype (upper) and CD25^{hi}FoxP3+ cells within the CD4+ lymphocyte (lower) populations from peripheral blood mononuclear cells (PBMC) (middle) and paired lesional biopsies (right). (c) Summarizes data from analyses of CD4+ cells from lesional biopsies and blood of psoriatic patients ($n = 6$), demonstrating the percentages of CD4+ cells that express T$_{reg}$ markers (bar indicates median value).
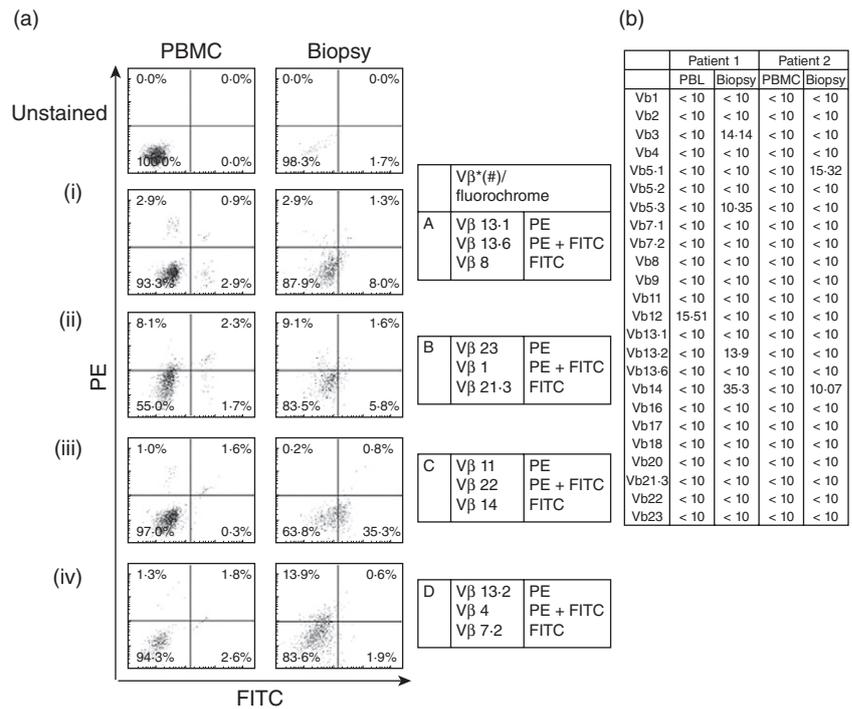
Fig. 5. CD4$^+$ T cells from psoriatic lesions exhibit biased T cell receptor (TCR) Vβ chain usage indicative of clonal expansion. (a) Representative flow cytometric plots of peripheral blood mononuclear cells (PBMC) and lesional biopsy samples, after staining with antibodies specific for a panel of TCR Vβ chains. The panels show the proportions of CD4$^+$ T cells expressing each Vβ chain from the paired samples of individual patients. (b) Complete data sets from two patients showing TCR usage as a percentage of CD4$^+$ cells.

	Patient 1		Patient 2	
	PBL	Biopsy	PBMC	Biopsy
Vb1	< 10	< 10	< 10	< 10
Vb2	< 10	< 10	< 10	< 10
Vb3	< 10	14·14	< 10	< 10
Vb4	< 10	< 10	< 10	< 10
Vb5·1	< 10	< 10	< 10	15·32
Vb5·2	< 10	< 10	< 10	< 10
Vb5·3	< 10	10·35	< 10	< 10
Vb7·1	< 10	< 10	< 10	< 10
Vb7·2	< 10	< 10	< 10	< 10
Vb8	< 10	< 10	< 10	< 10
Vb9	< 10	< 10	< 10	< 10
Vb11	< 10	< 10	< 10	< 10
Vb12	15·51	< 10	< 10	< 10
Vb13·1	< 10	< 10	< 10	< 10
Vb13·2	< 10	13·9	< 10	< 10
Vb13·6	< 10	< 10	< 10	< 10
Vb14	< 10	35·3	< 10	10·07
Vb16	< 10	< 10	< 10	< 10
Vb17	< 10	< 10	< 10	< 10
Vb18	< 10	< 10	< 10	< 10
Vb20	< 10	< 10	< 10	< 10
Vb21·3	< 10	< 10	< 10	< 10
Vb22	< 10	< 10	< 10	< 10
Vb23	< 10	< 10	< 10	< 10

numbers and phenotype were analysed by flow cytometry. Peripheral blood and lesional CD4$^+$ cells were co-stained with the natural T$_{reg}$ markers CD25 and FoxP3 and the induced regulatory cytokine IL-10. Representative examples are shown in Fig. 4b. The proportion of CD4$^+$ cells with a natural CD25^{hi}FoxP3$^+$ T$_{reg}$ phenotype in blood lies within the anticipated normal adult range (2–10%) [31], but there is no significant difference between the numbers circulating and in the lesions. Across all six patients tested, there is also no significant difference between peripheral blood and lesions in the numbers of CD4$^+$ cells positive for the induced regulatory cytokine IL-10 (Fig. 4c). However, in two patients there was a marked over-representation of IL-10$^+$CD4$^+$ cells in lesions, accounting for up to 20% of the CD4$^+$ population Fig. 4c). Although it cannot be excluded formally that the IL-10 was produced by Th2 rather than T$_{reg}$ cells [32] these results suggest that, overall, CD4$^+$ cells with an induced, but not natural, T$_{reg}$ phenotype can be over-represented in some psoriatic lesions.

Clonality of CD4$^+$ and Th17 cells in psoriatic lesions

If the lesional Th17 cells are the primary effectors of an autoimmune pathology, as is currently widely proposed, then their over-representation would be expected to be the result of a response to specific antigen. To test this, the clonality of CD4$^+$ cells within lesions and peripheral blood was compared by flow cytometric staining of lesional cells from four patients with an array kit of antibodies to a panel of 24 TCR Vβ chain sequences. A summary and representative data are shown in Fig. 5. As expected, the frequencies of

CD4$^+$ cells within peripheral blood expressing each TCR Vβ chain were distributed evenly. In contrast, all patients demonstrated marked over-representation of particular Vβ chains in the CD4$^+$ population from lesions. Although there was some overlap between patients in the chains affected, most notably Vβ5·1 in two cases, the patterns of preferential TCR expression varied between individuals.

Discussion

This is the first study to provide a full quantitation of both active and inactive Th17 cells within psoriatic lesions by flow cytometry. The results demonstrated that cells with the characteristic Th17 surface phenotype [4] are expanded dramatically in sites of psoriatic inflammation compared to peripheral blood, representing the predominant Th subset, and accounts for a median of 51–55% of all lesional CD4$^+$ T cells. The inflammatory activity of this lesional population was confirmed by staining for IL-17A, which revealed that many of the Th17 phenotype cells produced the cytokine *ex vivo* spontaneously with no further need for stimulation. The status of the minor fraction of the lesional cells with the Th17 surface phenotype that did not produce detectable IL-17A, even after potent non-specific stimulation, is unclear, and may point to a Th22 CD4 cell subtype [33] which shares some of the phenotypic markers as Th17 cells. Another explanation may be that a proportion of T cells in any highly activated population would be expected to exhibit signs of exhaustion or suppression [34].

We identified fewer natural T$_{reg}$ cells in psoriatic lesions than Sugiyama *et al.* [19], who reported that they were

functionally defective, but this discrepancy in numbers may be due to the use of different markers for the population. To isolate T_{reg} cells for functional studies Sugiyama *et al.* selected them by CD25 expression, which is up-regulated on activated as well as regulatory cells [31]. Here, enumeration of natural T_{reg} cells by dual staining for CD25 plus the characteristic transcription factor FoxP3 was more rigorous, excluding the single positive CD25+FoxP3− T cells with an activated, non-regulatory phenotype, which can comprise a relatively large population. This may be a conservative estimate, as some T_{reg} cells *in vivo* may lose phenotypic markers such as FoxP3 following repetitive TCR stimulation [35]. However, irrespective of any differences arising from the use of different markers, Th17 cells are far more common than natural T_{reg} cells in psoriatic lesions, and such a numerical advantage could potentially overwhelm the ability of even fully active T_{reg} cells to suppress [36]. Furthermore, the effectiveness of T_{reg} cells could be compromised further by their reported ability to differentiate into Th17 cells in psoriasis [20].

We show that CD4+ T cells producing the suppressive cytokine IL-10, corresponding to the induced T regulatory 1 (Tr1) subset [15], can be present in lesions and, unlike natural T_{reg} cells, their numbers can be enriched markedly relative to peripheral blood in particular patients. There may be therapeutic advantage in boosting local IL-10 responses, as production of the cytokine has been implicated previously in the inhibition of psoriatic keratinocyte and T cell proliferation [37].

Evidence from the current study points to the expansion of Th17 cells in psoriatic lesions being driven by antigen. Analysis of TCR Vβ chain usage revealed a skew towards limited clonality in lesional skin compared to peripheral blood, supporting and extending earlier observations of psoriatic skin T cells [38]. Recent sequencing of a panel of T cells cloned from psoriatic plaques indicated extensive sharing of TCR [39], and we confirm that similar over-representation can be found in unselected lesional cells isolated *ex vivo*. The variation between patients in the clonotypes expanded reflects the heterogeneity of human leucocyte antigen restriction and epitope selection seen in the pathogenic responses in other autoimmune diseases [40–42].

The ratio and activation status of Th17 and T_{reg} cells in psoriatic lesions may be important in locally controlling the pathogenesis of inflammation, and this balance may potentially be shifted therapeutically. For example, manipulating IL-10 levels could shift Th17 to a regulatory phenotype and ameliorate autoimmune or inflammatory diseases in which Th17 cells are involved [43]. Specificity of such treatment may be possible by targeting Th cells that recognize particular autoantigens. It may not be necessary to identify the autoantigens definitively, as one lesson from experimental models of autoimmune disease [31] is that reinstatement of self-tolerance to any single involved antigen can induce potent bystander effects on other, co-localized pathogenic responses.

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Disclosure

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