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ARTICLE

Pathogenesis of Psoriasis: Comparison of Natural Killer Cells, Interleukin-18, Intercellular Adhesion Molecule-1, Interleukin-2-Receptor-alpha and sCD44 Status in Patients and Controls

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Abstract

Background: Interleukin-18 (IL-18), soluble interleukin-2 receptor-alpha (sIL-2Rα), soluble intercellular adhesion molecule-1 (sICAM-1), soluble CD44 (sCD44) may have a role in psoriasis. **Objectives:** We aimed to investigate the role of these cytokines, adhesion molecules and soluble receptors in this disease. **Patients and Methods:** Seventy psoriasis patients and 20 healthy controls were included in this study. Severity of the disease was determined by estimation of psoriasis area severity index (PASI). Serum levels of IL-18, sIL-2Rα, sICAM-1 and sCD44 were determined by enzyme immunoassay. Enumeration of circulating NK cells was performed by flow cytometry. **Results:** Psoriasis patients had significantly (P<0.001) higher levels of IL-18, sIL-2Rα and sICAM-1 and significantly (P<0.01) lower percentages of NK cells ($CD56^+$, $CD56^+CD3^-$ and $CD56^+CD3^+$) as compared to controls. There were no significant differences in the levels of sCD44. IL-18 was significantly (P<0.01) higher among patients with severe as compared to mild and moderate psoriasis. Levels of sIL-2Rα and sICAM-1 were significantly (P<0.05) higher among patients with severe as compared to mild psoriasis. The percentage of NK-cells and the level of sCD44 were non-significantly related to severity of the disease. There were significant (P<0.01) positive correlations between serum levels of IL-18, sIL-2Rα and sICAM-1. There were also positive correlations (P<0.05) between PASI score and IL-18 and sICAM-1 levels. **Conclusion:** Increased IL-18 and sICAM-1 levels and their correlation with severity of psoriasis suggest that IL-18 may lead to increased Th1 response and up-regulation of ICAM-1 on monocytes culminating in increased cell infiltration and keratinocyte proliferation. IL-18 and sICAM-1 may serve as useful markers of psoriasis severity and targeting of both cytokines may be useful in treatment of the disease.

Key words: interleukin-18, ICAM-1, keratinocytes, NK cells, PASI-score, sCD44, sIL-2 receptor-α.

Abbreviations

CAM: cell adhesion molecules, ELISA: enzyme-linked immunosorbent assay, FITC: fluorescein isothiocyanate, IFN-γ : interferon-gamma, IL: interleukin, IL-2R: interleukin-2 receptor, MAb: monoclonal antibody, NK: natural killer, PASI: psoriasis area severity index, PE: phycoerythrin, sIL-2Rα: soluble IL-2R-alpha, SLE: systemic lupus erythematosus, Th1: T helper1, TNF-α: tumor necrosis factor-alpha, ESR: erythrocyte sedimentation rate.

Introduction

Psoriasis is an immunologically mediated disease. However, its exact pathogenesis is unknown. Although the precise mechanism responsible for immunocyte activation in the skin is not known, injection of interferon-gamma (IFN-γ) was reported to trigger the appearance of psoriatic lesions in genetically susceptible individuals (1). Recruitment and extravasation of leukocyte subsets through the locally modified endothelium, a process which is orchestrated by local cytokine production, were reported (2).

The release of cytokines from cutaneous cells may induce the expression of several cell adhesion molecules (CAMs) including ICAM-1, which mediates leucocyte/keratinocyte interactions and inflammatory responses (3). CD44, a lymphocyte homing receptor, is expressed on keratinocytes and may affect lymphocyte migration into lymphoid organs and sites of inflammation through lymphocyte-endothelial cell interaction (4,5). The pathological alterations of the microvasculature in psoriasis patients may be generated by altered homing processes (5).

IL-18 is a Th1-inducing cytokine which induces secretion of IFN-γ by T lymphocytes (6,7) and NK cells (8). IL-18 is secreted by monocytes (9), NK cells (8) and keratinocytes (6,10). The cutaneous Th1-type immune response leads to release of IFN-γ and IL-2 and increased expression of IL-2R (7). These effects exert proliferative signals on keratinocytes (11). Although dysregulation of several proinflammatory cytokines derived from keratinocytes has been implicated in the pathogenesis of psoriasis (2), the role of IL-18 and NK cells has not been well studied. This study was conducted to: 1) assess serum levels of IL-18, sIL-2Rα, sICAM-1 and sCD44; 2) enumerate the circulating NK cells; and 3) identify the relationship between these immunological parameters and the severity of psoriasis.

Materials and Methods

Study Population:

Psoriasis patients

This study included 70 patients (39 males and 31 females) with ages in the range of 5-67 years (28±19) from the Menoufiya University Hospital. Informed written consent was obtained before enrollment in the study and patients were subjected to thorough clinical examination. Those with other autoimmune disease (e.g. rheumatoid arthritis, systemic lupus erythematosis (SLE) and scleroderma) were excluded from the study. The duration of the disease in the selected patients ranged from 10 months to 25 years (15.7±10.6). ESR of these patients ranged from 15 to 80 mm/hour (33±21).

Severity of the disease was determined by estimation of psoriasis area severity index (PASI) (12). According to PASI, patients were classified as mild (n=31), moderate (n=21) and severe (n=18) cases. The clinical types of the disease were psoriasis vulgaris (n=3), guttate psoriasis (n=3), erythrodermic psoriasis (n=3), palmoplantar psoriasis (n=4), scalp psoriasis (n=17) and mixed psoriasis (n=40). Local treatment with or without systemic corticosteroids was used for our patients. None of the patients had received anticytokine therapy or reported a recent infection for at least 2 months before enrollment in the study. The procedures used in the study have been approved by the ethics committee of Faculty of Medicine, Menoufiya University, Shebin El-Kom, Egypt.

Controls

Twenty healthy individuals (11 males and 9 females) ranging in age from 7 to 65 years (22±19) without a family history of psoriasis or any other autoimmune diseases were selected as controls. A written consent was obtained from each individual before enrollment in the study.

Blood sampling

Venipuncture was performed under complete aseptic conditions and blood was drawn into 2 vacutainer tubes. One tube contained heparin for NK cell enumeration and the other with no additives for separation of serum. Sera were stored in aliquots at -70°C until used for the assay of the other studied immunological parameters.

Laboratory Procedures

Enumeration of NK cells

The percent of NK cell subsets was determined by Flow cytometry using OKT3 (CD3) and NKH-1 (CD56) monoclonal antibodies (MAbs) using a single laser Flow cytometer (Epics profile II, Coulter Epics, Hialeah,

FLA) with a software package (Quad Stat: Coulter). A whole blood staining technique was followed (13) using fluorescein isothiocyanate (FITC) or phycoerythrin (PE)-conjugated MAbs (Coulter Immunology). To monitor lymphocyte markers, bit maps were set on the lymphocyte population of the forward-angle light scatter versus a 90° light scatter histogram. The percentage of positively stained cells for each marker pair, as well as the percentage of doubly stained cells, was calculated.

Estimation of IL-18

Estimation of IL-18 was performed by ELISA (9), using a kit supplied by EuroClone Ltd (Paignton, Devon, UK). Samples were pipetted into the wells of microtiter strips which have been coated with a polyclonal antibody specific for IL-18. During the first incubation, the IL-18 antigen and a biotinylated polyclonal antibody specific for IL-18 were simultaneously incubated. After washing, the enzyme streptavidin-peroxidase was added. After the second incubation and washing, a substrate solution was added to induce a colored reaction. The intensity of color was determined using a microplate reader and the amount of IL-18 in each sample was determined using a linear standard curve according to the manufacturer's instructions.

Estimation of sIL-2R

Determination of sIL-2Rα was performed using a Quantikine ELISA Kit supplied by R&D Systems, Inc. (Minneapolis, MN, USA). MAb specific for IL-2Rα was pre-coated onto a microplate. Standards, samples and conjugate were pipetted into the wells and any sIL-2Rα present was sandwiched by the immoblized antibody and the enzyme-linked polyclonal antibody specific for IL-2Rα. After washing, a substrate solution was added to the wells and a color developed in proportion to the amount of the bound sIL-2Rα (14). After stopping the reaction, the intensity of the color was measured by microplate reader according to the manufacturer's instructions.

Assessment of sICAM-1

Assessment of sICAM-1 was done by ELISA Kit supplied by R & D Systems, Europe Ltd, (Abingdon, Oxon, UK). The test involved a double antibody ELISA (15), using antibodies directed against different epitopes on the ICAM-1 molecule. A second antibody conjugated with horseradish peroxidase was used. After washing and addition of a substrate, the reaction was stopped and absorbance was measured by microplate reader. Internal standards were used to construct a reference curve and the values of sICAM-1 were obtained.

Assessment of sCD44

Assessment of sCD44 was performed by ELISA (16), using a kit supplied by Diaclone Research (Besancon, France). MAb specific for sCD44 has been coated onto the wells of the microtiter plate. Samples including standards and unknowns were pipetted into these wells. After incubation and washing, a biotinylated MAb specific for sCD44 was added and after incubation, streptavidin-peroxidase was added. After incubation and washing, a substrate was added to induce a colored product, the intensity of which was directly proportional to the concentration of sCD44 present in the samples. The concentration of sCD44 in each sample was determined using a curve which was constructed by plotting the absorbance versus the concentration of sCD44 in the supplied standards.

Statistical analysis

Data were analyzed using the SPSS software package. Parametric tests (Student's t test and ANOVA) as well as non-parametric tests (Mann-Whitney and Kruskal-Wallis) were used for comparison of the quantitative results. Correlation co-efficient test was used for correlation of the different studied variables. The level of significance was set at 5%. Multiple linear regression was used where two or more independent variables were used to predict the value of a dependent variable.

Results

Interleukin-18 in psoriasis

Serum level of IL-18 was significantly higher among patients compared to the controls (Table 1). Patients with severe psoriasis had a significantly higher level compared to those with mild or moderate psoriasis (Table 2). A significant difference was also found between mild and severe cases and between moderate and severe cases. No significant difference was found between mild and moderate cases of the disease (Table 3).

Soluble IL-2R in psoriasis

Psoriasis patients had a significantly higher level of sIL-2Rα as compared to controls (Table 1). The level of sIL-2Rα increased with increasing severity of the disease, however, this relationship was not significant (Table 2). There was a significantly higher level of sIL-2Rα among severe compared to mild cases. However, there was no significant difference between mild and moderate nor between the moderate and severe cases (Table 3).

Table 1. The studied immunological parameters in psoriasis patients and controls.

The studied parameter	patients (70)	Controls (20)	Test of significance	p value
NK cells (%): $CD56^+$	8.4 ± 3.4	12.5 ± 3.6	4.78*	< 0.001
$CD56^+CD3^-$	5.0 ± 2.6	8.9 ± 2.6	4.44*	< 0.001
$CD56^+CD3^+$	2.5 ± 1.3	3.6 ± 1.6	3.23*	< 0.01
sIL-2Rα(pg/ml)	861 ± 261	471 ± 108	6.18*	< 0.001
IL-18 (pg/ml)	784 ± 511	7.0 ± 3.5	5.09**	< 0.001
sICAM-1 (ng/ml)	507 ± 182	347 ± 69	3.85*	< 0.001
sCD44 (pg/ml)	8.48 ± 0.67	8.70 ± 1.38	1.01*	> 0.05

*Data are expressed as mean ± SD.; *Student's t test.; **Mann-Whitney (Z) test.*

Table 2. The studied immunological parameters in relation to severity of psoriasis

The studied	Severity of the disease			Statistical	p
Parameter	Mild (n=31)	Moderate (n=21)	Severe (n=18)	significance	value
NK cells (%): $CD56^+$	8.0 ± 3.3	8.0 ± 3.4	9.3 ± 3.8	0.894*	> 0.05
$CD56^+CD3^-$	5.9 ± 2.7	5.5 ± 1.9	6.7 ± 3.1	0.933*	> 0.5
$CD56^+CD3^+$	2.4 ± 1.1	2.7 ± 1.7	2.2 ± 0.9	0.686*	> 0.05
sIL-2Rα(pg/ml)	777 ± 228	836 ± 280	958 ± 265	2.885*	> 0.05
IL-18 (pg/ml)	564 ± 420	539 ± 401	1450 ± 644	7.514**	< 0.05
sICAM-1 (ng/ml)	458 ± 164	484 ± 183	616 ± 173	5.028*	< 0.01
sCD44 (pg/ml)	8.3 ± 0.7	8.6 ± 0.6	8.6 ± 0.7	1.59*	> 0.05

*Data are expressed as mean ± SD ; *ANOVA (F) test. ' **Kruskal-Wallis* test. The severity of the disease was determined according to psoriasis area severity index (PASI).

Soluble ICAM-1 in psoriasis

Serum sICAM-1 level of patients was significantly higher than that of the controls (Table 1). It was significantly higher among severe cases than the mild cases of the disease (Table 2). There was no significant difference between moderate and severe cases nor between mild and moderate cases of psoriasis (Table 3).

Soluble CD44 in psoriasis

There were no significant differences in sCD44 levels of patients and controls (Table 1) nor in between patients with various degrees of the disease (Tables 2,3).

Percentages of NK cells in psoriasis

Patients had significantly lower percentages of $CD56^+$, $CD56^+CD3^-$ and $CD56^+CD3^+$ lymphocytes when compared to controls (Table 1 & Figure 1). There was no significant relationship between the percentage of NK cells and severity of the disease (Tables 2, 3 & Figure 2).

Correlation of the different studied variables among psoriasis patients:

IL-18 and sICAM-1 serum levels were positively correlated ($P<0.05$) with PASI score (Table 4). There were significant

Table 3. Comparison of the studied immunological parameters between patients with mild, moderate and severe psoriasis.

The studied Parameters	Mild versus moderate	Moderate versus severe	Mild versus severe
NK cells: $CD56^+$	>0.05	>0.05	>0.05
$CD56^+CD3^-$	>0.05	>0.05	>0.05
$CD56^+CD3^+$	>0.05	>0.05	>0.05
IL-18	>0.05	<0.01	<0.01
sIL-2Ra	>0.05	>0.05	<0.05
sICAM-1	>0.05	>0.05	<0.05
sCD44	>0.05	>0.05	>0.05

The severity of the disease was determined by psoriasis area severity index (PASI) score (see text) and comparison was performed by LSD test.

Table 4. Correlation between the different studied parameters in psoriasis patients

The studied Parameters	PASI	IL-18	sIL-2R	sICAM-1	sCD44
PASI					
IL-18	0.534*				
sIL-2Rα	0.257	0.660**			
sICAM-1	0.417*	0.775**	0.688**		
sCD44	0.071	- 0.12	- 0.187	- 0.063	
$CD56^+$	0.001	0.129	- 0.002	0.115	- 0.165
$CD56^+CD3^-$	0.125	0.285	0.180	0.124	- 0.209
$CD56^+CD3^+$	0.113	- 0.09	- 0.044	- 0.015	- 0.066

*The Spearman correlation coefficient test was used to correlate the different studied parameters. *p value<0.05; **p value<0.01*

positive correlations between the levels of Il-18, sIL-2Rα and sICAM-1. There were no significant correlations found between them and the other parameters. NK cell subsets or sCD44 were not significantly correlated with any of the studied parameters (Table 4).

Predictive value of the studied parameters

Linear regression analysis showed that IL-18, sIL-2Rα and sICAM-1 levels were significant predictors of psoriasis ($F = 3.942$, $P<0.01$).

Discussion

Psoriasis is characterized by abnormal epidermal proliferation and inflammation (17). Immune system involvement has been documented by the presence of activated T cells in psoriatic skin lesions and by cytokine involvement in the inflammatory response (18). Accumulating evidence suggests that psoriasis is mediated by T cells and is associated with a Th1 response (17). In this study, psoriasis patients had a significantly higher level of sIL-2Rα, a finding which has been reported by other investigators (18,19). The synthesis and expression of IL-2Rα represent an early sign of T cell activation, which is accompanied by release of sIL-2Rα (20). The sIL-2Rα is the most consistently increased activation marker related to Th1 immune response (19,20). The level of sIL-2Rα

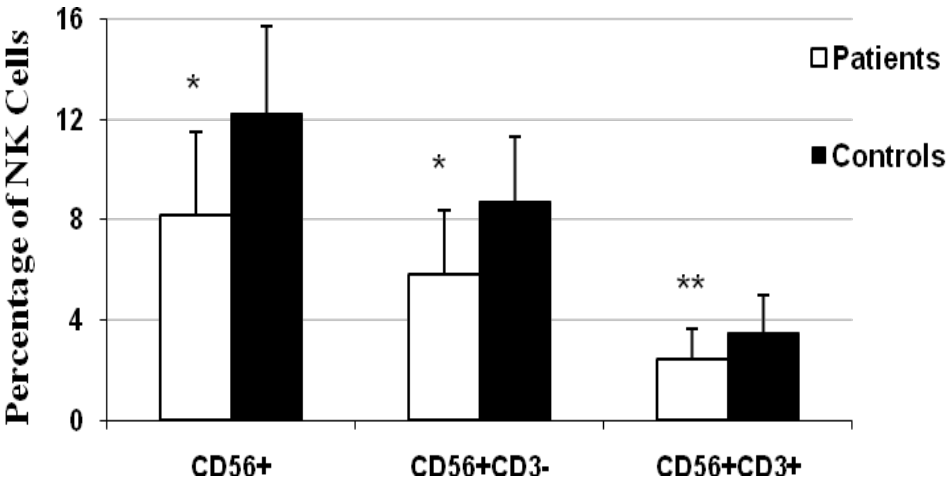

Figure 1. Percentages of natural killer (NK) cells in psoriasis patients and controls.
Data are expressed as mean ± SD (n=70 for patients and n=20 for controls). Patients had significantly (P<0.01) lower percentage of NK-cells (Student's t test). Patients received no treatment for 2 months before enrollment in the study.

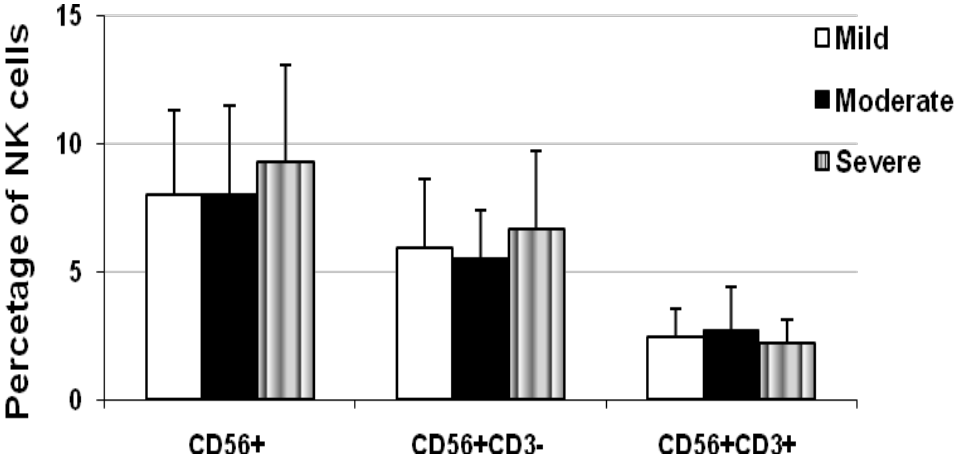

Figure 2. Percentages of natural killer (NK) cells in relationship to the severity of psoriasis. There was no significant difference between different degrees of the disease (ANOVA test).

found in our patients was significantly higher among severe compared to mild psoriasis although it was not significantly correlated with PASI score. This finding may indicate that T cells may have a role in pathogenesis of psoriasis. T lymphocytes were reported to play an important role in initiating the inflammatory responses that result in disease development, however, sIL-2Rα was not found as a marker of inflammation (21).

Our findings showed high levels of IL-18 in psoriasis patients and these levels were significantly higher in those with severe compared to mild disease. Moreover, these levels were positively correlated with both PASI score and sIL-2Rα level. A high-level of IL-18 and its correlation with PASI were previously reported (2,22,23). These results suggest that IL-18 may play an important role in Th1 immune response, primarily *via* its ability to induce IFN-γ production in T cells and NK-cells (7). Psoriasis was found to be associated with over-expression of Th1 cytokines and a relative underexpression of Th2 cytokines (6,7). As an IFN-γ- inducing factor (24), IL-18 is emerging as an important proinflammatory cytokine in localized inflammatory and immunologic diseases (6). Although the two major sources of IL-18 are monocytes and macrophages, keratinocytes were found to synthesize

IL-18 (22). The keratinocyte-derived IL-18 is implicated in development of the Th1 (7) and the cutaneous inflammatory responses in psoriasis (6). Although IL-18 was detected in keratinocytes of the normal human skin, its expression was markedly up-regulated in psoriasis (10). Moreover, IL-18 binding protein was reported to neutralize IL-18 activities and was suggested for psoriasis treatment (22). Therefore, keratinocytes may play an initiating role in the local IFN-γ-dependent inflammatory processes through expression, activation and secretion of IL-18 (7).

Our data demonstrated low percentages of peripheral blood NK cells (CD56+) among psoriasis patients, but these percentages were not significantly correlated with disease severity. Reduced cells expressing NK cell markers (CD16, CD56 and CD94) in peripheral blood were reported to be reduced in psoriasis (25,26). Psoriasis shares certain immunological features with recognized autoimmune conditions such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, in which a pathogenic role of NK cells was postulated (27,28). Moreover, cells expressing NK cell markers were demonstrated in psoriatic plaques (27). These findings suggest that NK cells may modulate autoimmune inflammation and act as a source of Th1 cytokines which are important in the psoriatic process (29). Injection of NK cells from psoriatic donors into autologous non-lesional psoriatic skin resulted in classic psoriasis histology with a significant increase in epidermal thickness and proliferation. On the other hand, injection of NK cells from normal donors into autologous normal skin did not induce the histology of psoriasis (30). The decrease of NK cell numbers in our study may be attributed to recruitment and trapping of these cells into psoriatic skin (25,27). These findings suggest that NK cells may have a role in the pathogenesis of psoriasis by releasing local cytokines such as TNF-α and IFN-γ which exert proliferative signals on to keratinocytes (11).

In this study, sCD44 was estimated to assess the role of the lymphocyte homing receptor (CD44) in pathogenesis of psoriasis, however, normal levels were found. Some investigators reported that CD44 receptor was involved in lymphocyte homing to inflamed skin (4) and that the pathological alterations of the microvasculature in psoriasis patients may be generated by altered homing processes (5). The inflammatory and endothelial cells revealed immunoreactivity for CD44 in lesional psoriatic as compared to non-lesional psoriatic or normal skin (31). Microarray analysis has shown expression of CD44 genes in psoriatic patients (32). Our results suggest that CD44 may have a minor role in the pathogenesis of psoriasis, a finding which is supported by other researchers: Increased sCD44 level was found in rheumatoid arthritis while normal levels were found in other types of arthritis including psoriasis vulgaris (33). Moreover, the general distribution of CD44 in psoriatic lesional epidermis resembled that in normal epidermis (34). Furthermore, adhesion in lymphocyte homing among psoriasis patients was through interaction of the lymphocyte adhesion molecule CD11a/CD18 with CD54 on endothelial cells (5).

This study found that patients had high levels of sICAM-1 and that these levels were positively correlated with PASI score. This finding was previously reported in various inflammatory conditions including psoriasis (2,22). We believe that our findings add to the existing evidence that suggests that over-expression of ICAM-1 on dermal vessels is important in the pathogenesis of psoriasis (35). Soluble ICAM-1 is inducible on several types of cells involved in inflammation (36) and its expression is necessary for leucocyte/keratinocyte interactions. ICAM-1 up-regulation in keratinocytes was observed in several inflammatory dermatoses such as psoriasis, atopic dermatitis and lupus erythematosus (37). ICAM-1 may play a role in the IFN-γ-induced adherence of T cells to keratinocytes by stimulating T cell activation, adhesion to endothelial cells and migration (21). Our data revealed that sICAM-1 levels were positively correlated with severity of the disease. Moreover, there was a significant positive correlation between sICAM-1 and IL-18 levels, a finding which was also found by Gangemi *et al* (22). Together, these findings suggest that IL-18 may up-regulate the expression of ICAM-1 which help adhesive interactions between ICAM-1 on monocytes and leucocyte function antigen-1 on T/NK-cells leading to generation of a stimulatory signal in cytokine cascade (38). ICAM-1 may promote cutaneous localization of T cells (39) by helping extravasation of activated T cells, thus contributing to inflammatory reaction and formation of psoriatic plaques (39) Therefore, targeting ICAM-1 may be an attractive therapeutic option (40).

In conclusion, IL-18 is over-expressed leading to a shift of T cells toward a Th1 immune response and to up-regulation of ICAM-1 molecules on monocytes. These actions induce increased activation of T cells and NK cells resulting in an increased expression of IL-2R and adhesion molecules and to increased leucocyte migration and keratinocyte proliferation. Our results suggest that IL-18 and ICAM-1 may possibly be markers of disease severity and may represent targets for immunomodulatory treatment of psoriasis.

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