SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION-3 (STAT3) AND PSORIASIS

Mahmoud Yousry M. Abdel-Mawla, Mohamed Abd El-kader Teama, Magda Ibrahim Assaf*, Eman Salah El-Din Mohamed Helmy.

*Dermatology and venereology & pathology*departments , Faculty of Medicine, Zagazig University*

ABSTRACT

Background: The exact pathogenesis of psoriasis remains unclear. Signal transducer and activator of transcription-3 (STAT3) is a possible important link between keratinocytes and immunocytes during psoriasis evolution. **Aims:** To detect the state of STAT3 activation in both lesional and non-lesional skin of patients with psoriasis and to correlate the degree of STAT3 activation with the severity of psoriasis. **Methods:** The study included (30) psoriasis patients and (30) age and sex matched healthy control subjects. Skin biopsy was taken from a lesional and a non-lesional site for every patient. A single biopsy site was done for every control subject. Immunohistochemical staining using anti-STAT3 antibodies was done. Statistical analysis was performed to detect the relation between the strength of STAT3 staining reaction and PASI (psoriasis area severity index) score. **Results:** The strength of immune-staining reaction for STAT3 is statistically higher in lesional sites than the non-lesional ones among psoriasis patients. The strength of STAT3 activation is statistically higher in patients with higher PASI scores. Moreover, the non-lesional sites demonstrated a significant STAT3 activation in comparison to the control group. **Conclusion:** Signal transducer and activator of transcription-3 is upregulated in lesional than non-lesional skin in psoriasis patients and the degree of its activation parallels the PASI score. The non-lesional skin in psoriasis can show STAT3 activation indicating a possible pre-psoriasis state. **Keywords:** Psoriasis – signal transducer and activator of transcription – Janus kinase pathway – cytokine signaling. **Abbreviations:** STAT; Signal transducer and activator of transcription**,** PASI; Psoriasis area severity index**,** JAKs; janus kinases, IL; interleukin**,** TH; T-helper**,** DCs; dendritic cells**,** TNF-α; tumour necrosis factor alpha**,** SCID; severe combined immunodeficiency, CD; cluster of differentiation.

INTRODUCTION

Psoriasis is a common inflammatory skin disorder affecting approximately 2% of the population [(1)]. Psoriatic lesions can be triggered by many factors including drugs, stress and bacterial infections in genetically susceptible persons. Moreover, it was found that psoriasis coexists with cardiovascular and inflammatory bowel diseases; suggesting a systemic character [(2)].

The pathogenesis of psoriasis remains unclear and it is controversial as to whether psoriasis results from a primary abnormality in epidermal keratinocytes or from deregulation of the immune system [(3)]. Apparently, different studies suggest that psoriasis is caused by an interaction between epidermal keratinocytes and the immune system [(4)].

The janus kinases (JAKs) and signal transducers and activators of the transcription (STATs) signaling pathways have been shown to be activated by a number of cytokines and growth factors. The JAKs associate with the intracellular domains of particular receptors and become activated by ligand binding to the receptors at the cell surface. Activated JAKs consecutively phosphorylate STATs at distinct tyrosine residues. The tyrosine-phosphorylated STATs leave the receptor complex, translocate to the nucleus to promote the transcriptional activation of ligand-inducible genes [(5)]. Four JAKs and seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6) have been identified [(6)].

Regarding STAT3, it is activated by cytokines of the IL-6 family [(7)] and other extracellular signaling ligands such as IL-10 family members and epidermal growth factor [(8)]. In the skin, STAT3 has many impacts on wound healing, hair cycling and carcinogenesis. Moreover, some studies demonstrated STAT3 activation in lesional psoriatic skin. As the expression of STAT3 in lesions from other non-psoriatic acanthotic inflammatory skin diseases showed a staining pattern similar to normal epidermis, this finding suggested that STAT3 activation in psoriatic keratinocytes might be necessary for development of psoriasis and it does not appear to be a secondary outcome of mere epidermal hyperplasia [(9)]. Furthermore, the critical role of STAT3 in T-cell differentiation was established by the finding that deletion of STAT3 in T cells abrogated T-helper 17 (TH17) differentiation [(10)].

The primary immunologic driving force in psoriasis was thought to be TH1 cells. However, the dependence of psoriasis on TH17 rather TH1 cells have defined psoriasis as a TH17-mediated disease [(11)]. So, STAT3 is a possible important link between keratinocytes and immunocytes during psoriasis evolution [(1)].

METHODS

This study included (30) psoriasis patients and (30) age and sex matched healthy control subjects selected from the outpatient unit of the Dermatology and Venereology Department at Zagazig University Hospitals during the period from July 2010 to July 2012. The inclusion criteria were: subjects who accepted to participate in the study, patients who had any of the different variants of psoriasis, patients with different grades of severity, patients who were firstly diagnosed or

who had been stopping treatment for a-3 months wash out period were included. Subjects refused to participate in the study, those less than 2 years of age and pregnants were excluded.

All patients were subjected to a full history taking with special interest in onset, course, duration of the disease and history of previous psoriasis medications. A complete dermatological examination was done to determine the clinical type of psoriasis and the affected sites. Assessment of disease severity was done using the psoriasis area severity index (PASI). The PASI score calculator accessed from: (http://pasitraining.com/calculator) [12] was used and the results were interpreted as follows: mild psoriasis = PASI was less than 15, moderate psoriasis = PASI was 15-25, severe psoriasis = PASI was more than 25.

Punch skin biopsies were taken using a sterile, disposable, 5mm diameter biopsy punch manufactured by Kai medical, Japan. One biopsy was taken from a lesional area and the other from a non-lesional area, for every patient. A single biopsy site was taken for every control subject. Biopsies were labeled and fixed immediately in 10% formalin containing bottles then embedded in paraffin to form paraffin blocks. A preliminary Hematoxylin and Eosin stained sections were done for histopathological confirmation of the diagnosis.

For immunohistochemical studies, the reagent used was a human polyclonal antibody (Anti-STAT3 antibody produced in rabbits, code number 1671, SIGMA-ALDRICH Co.LLC, USA). Properties of the used anti-STAT3 antibodies: antibody form; affinity isolated antibody, grade; prestige antibodies® powered by atlas antibodies, clone; polyclonal, physical form; buffered aqueous glycerol solution in phosphate-buffered saline, pH 7.2, containing 40% glycerol and 0.02% sodium azide, species reactivity; human, applications; immune-histochemistry (suitable for formalin-fixed, paraffin-embedded sections), immunoblotting (suitable), indirect immunofluoresence (suitable), and protein array (suitable), shipped in; wet ice, storage temperature; -20C, immunogen sequence; (GVTFTWVEKDISGKTQIQSVEPYKQQLNNM SFAEII MG YKIMDATNILVSPLVYLYPDIPKEEAFGKYCR PESQEHPEADPGSAAPYLKTKFICVTPTTCSN TIDLPMSPRTLDSLMQNNGEGAEPSAGGQFE SLTFDMELTSECA).

The steps for immunohistochemical staining were as follows: 1. Rinse in wash buffer, 2. Incubate with primary antibody for 30 minutes, 3. Rinse 2 times in wash buffer, 4. Incubate with peroxidase labeled polymer conjugated to a secondary antibody for 30 minutes, 5. Rinse 2 times in wash buffer, 6. Develop for 10 minutes using diaminobenzidine (DAB) as the substrate, 7. Rinse 2 times in distilled water, 8. Counterstain in Mayer's hematoxylin for 5 minutes, 9. Rinse 2 times in tap water, 10. Rinse in lithium carbonate water, diluted 1:5 from saturated solution, for 1 minute, 11. Rinse in tap water for 5 minutes, 12. Dehydrate in graded ethanol and xylene, 13. Cover slipping.

Immunohistochemical interpretation was done to assess the epidermal STAT3 staining reaction in the form of brown cytoplasmic or nuclear precipitate. The percentage of positive cells was calculated in 100 cells / 4 HPF. The grading for staining reaction was as follows: negative (-); if <5% of cells stained, weak positive (+); if 5%-25 % of cells stained, moderate positive (++); if 25%-50% of cells stained, strong positive (+++); if >50% of cells stained.

STATISTICAL ANALYSIS

Data were checked, entered and analyzed using SPSS version 19. Data were expressed as the mean ± standard deviation for quantitative variables, and the number and percentage for categorical variables. Chi-squared ($\chi 2$) or Fisher extract test, t-test and ANOVA (F test) were used when appropriate. $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient demographic characteristics: This study was conducted on (30) psoriasis patients plus (30) age and sex matched control subjects. Fifteen patients (50%) were females and fifteen patients (50%) were males. Their ages ranged between (10-78) years with a mean of (43.7±17.1) years **(Table1)**.

The psoriasis area severity index (PASI) ranged between (8-59.2) with a mean of (28.5±15.8). Seven patients (23.3%) had mild psoriasis, thirteen patients (43.3%) had moderate disease and ten patients (33.3%) had severe psoriasis as scored by PASI **(Table 2)**.

A positive family history of psoriasis was reported by only seven patients (23.3%). Twenty eight patients (93.3%) had psoriasis vulgaris (chronic plaque psoriasis) and two patients (6.7%) had other types (one guttate type and one erythrodermic on top of psoriasis vulgaris). There was no associated psoriasis co-morbidity in twenty one patients (70 %) while five patients (16.7 %) had hypertension and four patients (13.3%) had psoriatic arthritis **(Table 3)**.

Immunohistochemical results:

The immunohistochemical results for an epidermal cytoplasmic STAT3 staining reaction **(Table 4)** revealed that cases-lesional and non-lesional

samples showed a highly significant (P < 0.001) STAT3 expression when compared to control samples. Furthermore, the cases lesional samples showed a highly significant (P < 0.001) STAT3 expression when compared to the cases non-lesional samples.

Also, the immunohistochemial results for an epidermal nuclear STAT3 staining reaction **(Table 5)** revealed that cases-lesional and non-lesional samples showed a highly significant (P < 0.001) STAT3 expression and activation when compared to control samples. Furthermore, the cases lesional samples showed a highly significant (P < 0.001) STAT3 expression and activation when compared to the cases non-lesional samples.

Table (6) demonstrates that patients with higher PASI score revealed a statistically significant (P = 0.01) epidermal nuclear STAT3 staining reaction and subsequently more STAT3 activation as nuclear localization of STAT3 confirms its activation. However, there was no significant relation between the strength of STAT3 epidermal nuclear reaction and other parameters including (age, gender, family history, previous therapy, clinical type of psoriasis or associated co-morbidity) as shown in **(Table 6)**.

	Cases (n=30)		**Controls** (n=30)		**t**	**p**
Age (years)						
$\bar{x}$ ± SD	43.7 ±17.1		43.9±17.1		0.05	0.95
Range	10-78		10-78			
Gender	**n**	**%**	**n**	**%**	χ^2	**P**
Male	15	50.0	15	50.0	0.0	1.0
Female	15	50.0	15	50.0		

n = number, SD = standard deviation, $\bar{x}$ = mean

PASI	**n = 30**	
$\bar{x}$ ± SD	28.5 ± 15.8	
Range	(8 – 59.2)	
	n	**%**
Mild	7	23.3 %
Moderate	13	43.3 %
Severe	10	33.3 %

n = number, SD = standard deviation, $\bar{x}$ = mean, PASI = psoriasis area severity index

Table (3): The medical profile of psoriasis patients

	n	%
Family history		
Positive	7	23.3
Clinical type		
Psoriasis vulgaris	28	93.3
Others	2	6.7
Co-morbidity		
Negative	21	70.0
Positive		
▪ Hypertension	5	16.7
▪ Arthritis	4	13.3

N= number

Table (4): Immunohistochemical results for STAT3 epidermal cytoplasmic staining reaction in cases and control subjects

	STAT3 epidermal cytoplasmic staining reaction							
	Negative		**Positive**					
	(-)		Weak (+)		Moderate (++)		Strong (+++)	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cases (Non – lesional)	_	_	23	76.7	2	6.7	5	16.7
Cases (Lesional) $^{+}$	_	_	8	26.7	16	53.3	6	20.0
Controls *	_	_	30	100.0	0	0.0	0	0.0

n=number, χ^2= 43.4, P < 0.001^{*+}
* P < 0.05 when comparing control subjects with cases non-lesional or lesional
+ P < 0.05 when comparing cases lesional with cases non-lesional

Table (5): Immunohistochemical results for STAT3 epidermal nuclear staining reaction in cases and control subjects

	STAT3 epidermal nuclear staining reaction							
	Negative		Positive					
	(-)		Weak (+)		Moderate (++)		Strong (+++)	
	n	%	n	%	n	%	n	%
Cases (Non – lesional)	23	76.7	3	10.0	1	3.3	3	10.0
Cases (Lesional) +	6	20.0	7	23.3	9	30.0	8	26.7
Controls *	30	100.0	0	0.0	0	0.0	0	0.0

n=number, $\chi^2 = 46.4$, $P<0.001^{*+}$
* P < 0.05 when comparing control subjects with cases non-lesional or lesional
+ P < 0.05 when comparing cases lesional with cases non-lesional

PASI						
$\bar{x} \pm SD$	29.5±22	22±11.4	20.5±4.0	42.7±13.9	4.5	**0.01**
Range	8-59.2	10.2-44	14-24	15-58		
Median	22	23	23	48		
Co-morbidity						
No	4	6	7	4	2.64	0.45
Yes	2	1	2	4		

This table shows a statistically significant (P=0.01) relation between severity of psoriasis as scored by PASI and the strength of STAT3 epidermal nuclear staining reaction which subsequently indicates STAT3 activation.

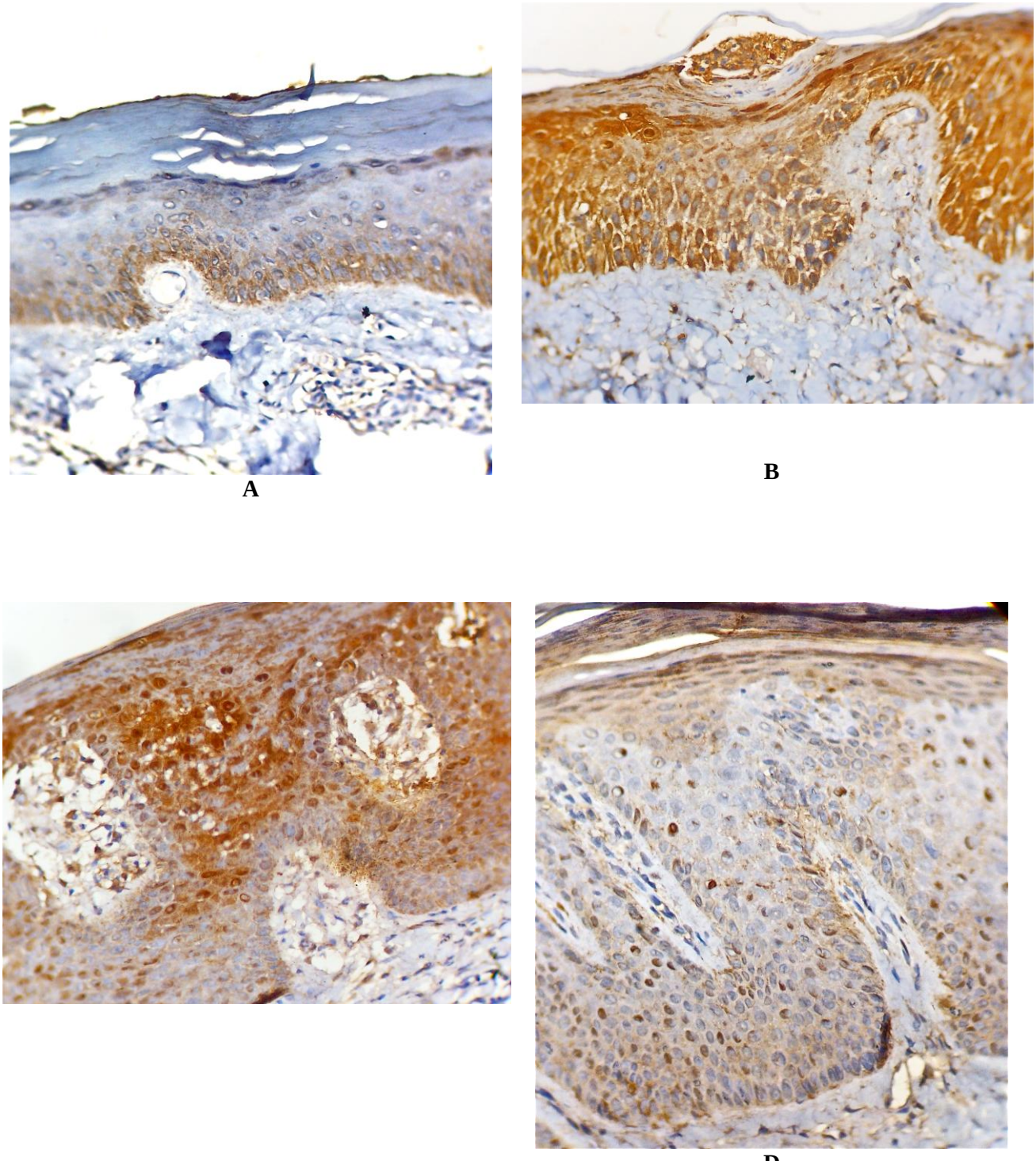

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Figure (1): Different patterns of immunohistochemistry results

A mild positive cytoplasmic reaction for STAT3 in the basal and suprabasal layers in a control subject.
A strong positive cytoplasmic reaction for STAT3 throughout the whole epidermis including a Munro 's microabscess (arrow) from a lesional skin in psoriasis vulgaris patient.
A strong positive nuclear and cytoplasmic reaction for STAT3 throughout the whole epidermis in patient with severe psoriasis vulgaris.
A moderately positive nuclear reaction for STAT3 throughout the whole epidermis in a patient with moderate psoriasis vulgaris.

DISCUSSION

Many new insights have been gained over the last few years that changed the view for psoriasis pathogenesis. These new results include: (i) the knowledge about the effects of signal transduction activation in psoriasis pathogenesis, (ii) the knowledge regarding the role of several types of immune cells in psoriasis such as DCs, TH17 cells, natural killer T cells and regulatory T cells, (iii) the profound success of anti-tumor necrosis factor (TNF)-α therapy in psoriasis patients and (iv) the role of new cytokines such as IL-22, IL-23 and IL-20 in psoriasis [(15)].

Signal transducer and activator of transcription 3 (STAT3) activation in keratinocytes is required during skin wound healing, and according to the hypothesis that psoriatic keratinocytes show an abnormal and exaggerated wound healing [(16)] response, the status of STAT3 in the lesional epidermis of psoriatic patients was the aim of some studies. Furthermore, a severe combined immunodeficiency (SCID)-human skin graft model revealed that STAT3 underwent activation in keratinocytes in the psoriasis-converted lesions following injection of pathogenic CD4+ immunocytes. These data provide compelling evidence that STAT3 activation impacts an important link between keratinocytes and immunocytes, both of which interdependently participate in the pathogenesis of psoriasis [(9)].

This study demonstrated that in psoriasis patients STAT3 activation is statistically higher in cases lesional skin than cases non-lesional or control sites. Furthermore, the non-lesional apparently normal skin from psoriasis patients showed a significantly higher STAT3 activation than the control sites.

Also, this study showed that patients with more disease severity as scored by PASI had more lesional STAT3 activation. This finding was due to a statistically significant (P=0.01) relation between PASI and cases lesional epidermal nuclear STAT3 staining reaction which indicates STAT3 activation. To the best of our knowledge this is the first study to correlate the PASI score and the strength of STAT3 activity in psoriasis patients, furthermore it adds new evidence upon the role of STAT3 in psoriasis pathogenesis.

Results for lesional sites coincide with those of **(Sano et al, 2005)** [(1)] who reported that STAT3 was activated in the lesional keratinocytes from virtually all the psoriatic patients. This up-regulation of STAT3 activation in psoriasis did not appear to be a secondary outcome of epidermal hyperplasia, because lesions from nonpsoriatic inflammatory skin diseases with characteristic acanthosis e.g. chronic dermatitis showed a STAT3 staining pattern similar to normal epidermis.

Furthermore, **(Sano et al, 2008)** [(9)] used K5.STAT3C transgenic mice to study the role of STAT3 in psoriasis because their epidermal keratinocytes harbored constitutively activated STAT3. The skin of K5.STAT3C mice appeared normal at birth without histological alterations, however, by 2 weeks of age, their skin was reddened, scaly and hyperkeratotic lesions developed in the tail, in which histological alterations were similar to human psoriasis.

Supporting the role of STAT3 activation in immunocytes during psoriasis evolution were the additional findings by **(Sano et al, 2005)** [(1)]. They illustrated that; like human psoriatic lesions, the infiltration of CD4+ cells was predominant in K5.STAT3C transgenic mice. Furthermore, the grafted skin from K5.STAT3C mice onto nude mice developed psoriatic lesions following tape stripping when in vitro-activated T-cells were topically injected, but did not develop either without injection of T cells, or in the grafts from normal mice even in the presence of T-cells [(1)].

Expectedly, a topical pretreatment of K5.STAT3C mice with STAT3 decoy oligonucleotides abrogated the de novo generation of tape stripping induced psoriatic lesions with less T-cell infiltrates. The STAT3 decoy treatment reversed preexisting psoriatic lesions as well, suggesting that an inhibition of STAT3 activation would be a reliable therapy for psoriasis [(17)].

In favor of our hypothesis regarding the important role of STAT3 in psoriasis pathogenesis, a STAT3 inhibitor (STA-21) was tested in psoriasis. Surprisingly, topical treatment with STA-21 not only inhibited the development of psoriasiform lesions in K5.STAT3C mice but also ameliorated psoriatic lesions in six of the eight psoriasis patients [(18)]. According to our findings, we believe that patients with higher PASI score should benefit more from this drug as they demonstrate more lesional STAT3 activation.

Regarding the cases non-lesional skin, there has been an earlier report about altered expression of angiogenesis and lymphangiogenesis markers in the non-lesional skin of plaque-type psoriasis. The authors stated that their finding is consistent with the fact that the characteristic vascular features of psoriasis are among the early phenotypic variations observed in the genesis of a lesion [(19)]. To our knowledge, this is the first study to compare the state of STAT3 activation in lesional and non-lesional skin in human psoriasis. Results from non-lesional skin that showed higher STAT3 activation than controls inspite of absence of any histopathological alternations in routine sections,

needs further explanation. We hypothesize that this finding represents a possible pre-psoriatic state indicating that psoriasis is actually a total skin disease and emphasizing on its systemic character to involve the whole integumentary system. In agreement with our hypothesis, **Farber et al** [(20)] stated that psoriasis is a disease of the total skin, which becomes clinically evident when a psoriatic lesion appears following some injury to the symptomless skin of a psoriasis patient. Although not all biopsy specimens of the symptomless skin show pathologic findings, the evolution of a psoriatic plaque can be envisioned as developing from a non visible phase into a visible state.

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محول الاشارة و المنشط للنسخ-3 و الصدفيه

تعد الصدفية واحدة من أكثر الأمراض الجلدية شيوعا و مع ذلك لا تزال حقيقة الآلية المرضية لحدوث الصدفية أمرا غير واضحا. وتشير العديد من الدراسات إلى أن الصدفية هي نتاج خلل في التفاعل بين الخلايا القرنية بالجلد وخلايا الجهاز المناعي.
لقد ثبت ان بروتينات محولات الاشارة و منشطات النسخ داخل الخلية يمكن تفعيلها من خلال عدد من السيتوكينات وعوامل النمو عن طريق المستقبلات الموجوده علي سطح الخلية. و تضم تلك المحولات عائله مكونة من سبعة أفراد و لكن يعد محول الاشارة و المنشط للنسخ- 3-فريدا من نوعه حيث يؤدي اعتلال الجين المكود قبل الولاده لدى فئران التجارب الي فقدان الجنين.

أن زيادة تفعيل محول الاشارة و المنشط للنسخ- 3 في الجلد قد يشكل رابطا هاما بين الخلايا القرنية و خلايا الجهاز المناعي من أجل ظهور مرض الصدفية.
ان الهدف من البحث هو الكشف عن مستويات النشاط المختلفة لمحول الاشارة و المنشط للنسخ- 3 في كل من الجلد المصاب بالصدفية و الجلد الذي يبدو صحيحا من الناحية الاكلينيكية في المرضى الذين يعانون من الصدفية. أيضا ،التعرف على مدى و كيفية الارتباط بين درجة نشاط محول الاشارة و المنشط للنسخ-3 و معامل شدة الصدفية.
و من خلال هذا البحث فقد وجدنا أن معدلات نشاط محول الاشارة و منشط النسخ- 3 ترتفع بشكل واضح بالجلد المصاب بالصدفيه عن أماكن الجلد التى لم تظهر تأثرا من الناحيه الاكلينيكيه بداء الصدفيه في نفس المريض مما يتناسب بشكل طردي مع معامل شدة الصدفيه. كما وجدنا أن هناك درجة ملحوظه من النشاط لهذا البروتين في الجلد الغير السليم ظاهريا و التي تفوق بكثير معدلات النشاط الطبيعيه في الجلد السليم مما يقد يفسر بوجود ما يسمى بمرحلة "ما قبل الصدفيه" و التى تؤكد أن الصدفية مرض يصيب كل السطح الجلدي حتى و ان لم يظهر ذلك على المستوى الاكلينيكي.