Egyptian Dermatology Online Journal
Volume 5 Number 1

SERUM LEVEL OF IL-17, IL-22, IFN-γ IN PATIENTS WITH PSORIASIS

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Egyptian Dermatology Online Journal 5 (1): 4, June 2009

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Accepted for publication in May 30th, 2009.

Abstract

Psoriasis is a chronic inflammatory skin disease that is thought to be mediated by Th1 cells, secreting IFN-γ. Interestingly, recent advances by cellular immunologists have identified a new distinct type of T-cell, called Th17 cell that play an essential pathogenic role in psoriasis. In this study we measured serum levels of IL-17, IL-22 and IFN-γ in 30 psoriatic patients and 30 healthy control using ELISA method, correlating their levels to disease severity, which was calculated by psoriasis area severity index (PASI) score. Serum levels of the studied cytokines were significantly elevated in comparison to normal control serum levels. Also serum levels of both IL-17 and IL-22 were significantly correlated with PASI score, while IFN-γ level was not. Our result indicating that psoriasis is a mixed Th1 and Th17 inflammatory environment disease.

Introduction

Psoriasis is a complex inflammatory skin disease that affects 2.3% of the population worldwide. Although the initial events triggering a psoriatic lesion are still unknown, many environmental factors have been shown to play a role in psoriasis pathogenesis. External triggers such as physical trauma, infection, stress, drug and alcohol can trigger an initial episode of psoriasis in those individual who already have a genetic predisposition [1]. This trigger activates dendritic cells, such as Langerhans cell, inducing their migration to skin draining lymphocytes. Here, antigen specific T-cell are primed by migrated skin dendritic cells to differentiate into effectors T-cells, then traffic to the skin, where they together induce the formation of a primary psoriatic plaque. During this step, some T-cell and dendritic cell start to infiltrate the epidermis, releasing proinflammatory cytokines which in turn stimulate keratinocyte proliferation [2]. Psoriasis can be considered as a T-cell mediated disease, with a

complex role for a variety of cytokine interaction between keratinocytes and T-lymphocyte. Nearly forty years ago, T-cells were divided into helper, cytotoxic and suppressor cells types. Twenty years later, T-helper cells were further divided into Th1 and Th2 subsets. More recently Th1, Th2 paradigm has been updated including a new subset called Th17 cell. Although, such tidy categorization may be attractive in its simplicity, it has become apparent that the original Th1, Th2 paradigm is much more complicated than originally appreciated. For example, psoriasis were commonly considered to be a Th1 mediated disease, but now we realize that such generalization was inaccurate and oversimplified [3]. The identification of Th17 subset has now broadened our understanding of inflammatory process in human disease, which through the production of both IL-17 and IL-22, induction of chemokines and recruitment of other effector cells population might have essential function in psoriasis pathogenesis [4].

Materials and Methods

Patients:

This study included thirty patients with psoriasis vulgaris and thirty healthy controls, all recruited from Dermatology Department, Zagazig University Hospitals. Patients diagnosed clinically and their disease severity was measured by PASI score. All patients did not receive any topical or systemic therapy for 1 month prior to the study and also none of our control group subjects have positive family history for psoriasis.

Serum:

Three ml venous blood samples were collected on sterile plane tube and were allowed to stand for 30 minutes at room temperature then centrifuged at 300 g for 5 minutes. Sera immediately separated and stored at -20 ℃ until the time of analysis.

Cytokine detection:

IL-17 assay kit: The RayBio® Human IL-17 Enzyme-linked Immunosorbent Assay (ELISA) kit is an in vitro ELISA for the quantitative measurement of human IL-17 in serum, plasma, cell culture supernatants and urine. This assay employs an antibody specific for human IL-17 coated on a 96-well plate. Standards and samples are pipetted into the wells and IL-17 present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated anti-human IL-17 antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of IL-17 bound. The stop solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm RayBiotech, Inc.

IL-22 assay kit: Employs the quantitative sandwich enzyme immunoassay technique. A mono-clonal antibody specific for IL-22 has been precoated onto a microplate. Standards and samples are pipetted into the wells and any IL-22 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for IL-22 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-22 bound in the initial step. The color development is stopped

and the intensity of the color is measured. R&D Systems, Inc. 614 McKinley Place NE.

IFN-γ assay kit: The RayBio® Human IFN-γ ELISA, kit is an in vitro ELISA for the quantitative measurement of human IFN-γ cell lysate and tissue lysate. This assay employs an antibody specific for human IFN-γ coated on a 96-well plate. Standards and samples are pipetted into the wells and IFN-γ present in a sample is bound to the wells by the immobilized antibody. The wells are washed and botinylated anti-human IFN-γ antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of IFN-γ bound. The stop solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm. RayBiotech, Inc.

For all the above 3 assays calibration curves were blotted on semi log papers and values of OD of samples calculated from the standard curve.

Results

This study include 30 psoriatic patients (15 males and 15 females), their age ranged from 26-59 years with a mean and SD of 40 ± 9.9 years old, disease severity of studied case measured by calculating PASI score. The average PASI was 27.66 ± 11.25, ranged from 1.2 - 48.6. Characteristic of studied case were shown in **table (1).**

	Cases	**Control**	**P**
	N=30	**N=30**	
Age : X ± SD	40.4 + 9.9	39.6 + 9	0.73
Range	26 – 59	26 – 58	
Gender			
Male	15 (50%)	16(53.30%)	0.79
Female	15 (50%)	14 (46.70%)	
Disease duration X ±SD	15.6 ± 7.5	-	
Range	3 – 30	-	
PASI X ± SD	27.66 ±11.25	-	
Range	1.2 – 48.6	-	

Table (1): Characteristics of patient and control groups

The mean serum levels of IFN-γ in psoriatic patient was 35 IU/ml, while, for normal healthy controls was 1.5 IU/ml. Mean serum level of IL-17 among studied psoriatic patient was 80.75 pg/ml, for normal healthy controls was 8.16 pg/ml. Finally serum level of IL-22 level for patient was 53.5 pg/ ml while for healthy control mean level it was 9.76 pg/ml.

Serum levels of studied cytokines were significantly higher in patients than those for control group. All serum cytokine levels are illustrated in **table (2).**

Serum cytokine level	Cases N=30	Control N=30	P
IFN-γ (IU/ml)			
X ± SD	33.4 ± 18.8	1.615 ± 0.85	
Range	5.6 – 65.4	0.12 – 3	
Median	35	1.5	<0.001**
IL-17 (pg/ml)			
X ± SD	88.5 ± 51.4	9.1 ± 3.5	
Range	17.2 – 172	2.5 – 15	
Median	80.75	8.16	<0.001**
IL-22 (pg/ml)			
X ± SD	61.3 ± 22.8	11.3 ± 5.5	<0.001**
Range	32.3 – 96	4.3 – 22	
Median	53.5	9.76	

Table (2): Serum levels of IFN-γ, IL-17 & IL-22 among cases and control

The mean serum levels of IL-17 and IL-22 in psoriatic patient found to be significantly correlated to disease severity, measured by PASI. While serum of IFN-γ was not correlated to PASI score as shown in **table (3).**

Cytokine	r	P	Significantly
IFN-γ	0.3	>0.05	Non significant
IL-17	0.52	<0.001**	Highly significant
IL-22	0.38	<0.05*	Significant

Table (3): Correlation between serum levels of IL-17, IL-22, IFN-γ and PASI score

Correlation between the serum levels of the studied cytokines and the disease duration was not significant as shown in **table (4)**.

Cytokine	r	P	Significantly
IFN-γ	0.07	>0.05	Non significant
IL-17	0.11	>0.05	Non significant
IL-22	0.07	>0.05	Non Significant

Table (4): Correlation between serum level of IL-17, IL-22, IFN-γ and disease duration

Discussion

Psoriasis is a common recurrent inflammatory skin disease, characterized by hyperproliferative epidermis and cutaneous lymphocyte infiltrate. The cause of psoriasis still unknown and because psoriasis affects the epidermis it was long regarded as an epidermal disease [1]. T-cells involved in psoriasis pathogenesis were initially thought to be Th1 differentiated because of the presence of elevated level of IFN-γ in psoriatic patients. However, the recent discovery of Th17 cell and its potential involvement in psoriasis generate more complexity to the disease [5-7]. Several recent studies have now been reclassified psoriasis as Th17 disease [8-13]. Documenting psoriasis as a Th17 disease will lead to a paradigm shift in how scientists and clinicians view the disease. That conflict in studies raise the logical question is psoriasis supposed to be a Th1 or Th17 mediated disease. Here in this study by correlating level of both Th1 cytokine (IFN-γ) and Th17 cytokines (IL-17, IL-22), with disease severity, it is a trial to answer that question.

Recent progress in understanding of psoriasis has shown that both local and systemic cytokines collaboratively play a role in psoriasis pathogenesis. Although several recent studies have identified higher levels of IL-17 and IL-22 expression in psoriatic skin lesion, few studies considered their serum levels. To the best of our knowledge, this study might be the second one interested in Th17 cytokines serological markers after Caproni et al., study[14]. We evaluated serum cytokines levels using ELISA, a simple laboratory blood sample method, patient independent, observer independent and accurate marker for cytokine levels detection, while disease severity was calculated by PASI score.

Our result confirmed a well established previously published data concerning elevated IFN-γ level in psoriatic patients [15-19], as IFN-γ induce cytokine secretion, that promote inflammatory cascade and Th1 cell accumulation within epidermis.

The view that psoriasis is a Th1 mediated disease mainly was supported by data collected from several previous studies observed high IFN-γ expression, but psoriasis can not be explained solely on the basis of Th1 cell activation. In fact infiltration of Th1 cell in the epidermis is a common response to intrinsic or extrinsic antigens in person, in whom psoriasis never develop. Albansi et al., [20] explained this paradox by the existence of a unique subgroup of other cytokine produced by psoriatic T-cells. However, Blauvet [1] in his review about psoriasis pathogenesis, explored alternative possible concept about elevated IFN-γ level, suggesting it as a secondary phenomenon in response to another primary abnormality.

Recently a couple of studies [21,22] detected proportion of Th17 cells share the ability to

produce IFN-γ beside IL-17, which named Th1/ Th17. Here, we suggested that, this subclone cell could be responsible for elevated IFN-γ level not only the Th1 cells as previously thought.

In our study there was no correlation between PASI score and serum level of IFN-γ (Table 3) indicating that IFN-γ has a role in psoriasis but not the proximal regulator or sole player in its pathogenesis.

Th17 cells were first identified in 2000 and their discovery provoked several researchers to find out the differences between newly discovered cells and common Th1 cells. Cox et al. [22] observed that, Th1 express higher levels of CXCR3 receptors, while Th17 express IL-23 R, which mediate its proliferation, also CCR6 and CCR4 which mediate its chemotaxis to CCL27 expressed by cutaneous venules and CCL20 by both keratinocytes and endothelial cells. While, Annunziato et al. [23] revealed that Th17 is less susceptible than Th1 to the suppressive activity of Treg cells clone, also observed that Th17 cells memory cells, the only memory cell that continues to express CCR6 even after prolonged antigenic activation, thereby maintaining the possibility of rapid recruitment in response to CCR20 expression by keratinocyte. This finding may have important implication for the long term maintenance of Th17 influx, supporting their role in chronically inflamed skin disease.

Upon antigenic stimulation CD4+ T-cells differentiate to either Th1 or Th17 according to local cytokine milieu environment. IL-12 induces differentiation towards Th1, while IL-23 induces its differentiation towards Th17 cells [24-29]. Targeting IL-23 as a master mediator of Th17 development leads to dramatic therapeutic benefit in psoriatic individual as ustekinumab, a novel therapeutic agent that binds to P40 protein subunit of IL-23 thereby, preventing interaction with their surface receptor expressed on Th17 cells and down regulating their proliferation [8,11,30]. Th17 cell produce both IL-17 and IL-22 cytokines, in our study serum level of both these cytokines were significantly elevated and significantly correlated to PASI score, approving that Th17 and its cytokine might have essential pathogenic role in psoriasis pathaogenesis.

IL-17 plays important direct role in creating proinflammatory and chemotactic environment, enhance IL-6, IL-8 and ICAM-1 expression by keratinocyte, promote lymphocyte infiltration within epidermis, at the same time promote more rapid recruitment of neutrophil through induced chemokine expression [31-35].

On the other hand, keratinocyte proliferation appear to be indirectly stimulated by IL-22 [36-39] as it down regulate genes, that control terminal differentiation, resulting in altered differentiation and parakeratosis as approved by Norgales et al. study [40], they found that IL-22 treated skin developed acanthosis and parakeratosis. The same as we observed in this study. Both Th17 cytokines (IL-17 & IL-22) and Th1 cytokine (IFN-γ) were significantly elevated in psoriatic patient serum. However Th17 cytokine only found to be significantly correlated to disease severity consequently to these results, we recommend that psoriasis is mixed Th1 and Th17 inflammatory skin disease both of them are independently capable of inducing disease, while Th17 may be primary regulator of psoriasis inflammation, particularly in driving epidermal activation, whereas Th1 role cant be ignored as observed by Zaba et al. [13], who studied effect of both acetretin or etanercept in psoriatic patient by watching 20 patients' immune reaction after receiving those drugs they concluded that for final disease resolution Th1 cells must be eliminated. If psoriasis proven to be a mixed Th1 and Th17 disease, their cytokines will be an attractive target for future therapies, leading to the

development of more specific and effective drug. The more scientists understand about how psoriasis work the better equipped they are to create more specific and effective drug. So most anti-cytokine drug currently in use impact Th17 pathway even though they were developed years before its discovery e.g. cyclosporine found to normalize IL17 expression as detected by Lowes and Bowcok. [41], also Etanercept down regulate Th17 cell cytokine expression [13]. More recently, human therapies specifically targeting Th17 appears to be highly effective. However, all these data were collected from experimental animals model and the potential safety of this treatment may be limited by the role of Th17 cell in normal host defence against infection [42,43].

To sum up, our results suggest that psoriasis is a mixed Th1 and Th17 inflammatory mediated disease. Th17 cells could warrant further attention for future studies as a therapeutic target.

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الملخص العربي

مستوى انترلوكين-١٧ وانترلوكين-٢٢ وانترفيرون-جاما

في مصل الدم لمرضى الصدفية

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مرض الصدفية هو مرض جلدي مزمن يعتقد أنه يتكون بواسطة الخلايا الليمفاوية الثيموسية المساعدة التي تفرز انتلوكين-جاما. وتعرفت الدراسات الحديثة على وجود الخلايا الليمفاوية الثيموسية-١٧ التي وجد أنه قد تلعب دوراً مهماً في نشوء مرض الصدفية.

في هذه الدراسة قمنا بقياس مستوى انترلوكين-١٧، ٢٢ وانترفيرون-جاما في مصل الدم على ثلاثين من مرضى الصدفية وثلاثين انساناً سليماً للمقارنة بواسطة الاليزا، مع دراسة مقارنة احصائية بين المستويات المختلفة لشدة المرض لمرضى الصدفية والقياسات المختلفة لانترلوكين-١٧،٢٢ وانترفيرون-جاما.

وقد خلصت الدراسة الى وجود علاقة وثيقة ومتزايدة بين زيادة مستويات انترلوكين-١٧، ٢٢ وشدة المرض لمرضى الصدفية مع عدم وجود علاقة واضحة بالنسبة لانترفيرون-جاما واستنتجنا الى أن مرض الصدفية قد يكون نتيجة للخلايا الليمفاوية الثيموسية المساعدة ١، ١٧.