BRITISH JOURNAL OF BIOMEDICAL SCIENCE, 2016
VOL. 73, NO. 4, 174–179
http://dx.doi.org/10.1080/09674845.2016.1207869

Immunophenotyping of T cells in the peripheral circulation in psoriasis

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ABSTRACT

Background: Psoriasis is a T-helper (Th)-1/Th17-mediated chronic inflammatory disease. Cytokine mediated interaction between T lymphocytes and keratinocytes lead to keratinocyte hyper-proliferation, which leads to further inflammation in the psoriatic plaques. There is an increased population of T-helper cells in the skin lesions as well as in the peripheral circulation in psoriasis. However, the relative percentage of each T-cell phenotype in the disease pathogenesis is understudied. Our aim was to study the immune-phenotype of the different T-helper/T-reg cell subsets in patients with psoriasis, with respect to healthy controls.

Materials and methods: A total of 189 cases of psoriasis and 189 age- and gender-matched healthy controls were recruited in this cross-sectional study. Disease severity was determined by psoriasis area severity index (PASI) scoring. Peripheral blood mononuclear cells were isolated by Ficoll-Paque density centrifugation, and T-cell immunophenotyping was done by flow cytometric analysis.

Results: In psoriasis, we observed an imbalance in T-cell immunophenotype, characterised by an increase in Th1/Th17 cells and a relative decrease in Th2/T-reg cells, as compared to the healthy controls. We also found that the percentage of Th1/Th17 cells showed a linear trend, increasing with increasing disease severity (PASI).

Conclusion: Our results suggest an immune-dysregulation in psoriasis associated with a predominance of Th1/Th17 phenotype, especially with increasing severity of the disease.

ARTICLE HISTORY
Received 21 March 2016
Accepted 26 June 2016

KEYWORDS
Immunophenotyping; T-helper cells; T-reg cells; T-cell subsets; psoriasis

Introduction

Psoriasis is a common immune-mediated chronic, inflammatory skin disease 2 characterised by hyper-proliferative keratinocytes and infiltration of T cells, dendritic cells, macrophages and neutrophils. Though the pathogenesis of psoriasis is not clear, there is ample evidence indicating that the chronic activation of cutaneous T cells plays a critical role in psoriasis development.[1]

Psoriatic lesions are known to develop through an immune deregulation pathway involving a dominant type 1 T-helper (Th1) cell response and dysfunction of Th2 cells.[2–4] Markedly higher levels of IFN-γ and a relatively lower IL-4 concentration in psoriatic lesions clearly indicate the presence of an imbalance towards the Th1 response.[5] A study involving simultaneous measurement of multiple Th1 and Th2 serum cytokines in psoriasis showed that IFN-γ and IL-8 cytokines were elevated in psoriatics and correlated with parameters of disease severity while IL-10 and IL-12 were decreased, thus indicating the predominance of Th1 subset.[6] Another study has provided evidence that treatment with IL-4 attenuates Th17 cell response in psoriasis by decreasing the IL-17 present in the psoriatic skin lesions,[7] thus indicating that Th2 cells play an important role in inflammatory regulation.

Thus, psoriasis is characterised by increased systemic and local production of Th1 and pro-inflammatory cytokines, indicating the dominance of Th1 lymphocytes and a relative deficiency of the Th2 cells in the plasma and skin lesions of psoriatic patients.[8–10] Regulatory T cells (T-reg) were also reported to be both quantitatively and functionally deficient in their ability to suppress T-cell activation,[11–15] which could explain the reason for reduced regulatory restraint and the consequent hyper-proliferation of psoriatic pathogenic T cells.[16]

It has recently been demonstrated that a new subset of IL-17 producing $CD4^+$ Th cells, Th-17 cells are also important in mediating inflammation in lesions of psoriasis.[17,18] IL-17 expression can be detected in biopsies from psoriatic skin lesions but not in the normal skin, indicating that Th17 cells are involved in the pathogenesis of psoriasis.[19] Recent studies have highlighted that Th17 cells secrete IL-17 which mediate inflammation in psoriasis and arthritis associated with psoriasis and other autoimmune diseases such as rheumatoid arthritis and

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MP, DPD and SI have contributed equally to the study and hence are co-first authors for this research work.

ankylosing spondylosis.[20–23] Th1 and Th17 cells are known as distinct polarised Th cell types, as they are increased in the psoriatic lesions and peripheral blood.[24]

Thus, alterations in the number and function of different subsets of T cells that vary with duration and severity may contribute to the disease pathogenesis. Several studies have established the role of T lymphocytes in the pathogenesis of psoriasis and the disease management by effective treatment modalities. However, there are only a few studies that explore the relative number of different T-cell subsets in circulation of patients with psoriasis.[25,26] Hence, we undertook to study whether psoriatic patients show a peculiar pattern of T-helper/ T-reg cell subsets in circulation of patients with psoriasis with respect to healthy subjects and to correlate with the disease severity and clinical course, thus providing an overview of the immuno-phenotype of different T-cell subsets in the pathogenesis of psoriasis.

Materials and methods

A total of 189 patients with psoriasis and psoriatic arthritis, aged 18–60 years, who were diagnosed and classified according to international psoriasis council consensus classification of psoriasis [27] and by CASPAR criteria [28], respectively, at the Department of Dermatology of Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India, were included in this hospital-based cross-sectional study. Patients with cutaneous or extra-cutaneous inflammation and infections, malignancies, diabetes, pre-existing cardiovascular disease, hypertension, smoking and undergoing systemic therapy in the last three months were excluded from the study. A total of 189 age- and gender-matched healthy individuals, without any skin and infectious diseases and without a family history of autoimmune diseases, were recruited as healthy controls.

The study was approved and reviewed by the JIPMER Institute Ethics Committee (Human Studies). The study participants had the study procedure explained in detail, and written informed consent was obtained from all of them. The study was performed according to the WMA Declaration of Helsinki ethical principles for medical research involving human subjects.

The clinical characteristics including disease severity as assessed by psoriasis area severity index (PASI) scoring,[29] duration of psoriasis, past therapies, associated comorbidities and the detailed family history were recorded. Five millilitres of peripheral venous blood was collected from each study subject in heparinised vials for isolation of peripheral blood mononuclear cells (PBMCs). Routine biochemical investigations such as blood glucose, serum lipids, serum creatinine and liver function tests were done.

Flow cytometric analysis

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinised venous blood using density gradient centrifugation on Ficoll-Paque. The isolated peripheral blood lymphocytes were analysed according to their immunofluorescence reactivity using a FACS Calibur cytometer (Becton Dickinson, California, USA). Surface markers on blood were performed by 4-colour immunofluorescence analyses using the antibodies conjugated to fluorescein isothiocyanate (FITC), phycoerythrin (PE), peridinin chlorophyll protein (PerCP), allophycocyanin (APC) and Alexa Fluor® 647. At least 30,000 lymphocytes were collected for each antibody combination. Th1, Th2, Th17 cells and T-reg cells were analysed as per the technical protocol of BD Pharmingen's (BD Biosciences, California, USA) Human T-helper/T-reg phenotyping kit which includes a cocktail of fluorescent antibodies that are specific for human T-cell antigens (Figure 1).

Statistical analysis

Data analysis was performed using SPSS 20 software. Baseline characteristics of the patients with psoriasis were analysed by descriptive statistics. The independent t-test was applied to assess the significance of differences between healthy controls and psoriatic patients at baseline. The normality of continuous data (data related to variables such as age of onset of psoriasis, duration of disease symptoms, T-cell counts) was assessed by Kolmogrov–Smirnov test. The normally distributed data were described by mean and standard deviation, and non-Gaussian data were described by the median and inter-quartile range. The Mann–Whitney U-test was used to evaluate the differences in the percentage of circulating T-helper and T regulatory cells in peripheral blood mononuclear cells of psoriasis patients and healthy controls. Association of biochemical variables with disease severity were done by Spearman's rank correlation. A two-sided p value < 0.05 was considered as significant.

Results

The baseline characteristics of the study subjects are shown in Table 1. There were no significant differences between cases and controls in their baseline characteristics of age, gender, body mass index (BMI], waist hip ratio (W/H]. The mean (IQR) duration of illness for the patients group was 41.25 ± 10.36 months. The mean PASI score in patients was 15.02 ± 5.24.

Flow cytometric analysis of the peripheral blood mononuclear cells revealed an increase in the percentages of Th1 cells as described by the $CD4^+$ IFN-γ^+ cells in patients with psoriasis compared with healthy individuals (Figure 2(a)). The percentages of Th2 cells described as $CD4^+$ IL-4^+

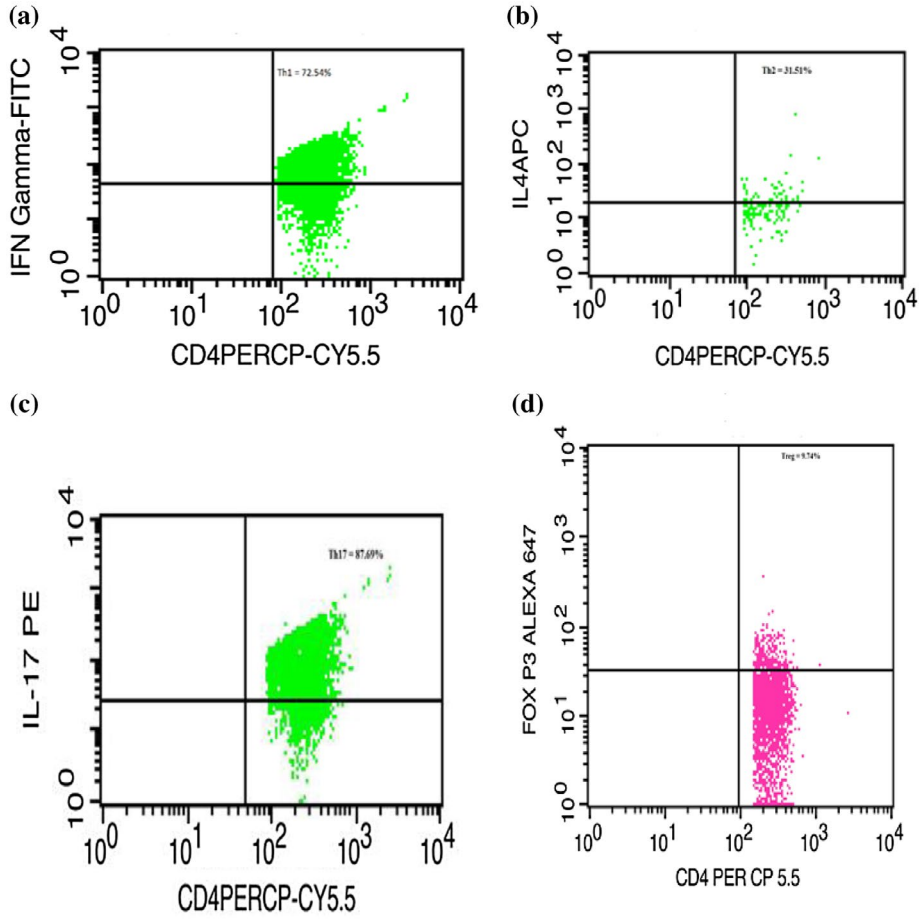

Figure 1. Flow cytometric analysis of PBMCs of a psoriasis patient that shows the percentages of different T-cell subsets. (a) IFN- γ^+CD4^+ cells (Th1 cells) are positive for FITC and PerCP-CY5.5 (Th1 = 72.54%) (b) IL-4^+ $CD4^+$ cells (Th2 cells) are positive for FITC and APC (Th1 = 31.51%) (c) IL-17^+ $CD4^+$ cells (Th17 cells) are positive for FITC and PE (Th17 = 87.69%) (d) $FoxP3^+$ $CD4^+$ cells (Treg cells) are positive for FITC and Alexa Fluor® 647 (Treg = 9.74%). (FITC-fluorescein isothiocyanate, PE-phyco-erythrin, PerCP peridinin chlorophyll protein, APC-allophycocyanin)

Table 1. Comparison of baseline characteristics between cases and controls.

Parameter	Cases (n = 189) (Mean ± SD)	Controls (n = 189) (Mean ± SD)	P value (Unpaired t-test)
Patient characteristics			
Age	41.9 ± 9.3	40.2 ± 8.2	0.44
Gender (M:F)	110:79	110:79	–
BMI (kg/m^2)	24.8 ± 3.1	23.1 ± 4.1	0.67
W/H ratio	0.96 ± 0.05	0.92 ± 0.04	0.38
Duration of disease (months)	41.2 ± 10.4	–	–
PASI	15.0 ± 5.2	–	–
Biochemical parameters			
Fasting glucose (mmol)	5.29 ± 0.39	5.24 ± 0.62	0.47
Uric acid (mmol)	0.27 ± 0.07	0.23 ± 0.02	0.34
Total cholesterol (mmol)	8.84 ± 1.34	8.59 ± 1.22	0.14
LDL cholesterol (mmol)	6.40 ± 1.66	5.85 ± 1.24	0.31
VLDL cholesterol (mmol)	1.85 ± 0.47	1.63 ± 0.52	0.15
HDL cholesterol (mmol)	1.73 ± 0.40	1.95 ± 0.18	0.25

cells are found to be downregulated in patients with psoriasis, compared with healthy individuals (Figure 2(b)).

$CD4^+$ cells which stained positive for IL-17 A were taken as Th-17 cells, and there was an upregulation of Th17 cells in patients with psoriasis compared with healthy individuals (Figure 2(c)). We found a decreased trend in the expression of T-reg cells which were $CD3^+$ $CD4^+$ $CD25^+$ $FoxP3^+$ cells, in patients with psoriasis compared with healthy individuals (Figure 2(d)). Our results also showed that the percentage of Th1/Th17 cells correlated positively with PASI ($r = 0.78$, $p < 0.0001$; $r = 0.91$, $p < 0.0001$) (Figures 3 and 4), and there was no significant correlation of percentage of Th2/T-reg cells ($r = 0.36$, $p = 0.145$; $r = 0.10$, $p = 0.356$) with PASI.

Discussion

Psoriasis is an inflammatory skin disease known to be driven by cutaneous T cells, where the regulatory and effector T cells interact *in vivo*. Studies looking at the

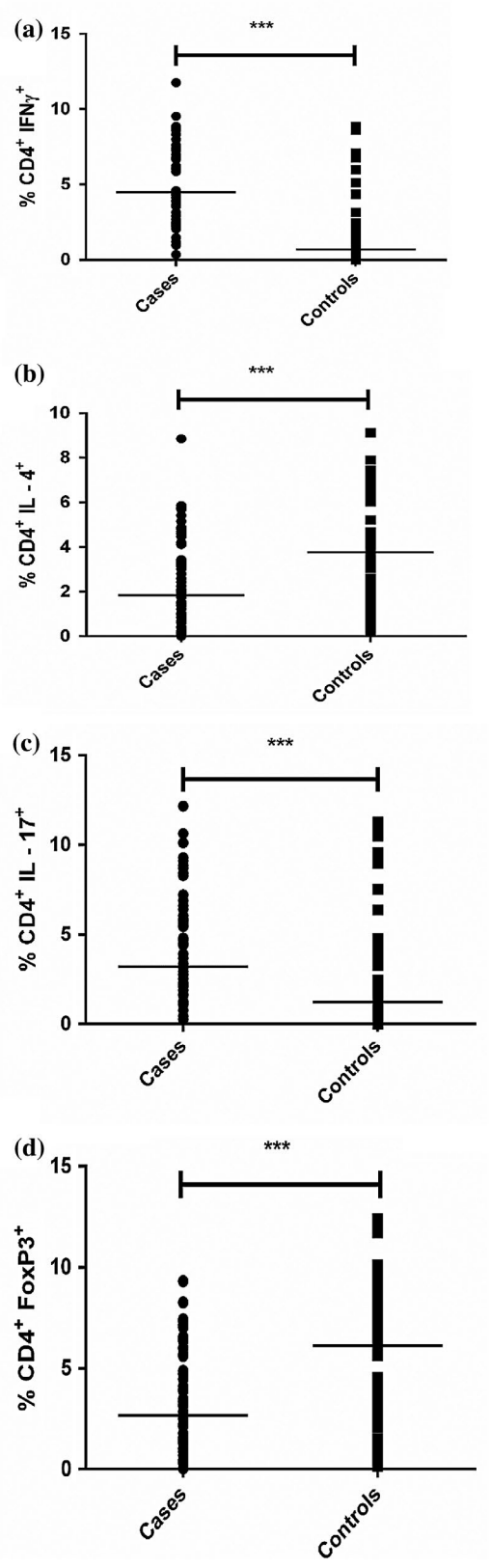

Figure 2. Comparison of percentage of circulating T-helper and T regulatory cells in peripheral blood cells of psoriasis patients and healthy controls. (a) $CD4^+$ $IFN\gamma^+$, (b) $CD4^+$ $IL\text{-}4^+$, (c) $CD4^+$ $IL\text{-}17^+$, (d) $CD4^+$ $FoxP3^+$. Mann–Whitney U-test (two tailed) (a–d) was used to analyse these data. Each symbol represents individual samples, and horizontal lines show the median values (a–d). ($^{***}p < 0.001$)

relative percentage of different T-cell subsets in the circulation of patients with psoriasis are limited.

We observed a significant elevation in the percentage of $CD4^+$ $IFN\text{-}\gamma^+$ cells and a significant reduction in the percentage of as $CD4^+$ $IL\text{-}4^+$ cells. Similar findings were observed in a previous study based on whole blood flow cytometric assay that showed an increased IFN-*γ* expression and decreased IL-4-positivity in CD4 lymphocytes in psoriasis compared to healthy controls, thus provided an evidence for an altered TH1/TH2 balance in psoriasis.[30] Prens et al. observed a significantly increased number of $IL\text{-}4R^+$ cells on the epithelial cells from psoriatic patients as compared with healthy controls.[31] This contradicts our observations of $IL\text{-}4^+$ $CD4^+$ cells described as Th2 population that were decreased in psoriasis. However, this can be justified by a hypothesis that there may be a shift from a Th1 to a Th2 cytokine response, representing a physiological attempt of Th2 cells to downregulate the pro-inflammatory activities of IL-1 produced by Th1 cells in psoriasis.[32] Another study supported our hypothesis indirectly by stating that therapy with IL-4 a Th2 cytokine attenuates Th17 cell response in psoriasis by decreasing the intralesional IL-17.[7] Hence, there is a protective role suggested for $IL\text{-}4^+$ $CD4^+$ or the Th2 cells that were decreased in psoriasis.

We also observed an increase in the counts of Th17 cells and a decrease in the counts of T-reg cells in the peripheral blood of patients with psoriasis compared with healthy controls. Results of several studies are in line with our findings. Kagami et al. concluded that the circulating Th17, Th22 and Th1 cells are increased in psoriasis patients compared to healthy individuals.[33] Benham et al. reported that increased frequencies of IL-17 and IL-22 producing $CD4^+$ T cells were a feature of both psoriasis (Ps) and psoriatic arthritis (PsA), and thus demonstrated their critical roles in the pathogenesis of Ps and PsA.[34] Keijsers et al. suggested that regulatory T cell vs. T-helper cell balance is essential in the transition from symptomless to lesional psoriatic skin and showed an increased Foxp3/CD4 ratios in the symptomless skin than in lesional psoriatic skin.[35] Mehta et al. demonstrated that CD146 + T cells produce the majority of IL-17A at the active site of inflammation in psoriasis.[36] Quaglino et al. observed an upregulation of Th1 and Th17 and downregulation of T-reg subsets at baseline, and the etanercept response was associated with a reversal of the Th1/Th17 activation and a relative upregulation of Th2 and T-reg subsets.[25] The above results strongly match with the findings obtained in our study that Th17 cells are increased in the circulation of psoriasis patients compared to controls.

We found a decreased circulating T-reg population in psoriasis compared to controls. Karamehic et al. hypothesised that the deficit of T-reg cells in peripheral blood and the skin lesions contributed to the pathological process of psoriasis and observed that the ratio of $CD4^+$ $CD25^+$ T cells in the control group was significantly higher than in the patients with psoriasis.[26] This is in accordance with the results of this study. We observed that on increasing

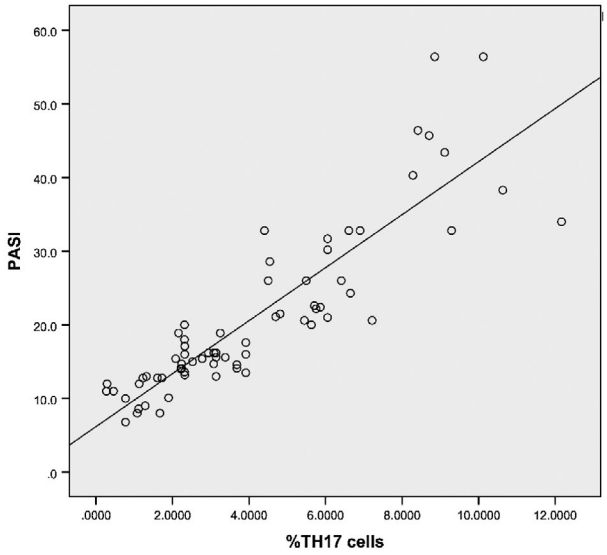

Figure 3. Scatter plot showing the correlation between Th17 and PASI. (r=0.78, p<0.0001)

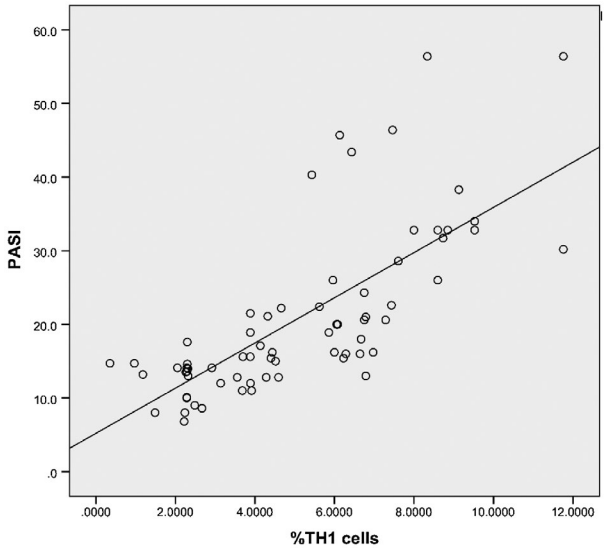

Figure 4. Scatter plot showing the correlation between Th1 and PASI. (r=0.913, p<0.0001)

percentages of Th1 and Th17 cells, the disease severity also increased linearly. However, we did not observe a statistically significant correlation between the levels of $CD4^+$ $CD25^+$ $FoxP3^+$ cells and $CD4^+$ $IL\text{-}4^+$ with the disease severity. This is similar to the findings of Karamehic et al., [26] which showed no significant correlation of $CD4^+$ $CD25^+$ cells with disease severity. In contrast to our findings, Zhang et al. reported that both circulating Th17 and $FoxP3^+$ T-reg cells were increased in paediatric psoriasis patients and correlated positively with the disease severity.[16]

A previous study has related the cytokine levels with the disease severity and found significantly elevated levels of serum TNF-α, IFN-γ, IL-6, IL-8, IL-12 and IL-18 levels in active psoriatic patients than in controls and the levels of IFN-γ and IL-18 correlated positively with the clinical severity and activity of psoriasis.[30] Also, a recent Korean study concluded that the morphological phenotype of psoriasis was not influenced by a specific activation of either the Th-1 or Th-17 pathway rather the cytokine profile determined the disease activity in the psoriatic lesions of Korean psoriatics.[37]

We note limitations in our study. We did not evaluate the pattern of other peripheral T-cell subsets such as Th22/Th33 of the psoriasis patients, which would have further contributed to the disease pathogenesis. We have not analysed the genetic polymorphisms of the T-helper/T-reg cytokine genes that would have aided in establishing the genotype–phenotype correlation of the psoriasis pathogenesis.

In conclusion, our results indicate that there is immune-dysregulation among the different subsets of T-helper and T-reg cells in psoriasis, with a predominance of Th1/Th17 phenotype, especially with increasing severity of the disease. Thus, our work is a progress in biomedical science because it helps not only in the comprehension of disease pathogenesis and progression but also in deciding the appropriate therapeutic targets with anti-cytokine therapy and improving the efficacy of various treatment regimens.

Acknowledgements

Funding by Department of Biotechnology (DBT), New Delhi, India [grant number BT/PR6033/GBD/27/373/2012], is gratefully acknowledged.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Department of Biotechnology (DBT), New Delhi, India [Grant number BT/PR6033/GBD/27/373/2012]

Summary table.

What is known about this subject:
- Psoriasis is characterised by chronic activation of cutaneous T lymphocytes that leads to keratinocyte hyperproliferation
- There is increased production of pro-inflammatory cytokines which plays a critical role in disease pathogenesis
- There is alteration in the different T lymphocyte subsets in patients with psoriasis

What this paper adds:
- There is a peculiar pattern of T-helper/ T-reg cell subsets in circulation of patients with psoriasis.
- There is an increase in the Th1/Th17 phenotype and a decrease in the Th2/T-reg phenotype in patients with psoriasis, compared to healthy controls
- The observed phenotypic pattern of T lymphocytes is more evident as the severity of the disease increases

References

[1] Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. Cell. Mol. Immunol. 2012;9:302–309.
[2] Yawalkar N, Karlen S, Hunger R, et al. Expression of interleukin-12 is increased in psoriatic skin. J. Invest. Dermatol. 1998;111:1053–1057.

[3] Nickoloff BJ. Cracking the cytokine code in psoriasis. Nat. Med. 2007;13:242–244.
[4] Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis – Part II: Immune cell subsets and therapeutic concepts. J. Allergy. Clin. Immunol. 2011;127:1420–1432.
[5] Zhu K, Ye J, Wu M, et al. Expression of Th1 and Th2 cytokine-associated transcription factors, T-bet and GATA-3, in peripheral blood mononuclear cells and skin lesions of patients with psoriasis vulgaris. Arch. Dermatol. Res. 2010;302:517–523.
[6] Jacob SE, Nassiri M, Kerdel FA, et al. Simultaneous measurement of multiple Th1 and Th2 serum cytokines in psoriasis and correlation with disease severity. Mediators. Inflamm. 2003;12:309–313.
[7] Guenova E, Skabytska Y, Hoetzenecker W, et al. IL-4 abrogates T(H)17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. Proceedings of the National Academy of Sciences of the United States of America. 2015;112:2163–2168.
[8] Bonifati C, Ameglio F. Cytokines in psoriasis. Int. J. Dermatol. 1999;38:241–251.
[9] Szabo SK, Hammerberg C, Yoshida Y, et al. Identification and quantitation of interferon-γ producing T Cells in psoriatic lesions: Localization to both CD4+ and CD8+ subsets. J. Invest. Dermatol. 1998;111:1072–1078.
[10] Friedrich M, Krammig S, Henze M, et al. Flow cytometric characterization of lesional T cells in psoriasis: intracellular cytokine and surface antigen expression indicates an activated, memory/effector type 1 immunophenotype. Arch. Dermatol. Res. 2000;292:519–521.
[11] Zhang L, Yang XQ, Cheng J, et al. Increased Th17 cells are accompanied by FoxP3+ Treg cell accumulation and correlated with psoriasis disease severity. Clin. Immunol. 2010;135:108–117.
[12] Jorn Bovenschen HJ, van de Kerkhof PC, van Erp PE, et al. Foxp3+ regulatory T Cells of psoriasis patients easily differentiate into IL-17A-producing cells and are found in lesional skin. J. Invest. Dermatol. 2011;131:1853–1860.
[13] Soler DC, Sugiyama H, Young AB, et al. Psoriasis patients exhibit impairment of the high potency CCR5+ T regulatory cell subset. Clin. Immunol. 2013;149:111–118.
[14] Zhang HY, Yan KX, Huang Q, et al. Target tissue ectoenzyme CD39/CD73-expressing Foxp3+ regulatory T cells in patients with psoriasis. Clin. Exp. Dermatol. 2015;40:182–191.
[15] Quaglino P, Ortoncelli M, Comessatti A, et al. Circulating CD4+CD25 bright FOXP3+ T cells are upregulated by biological therapies and correlate with the clinical response in psoriasis patients. Dermatol. 2009;219:250–258.
[16] Zhang L, Li Y, Yang X, et al. Characterization of Th17 and FoxP3 (+) Treg cells in pediatric psoriasis patients. Scand. J. Immunol. 2016;83:174–180.
[17] Blauvelt A. T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. J. Invest. Dermatol. 2008;128:1064–1067.
[18] Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, et al. Psoriasis is characterized by accumulation of immunosti mulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. J. Invest. Dermatol. 2009;129:79–88.
[19] Teunissen MB, Koomen CW, de Waal Malefyt R, et al. Interleukin-17 and interferon-γ synergize in the enhancement of proinflammatory cytokine production by human keratinocytes. J. Invest. Dermatol. 1998;111:645–649.
[20] Ortega C, Fernandez-A S, Carrillo JM, et al. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J. Leukoc. Biol. 2009;86:435–443.
[21] Marinoni B, Ceribelli A, Massarotti MS, et al. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. Auto Immun Highlights. 2014;5:9–19.
[22] Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum. 2009;60:1647–1656.
[23] Eysteinsdóttir JH, Sigurgeirsson B, Ólafsson JH, et al. The role of Th17/Tc17 peripheral blood T cells in psoriasis and their positive therapeutic response. Scand. J. Immunol. 2013;78:529–537.
[24] Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J. Invest. Dermatol. 2008;128:1207–1211.
[25] Quaglino P, Bergallo M, Ponti R, et al. Th1, Th2, Th17 and regulatory T cell pattern in psoriatic patients: Modulation of cytokines and gene targets induced by etanercept treatment and correlation with clinical response. Dermatology. 2011;223:57–67.
[26] Karamehic J, Zecevic L, Resic H, et al. Immunophenotype lymphocyte of peripheral blood in patients with psoriasis. Med. Arch. 2014;68:236–238.
[27] Griffiths CE, Christophers E, Barker JN, et al. A classification of psoriasis vulgaris according to phenotype. Br. J. Dermatol. 2007;156:258–262.
[28] Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665–2673.
[29] Langley RG, Ellis CN. Evaluating psoriasis with psoriasis area and severity index, psoriasis global assessment, and lattice system physician's global assessment. J. Am. Acad. Dermatol. 2004;51:563–569.
[30] Szegedi A, Aleksza M, Gonda A, et al. Elevated rate of Thelper1 (TH1) lymphocytes and serum IFN-γ levels in psoriatic patients. Immunol. Lett. 2003;86:277–280.
[31] Prens E, Hegmans J, Lien RC, et al. Increased expression of interleukin-4 receptors on psoriatic epidermal cells. Am. J. Pathol. 1996;148:1493–1502.
[32] Jain S, Kaur IR, Das S, et al. T helper 1 to T helper 2 shift in cytokine expression: an autoregulatory process in superantigen-associated psoriasis progression? J. Med. Microbiol. 2009;58:180–184.
[33] Kagami S, Rizzo HL, Lee JJ, et al. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J. Invest. Dermatol. 2010;130:1373–1383.
[34] Benham H, Norris P, Goodall J, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res. Ther. 2013;15:R136.
[35] Keijsers RR, van der Velden HM, van Erp PE, et al. Balance of Treg vs. T-helper cells in the transition from symptomless to lesional psoriatic skin. Br. J. Dermatol. 2013;168:1294–1302.
[36] Mehta NN, Dagur PK, Rose SM, et al. IL-17A production in human psoriatic blood and lesions by CD146+ T Cells. J. Invest. Dermatol. 2015;135:311–314.
[37] Roh NK, Han SH, Youn HJ, et al. Tissue and serum inflammatory cytokine levels in korean psoriasis patients: A comparison between plaque and guttate psoriasis. Ann. Dermatol. 2015;27:738–743.