Orginal Article

Significance of Fucosyltransferase 8 and Transforming Growth Factor-β1 Expression in Plaque Psoriasis: A Clinical and Immunohistochemical Study

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Abstract

Aim: Psoriasis is a chronic disease characterized by epidermal hyperproliferation and dermal inflammation. Fucosyltransferase 8 (FUT8) is a single-core fucosylation enzyme in mammalian cells. Transforming growth factor-beta (TGF-β), a multipotent cytokine, was identified in epidermal keratinocytes. This study aimed to assess the expression of FUT8 and TGF-β1 in psoriatic skin compared with control skin using immunohistochemistry and to explore the link between these expressions with accessible clinical and pathological information.

Materials and Methods: This was a case-control study that included 60 participants: thirty cases with chronic psoriasis vulgaris and 30 gender- and age-matched normal controls. A comprehensive medical history and examination were conducted, and the severity of psoriasis was evaluated using the psoriasis area and severity index score. Immunohistochemical analysis of FUT8 and TGF-β1 was conducted.

Results: FUT8 expression in keratinocytes gradually increased from control skin to perilesional and lesional skin. Regarding the dermis, FUT8 exhibited significant differences between lesional and perilesional skin and controls in terms of the expression of inflammatory cells (χ^2=40.0, $P < 0.001$), percentage of positive cells, and H-score of inflammatory cells ($P = 0.002$, $P < 0.001$), respectively. Significant positive correlations were observed among TGF-β1 and FUT8 in terms of the percentage of positive cells and H-score in the lesional epidermis ($P = 0.013$, $P < 0.001$, respectively).

Conclusion: FUT8 and TGF-β1 were shown to be overexpressed in psoriasis, showing correlations with severity and with each other, suggesting their potential involvement in the development of psoriasis.

Keywords: Fucosyltransferases, immunohistochemistry, psoriasis, transforming growth factor beta 1

Introduction

Psoriasis is a multisystem immune-related disorder that generally affects the skin, joints, or both. The prevalence rate of this condition in the western population is approximately 2-3%, whereas that in Egypt varies from 0.19% to 3%.[1]

Psoriasis can manifest in several clinical forms, including pustular, erythrodermic, and guttate psoriasis. The chronic plaque variant, which affects approximately 90% of patients, typically presents as scaly erythematous lesions involving the extensor areas, trunk, and scalp.[2]

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Psoriasis is a multifactorial disorder with multifaceted pathogenesis that involves an abnormal immune reaction in the skin, genetic predisposition, and exposure to several environmental agents, such as trauma, infections, and drugs.[3]

The injurious inflammatory processes associated with psoriasis extend beyond the skin and are responsible for a growing list of coexisting comorbidities, such as chronic

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kidney disorder, gastrointestinal disorders, mood disorders, cancer, and cardiovascular and metabolic diseases (obesity, hypertension, dyslipidemia, and diabetes).[4]

Fucosylation is a frequent posttranslational alteration of glycolipids and glycoproteins.[5] The human genome encodes 13 different fucosyltransferase (FUTs), with α-(1,6)-FUT8 being the only one that catalyzes α-(1,6)-linked core fucosylation in the Golgi apparatus.[6,7] Fucose is added to asparagine-linked N-acetylglucosamine (GlcNAc) moieties by FUT8, which is a characteristic shared by N-linked glycan core structures.[8]

Conserved throughout evolution, a family of secreted polypeptide factors called transforming growth factor-beta (TGF-β) regulates several aspects of physiological embryogenesis, adult tissue homeostasis, and cell growth and differentiation. Additionally, its members are involved in the pathophysiological processes that lead to different diseases.[9,10]

In human tissue, TGF-β1, TGF-β2, and TGF-β3 are the three isoforms, and skin is a significant target for TGF-β1, playing a vital role in etiopathogenesis of psoriasis, and epidermal keratinocytes have been shown to express its receptors.[9,11]

Kim et al.[12] claimed that core fucosylation only affects the way TGF-β receptors move across their cell surfaces. The pharmacological or genetic suppression of TGF-β RII's N-linked glycosylation significantly decreased the receptor's ability to move over its cell surface and hampered its interaction with the TGF-β1 ligand. Furthermore, Gao et al.[13] discovered that FUT8 controls the proliferation, migration, and fibrosis of human embryonic lung fibroblasts that are stimulated by TGF-β1.

Therefore, this study aimed to investigate the immunostaining of FUT8 and TGF-β1 in skin biopsies of lesional and perilesional skin biopsies from psoriatic skin compared with normal control skin.

Materials and Methods

Study Cohort

This designed case-control study was conducted on 30 cases of psoriasis vulgaris diagnosed using clinical and histopathological methods, in addition to 30 age- and sex-matched normal subjects who were designated as controls.

Every participant signed a written informed consent form before initiating the research work, and approval for the study was obtained from the Menoufia University Faculty of Medicine Research Ethics Committee, which agreed with the Declaration of Helsinki 1975 (reviewed in 2000) (approval number and date: 8/2021 DERMA 13). Selected cases were asked to discontinue local anti-psoriatic (15 days) or systemic (1 month) anti-psoriatic therapy before the beginning of the study.

Exclusion criteria: Any case with one or more of the following was excluded from the study:

- Dermatological diseases except plaque psoriasis.

- Any systemic autoimmune or inflammatory disease.

Full history taking with an emphasis on disease duration in years, course, and onset of psoriasis was obtained from every case where early-onset psoriasis was defined as psoriasis started before the age of 40 years or late-onset psoriasis as psoriasis started after the age of 40 years old.[1]

Full physical and dermatological examinations were performed to evaluate the lesion site and involvement of the palm, sole, and scalp. In addition, evidence of Koebner's phenomenon was also assessed. The severity of psoriasis was assessed using the psoriasis area and severity index (PASI) score. Mild cases were defined as PASI < 7, moderate cases as PASI 7-12, and severe cases as PASI > 12.[14]

Skin biopsies: First, 3 mm punch skin biopsies were taken from the involved skin (lesional skin), perilesional skin (2 cm away from the lesion),[15] and coordinated skin sites of control subjects. Then, 10% neutral formalin was used for fixation, and paraffin blocks were formed. Furthermore, 4 μm thick sections were cut as follows: one section for regular hematoxylin and eosin stain histological examination and an additional two sections for immunostaining using FUT8 and TGF-β1 as primary antibodies.

Immunohistochemical Staining

The streptavidin-biotin-amplified system was employed for immunostaining. Anti-FUT8 immunoglobulin G Rabbit Polyclonal Antibody (0.1 mL concentrated and diluted 1:100) (Abbexa Ltd, Cambridge, UK, catalog no. abx338636) and Polyclonal anti-TGF-β1 antibody (Chongqing Biospes Co., Ltd, China; 100 μL, catalog no. YPA1196) were used as primary antibodies. Heat retrieval was performed using citrate buffer for the two primary antibodies. Human breast cancer tissue and human bone marrow tissue slides were prepared as positive controls for FUT8 and TGF-β1 individually. In contrast, negative control slides were checked each time.

Analysis of FUT8 and TGF-β1 Expressions

FUT8 and TGF-β1 immunostaining were evaluated semiquantitatively. The positivity of expression was recognized as cytoplasmic or nucleocytoplasmic brownish

staining for FUT8[16] and cytoplasmic staining for TGF-β1[17] by 3,3'-diaminobenzidine reaction. The percentage of positive cells was then evaluated. In terms of stain intensity, there were three categories for stain intensity: mild, moderate, and strong. The H-score (histo-score) was calculated using the following formula: H-score= 1 x percentage of cells with mild intensity + 2 x percentage of cells with moderate intensity + 3 x percentage of cells with strong intensity.[18] Furthermore, FUT8 and TGF-β1 expressions in epidermal and dermal inflammatory cells were evaluated, and H-scores were recorded.

Statistical analysis

Revision of the collected data was done for accuracy, and then the data were coded and analyzed using the Statistical Package for Social Sciences (SPSS version 23) program. A suitable evaluation agreed with the type of data obtained for each parameter. Numbers and percentages were presented using qualitative data, whereas quantitative data were presented as mean and standard deviation. Correlations were detected using appropriate statistical tests. *P* value ≤ 0.05 was the level of significance.[19]

Results

Demographic Data of the Study Groups

Cases of plaque psoriasis were 18 (60%) male and 12 (40%) female patients. The age range was 18-75 years with 44.83±15.64 years as $\bar{X}$ ± standard deviation (SD) value. The control group comprised 20 (66.7%) males and 10 (33.3%) females. The age range was 20-70 years with 39.67±14.63 years as $\bar{X}$ ± SD value. Age and sex differences between cases and controls were not statistically significant (*P* > 0.05 for both). The clinical data of the cases are presented in Table 1.

Histopathological data of the studied cases: Ten cases (33.3%) patients had mild acanthosis, seven cases (23.3%) had moderate acanthosis, and 13 cases (43.3%) had notable acanthosis. Additionally, 15 cases (50%) patients were characterized by mild hyperkeratosis, 9 cases (30%) had moderate hyperkeratosis, and 6 cases (20%) had marked hyperkeratosis. In 9 cases (30%), parakeratosis was mild; in 10 cases (33.3%), it was moderate; and in 11 cases (36.7%), it was significant. Suprapapillary thinking was found in all (100%) patients with psoriasis, whereas Munro's microabscesses and spongiform pustules were found in 4 (13.3%) and 3 (10%) cases, respectively. All patients (100%) exhibited blood vessel dilation in the papillary dermis. Inflammation was mild in 11 (36.7%) cases, moderate in 11 (36.7%), cases, and marked in 8 (26.7%) cases.

Table 1. Clinical information of the studied patients (n = 30)

Variables	n	%
Onset		
Early	17	56.7
Late	13	43.3
Course		
Stationary	18	60.0
Progressive	12	40.0
Duration (years)		
Minimum-maximum	1.0-10.0	
$\bar{X}$ ± SD	5.70±3.58	
Median (IQR)	6.0 (2.0-9.0)	
Family history		
Positive	10	33.3
Negative	20	66.7
Risk factors		
Yes	**10**	**33.3**
HTN	1	3.3
Smoking	6	20.0
T2DM	3	10.0
No	20	66.7
Site of affection		
Extremities	9	30.0
Axial and extremities	14	46.7
Axial	7	23.3
Scalp affection		
Positive	21	70.0
Negative	9	30.0
Nail affection		
Positive	8	26.7
Negative	22	73.3
Joint affection		
Yes	7	23.3
No	23	76.7
Palm and sole affection		
Yes	9	30.0
No	21	70.0
Itching		
Yes	19	63.3
No	11	36.7
Koebnerization		
Yes	11	36.7
No	19	63.3
PASI score		
Minimum-maximum	3.0-15.0	
$\bar{X}$ ± SD	9.28±3.74	
Median (IQR)	8.60 (6.0-13.0)	
Severity		
Mild	10	33.3
Moderate	9	30.0
Severe	11	36.7

$\bar{X}$: Mean, SD: standard deviation, IQR: Interquartile range, T2DM: Type 2 diabetes mellitus, PASI: Psoriasis area and severity index, HTN: Hypertension

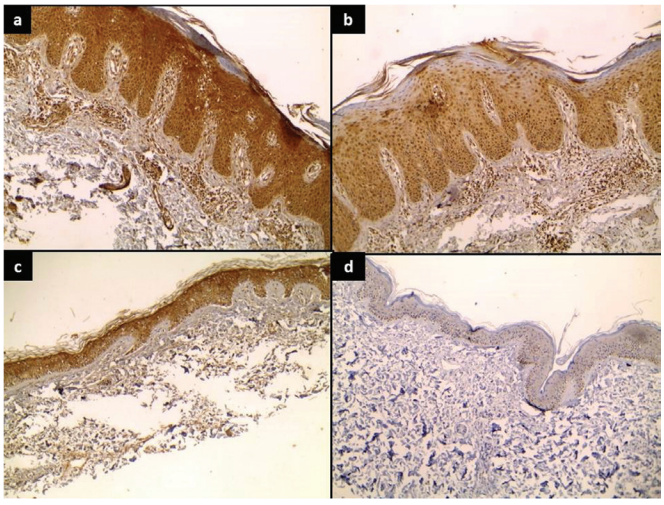

Figure 1. Immunohistochemical staining of FUT8 showed (a) strong expression in lesional skin (IHC, x100); (b) moderate expression in lesional skin (IHC staining, x100); (c) moderate expression in perilesional skin (IHC staining, x40); (d) negative expression in control skin (IHC staining, x40)

FUT8: Fucosyltransferase 8, IHC: Immunohistochemistry

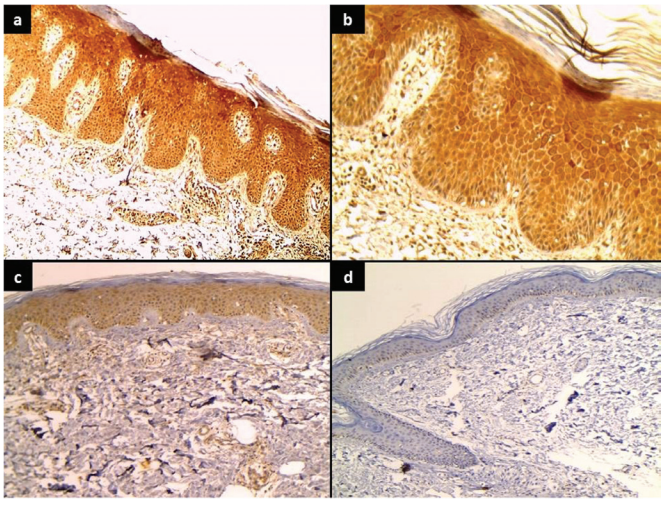

Figure 2. Immunohistochemical staining of TGF-β1 showed (a) strong expression in lesional skin (IHC, x100); (b) high-power view showed strong expression in lesional skin (IHC staining, x400); (c) mild expression in perilesional skin (IHC staining, x40); (d) negative expression in control skin (IHC staining, x40)

TGF-β1: Transforming growth factor-beta, IHC: Immunohistochemistry

Immunohistochemical staining of FUT8 and TGF-β1 in lesional, perilesional, and control skin is was demonstrated in Figure 1 for FUT8 and Figure 2 for TGF-β1.

Evaluation of FUT8 Immunohistochemical Expression in Control and Lesional and Perilesional Skin of the Studied Cases

In terms of the epidermis, statistically significant differences were found among the lesional and perilesional skin of the studied cases and controls regarding the FUT8 status (χ^2=12.306, P = 0.001), intensity (χ^2=16.610, P = 0.002), percentage of positive cells, and H-score (H=36,697, 47,455, respectively, P < 0.001 for both) with an ongoing, progressive higher expression of FUT8 in keratinocytes from the control skin than in the perilesional and lesional skin (Table 2).

Concerning the dermis, there were statistically significant differences between the lesional abd perilesional skin of the studied cases and controls regarding the FUT8 status in inflammatory cells (χ^2=40.0, P < 0.001), percentage of positive cells (inflammatory) (H=12,037, P = 0.002), and H-score (inflammatory) (H=16,224, P < 0.001) Table 2.

Evaluation of TGF-β1 Immunohistochemical Expression Between Control Skin and Lesional and Perilesional Skin of the Studied Cases

Regarding the epidermis, statistically significant differences were detected between the lesional and perilesional skin of the studied cases and control skin regarding status (χ^2=29,515, P < 0.001), percentage of positive cells, and H-score of TGF-β1 (H=7,462 and 11,008; P = 0.024 and 0.004, respectively) Table 3.

Regarding the dermis, a statistically significant difference was observed in the TGF-β1 status between the control skin and the lesional and perilesional skin of the studied cases (χ^2=47,312, P < 0.001), as shown in Table 3.

There was an ongoing progressive higher expression of TGF-β1 in keratinocytes and dermal inflammatory cells from control skin in comparison with perilesional and lesional skin, as presented in Table 3.

Correlation Between FUT8 and TGF-β1 Regarding Percentage of Positive Cells and H-score of Expression in the Epidermis of Lesional Skin

There were significant positive correlations between TGF-β1 and FUT8 regarding the percentage of positive cells (r=0.448, P = 0.013) and H-score in the epidermis of lesional skin (r=0.694, P < 0.001) (Figure 3a, b).

Moreover, there were significant positive correlations between TGF-β1 and FUT8 in the dermis of lesional skin regarding the percentage of positive cells (r=0.448, P = 0.013) and H-score (r=0.694, P < 0.001) (Figure 3c, d).

Relationship between FUT8 and TGF-β1 and clinical information of the studied cases: A statistically significant association was found between FUT8's strong intensity of expression in the epidermis of lesional skin and the presence of itching (χ^2=8,585, P = 0.015) (Figure 4a). There was a

Table 2. Comparison of FUT8 immunohistochemical expression in patients' lesional and perilesional skin and control skin

	Lesional, (n = 30)		Perilesional, (n = 30)		Control, (n = 30)			
FUT8	**n**	**%**	**n**	**%**	**n**	**%**	**Test of sig. (p)**	**Sig. bet. grps.**
Epidermis								
Status								
Positive	**30**	**100.0**	**30**	**100.0**	**23**	**76.7**	χ^2=12,306* (^{MC}p=0.001)*	p_1= - $^{FE}p_2$=0.011* $^{FE}p_3$=0.011*
Negative	0	0.0	0	0.0	7	23.3		
Localization								
Cytoplasmic	30	100.0	30	100.0	23	100.0	-	-
Intensity								
Mild	11	36.7	20	66.7	19	82.6	χ^2=16,610* (^{MC}p=0.002)*	p_1=0.018* p_2=0.001* $^{MC}p_3$=0.449,
Moderate	9	30.0	8	26.7	4	17.4		
Severe	10	33.3	2	6.7	0	0.0		
Percentage of positive cells								
Min.-max.	40.0-90.0		40.0-90.0		10.0-70.0		H=36,697* (<0.001)*	p_1=0.511 p_2<0.001* p_3<0.001*
$\bar{X}$ ± SD	74.67±16.97		71.67±16.21		37.83±15.94			
Median (IQR)	80.0 (70.0-90.0)		70.0 (60.0-90.0)		40.0 (30.0-50.0)			
H-score								
Min.-max.	70.0-270.0		40.0-270.0		10.0-80.0		H=47,455* (<0.001)*	p_1=0.016* p_2<0.001* p_3<0.001*
$\bar{X}$ ± SD	145.3±64.69		99.0±48.52		43.04±18.20			
Median (IQR)	120.0 (90.0-180.0)		90.0 (70.0-120.0)		40.0 (30.0-55.0)			
Dermis								
Status (inflammatory)								
Positive	30	**100.0**	**18**	**60.0**	**6**	**20.0**	χ^2=40.0* (<0.001)*	p_1<0.001* p_2<0.001* p_3=0.002*
Negative	0	0.0	12	40.0	24	80.0		
Intensity (inflammatory)								
Mild	11	36.7	9	50.0	4	66.7	χ^2=4,926 (^{MC}p=0.290)	p_1=0.227, $^{MC}p_2$=0.276 $^{MC}p_3$=1,000,
Moderate	9	30.0	7	38.9	2	33.3		
Severe	10	33.3	**2**	**11.1**	**0**	**0.0**		
Percentage of positive cells (inflammatory)								
Min.-max.	40.0-90.0		60.0-90.0		30.0-70.0		H=12,037* (0.002)*	p_1=0.845 p_2=0.001* p_3=0.001*
$\bar{X}$ ± SD	74.67±16.97		77.22±12.27		41.67±16.02			
Median (IQR)	80.0 (70.0-90.0)		80.0 (70.0-90.0)		35.0 (30.0-50.0)			
H-score (inflammatory)								
Min.-max.	70.0-270.0		70.0-270.0		30.0-80.0		H=16,224* (<0.001)*	p_1=0.127 p_2<0.001* p_3=0.005*
$\bar{X}$ ± SD	145.3±64.69		112.2±51.51		58.33±17.22			
Median (IQR)	120.0 (90.0-180.0)		90.0 (80.0-120.0)		60.0 (50.0-70.0)			

IQR: Interquartile range, SD: Standard deviationi χ^2: Chi-square test, H: Kruskal-Wallis test. Pairwise contrast between each two groups was done using post-hoc test (Dunn's for multiple comparisons test), FE: Fisher's exact test, MC: Monte Carlo, *: $P \leq 0.05$ is the level of significance. p: Comparison between the three studied groups, p_1: Comparison between lesional and perilesional, p_2: Comparison between lesional and control; p_3: Comparison between perilesional and control

statistically significant relationship between a higher FUT8 percentage of positive cells in the epidermis of lesional skin and smoking (U=33.0, $P = 0.044$) and higher disease severity (H=8,674, $P = 0.013$) (Figure 4b, c, respectively).

There was a statistically significant relationship between high FUT8 mean H-scores and the progressive course of psoriasis (U=46.50, $P = 0.008$), concomitant axial and extremity involvement (H=9,216, $P = 0.010$), and higher disease severity (H=11,113, $P = 0.004$) (Figure 4d-f, respectively).

Regarding TGF-β1, there was a statistically significant relationship between TGF-β1's strong intensity of expression and progressive course (χ^2=6,941, $P = 0.017$), PASI score of the studied cases (H=13,710, $P = 0.001$), and severe disease (χ^2=12,285, $P = 0.006$) (Figure 5a-c, respectively).

Table 3. Comparing TGF-β1 immunohistochemical expression in patients' lesional and perilesional skin and control skin

	Lesional, (n = 30)		Perilesional, (n = 30)		Control, (n = 30)			
	n	%	n	%	n	%	Test of sig. (p)	Sig. bet. grps.
Epidermis								
Status								
Positive	**30**	**100.0**	**22**	**73.3**	**12**	**40.0**	χ^2=29,515* (<0.001)*	$^{FE}p_1$=0.005* p_2<0.001* p_3=0.009*
Negative	0	0.0	8	26.7	18	60.0		
Localization								
Cytoplasmic	30	100.0	22	100.0	12	100.0	-	-
Intensity								
Mild	15	50.0	17	77.3	9	75.0	χ^2=5,258 (^{MC}p=0.217)	$^{MC}p_1$=0.091, $^{MC}p_2$=0.371, $^{FE}p_3$=1,000,
Moderate	12	40.0	5	22.7	3	25.0		
Severe	3	10.0	0	0.0	0	0.0		
Percentage of positive cells								
Min.-max.	30.0-90.0		0.0-90.0		30.0-70.0		H=7,462* (0.024)*	p_1=0.185. p_2=0.007* p_3=0.087,
$\bar{X} \pm SD$	68.67±19.95		54.0±35.58		48.33±13.37			
Median (IQR)	70.0 (50.0-90.0)		70.0 (0.0-80.0)		50.0 (40.0-55.0)			
H-score								
Min.-max.	30.0-240.0		0.0-140.0		30.0-100.0		H=11,008* (0.004)*	p_1=0.008* p_2=0.004* p_3=0.387
$\bar{X} \pm SD$	114.3±63.66		64.67±45.69		58.33±19.46			
Median (IQR)	95.0 (50.0-180.0)		75.0 (0.0-90.0)		55.0 (45.0-70.0)			
Dermis								
Status (inflammatory)								
Positive	30	100.0	**12**	**40.0**	**4**	**13.3**	χ^2=47,312* (<0.001)*	p_1<0.001* p_2<0.001* p_3=0.020*
Negative	0	0.0	18	60.0	26	86.7		
Intensity (inflammatory)								
Mild	15	50.0	9	75.0	3	75.0	χ^2=2,742 (^{MC}p=0.670)	$^{MC}p_1$=0.364, $^{MC}p_2$=0.742, $^{FE}p_3$=1,000,
Moderate	12	40.0	3	25.0	1	25.0		
Severe	3	10.0	0	0.0	**0**	**0.0**		
Percentage of positive cells (inflammatory)								
Min.-max.	30.0-90.0		50.0-90.0		50.0-70.0		H=2,385 (0.303)	p_1>0.05, p_2>0.05, p_3>0.05,
$\bar{X} \pm SD$	68.67±19.95		75.0±12.43		60.0±11.55			
Median (IQR)	70.0 (50.0-90.0)		75.0 (70.0-85.0)		60.0 (50.0-70.0)			
H-score (inflammatory)								
Min.-max.	30.0-240.0		60.0-140.0		50.0-100.0		H=1,931 (0.381)	p_1>0.05 p_2>0.05 p_3>0.05
$\bar{X} \pm SD$	114.3±63.66		90.83±25.39		72.50±20.62			
Median (IQR)	95.0 (50.0-180.0)		85.0 (75.0-95.0)		70.0 (60.0-85.0)			

IQR: Interquartile range, SD: Standard deviation, χ^2: Chi-square test, FE: Fisher's exact, MC: Monte Carlo, H: Kruskal-Wallis test. Pairwise contrast between each two groups were performed using the post hoc test (Dunn's for multiple comparisons test); *: $P \leq 0.05$ is the level of significance. p: Comparison between the three studied groups; p_1: Comparison between the lesional and perilesional groups; p_2: Comparison between the lesional and control groups; p_3: Comparison between the perilesional and control

The percentage of FUT8-positive cells in the epidermis of lesional skin and the PASI score of the studied cases showed a statistically significant positive correlation (r=0.512, P = 0.004). Indeed, there was a positive correlation between the H-score of FUT8 in the lesional skin's epidermis and the PASI score of the cases under study (r=0.626, $P < 0.001$). Similarly, a substantially positive correlation was found between the H-score of TGF-β1 in the lesional skin's epidermis and the PASI score (r=0.854, $P < 0.001$) (Figure 5d-f, respectively).

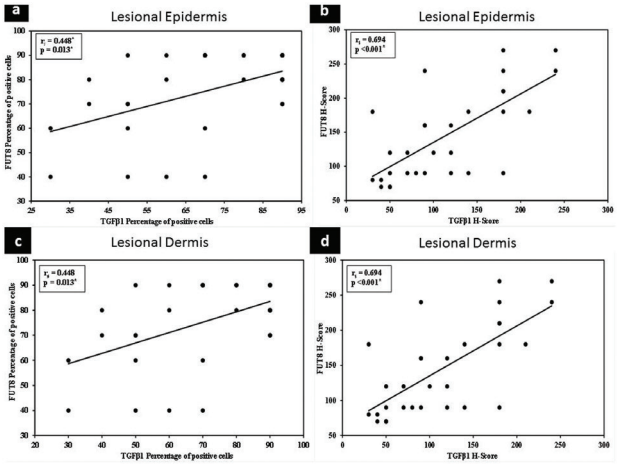

Figure 3. Statistically significant positive correlations between TGF-β1 and FUT8 regarding (a) the percentage of positive cells (r=0.448, P = 0.013) and (b) the H-score in the epidermis of lesional skin (r=0.694, $P < 0.001$). Statistically significant positive correlations between TGF-β1 and FUT8 in the dermis of lesional skin regarding (c) percentage of positive cells (r=0.448, P = 0.013) and (d) H-score (r=0.694, $P <$ 0.001)

TGF-β1: Transforming growth factor-beta, FUT8: Fucosyltransferase 8

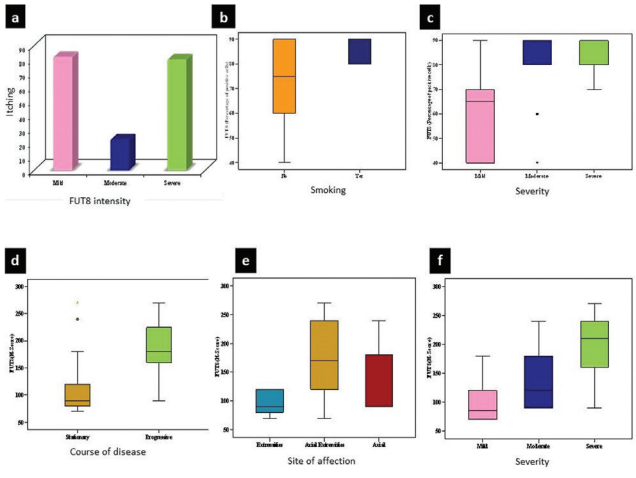

Figure 4. Statistically significant relationship between strong FUT8 expression in the epidermis of lesional skin and (a) presence of itching (χ^2=8,585, P = 0.015). Statistically significant relationship between higher FUT8 percentage of FUT8-positive cells in the epidermis of lesional skin and (b) smoking (U=33.0, P = 0.044) and (c) higher disease severity (H=8,674, P = 0.013). A statistically significant relationship between high FUT8 mean H-score and (d) progressive course of psoriasis (U=46.50, P = 0.008), (e) concomitant axial and extremity affection (H=9,216, P = 0.010) and (f) higher disease severity (H=11,113, P = 0.004)

FUT8: Fucosyltransferase 8

Relationship between FUT8 and TGF-β1 and histopathological data of the studied cases: There were significant relationships regarding the mean H-score of FUT8 lesional skin epidermis and hyperkeratosis (H=7,643, P = 0.022) and there were statistically significant relationships regarding the mean percentage of positive cells of TGF-β1 in epidermis of lesional skin and acanthosis (H=6,453, P = 0.040), hyperkeratosis (H=14,286, P = 0.001), parakeratosis (H=7,473, P = 0.024), and inflammation (H=8,108, P = 0.017) (Figure 6).

Discussion

This study reported that increased expression of FUT8 and TGF-β1 in psoriasis was associated with disease severity and also correlated with each other, suggesting their potential involvement in the development and progression of psoriasis.

Psoriasis is a prolonged, immune-mediated, inflammatory dermatosis. It is a lifelong disorder that has a negative impact on patients' quality of life.[20] The etiology of this condition is multifactorial and includes genetic aberrations, environmental causes, and abnormal immune responses.[3]

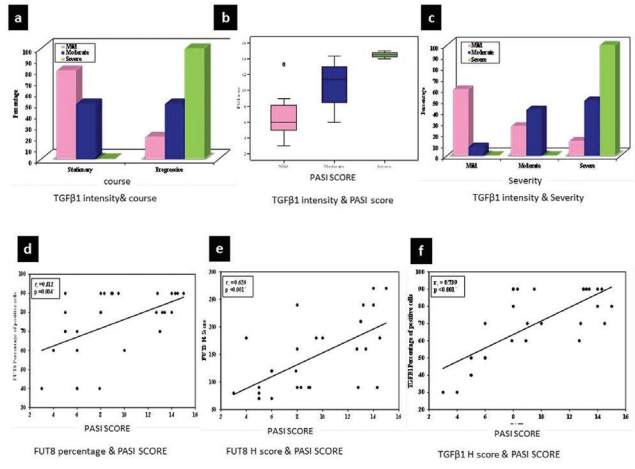

Figure 5. Statistically significant relationship between TGF-β1 strong intensity of expression and (a) progressive course (χ^2=6,941, P = 0.017), (b) PASI score of the studied cases (H=13,710, P = 0.001) and (c) severe disease (χ^2 = 12,285, P = 0.006). Statistically significant positive correlation between the percentage of FUT8-positive cells in the epidermis of lesional skin and the PASI score of the studied cases (r=0.512, P = 0.004) (d). Significant positive correlation between the H-score of FUT8 in the epidermis of lesional skin and the PASI score of the studied cases (r=0.626, $P < 0.001$) (e) and a significant positive correlation between the H-score of TGF-β1 in the epidermis of lesional skin and the PASI score (r=0.854, $P < 0.001$) (f)

TGF-β1: Transforming growth factor-beta, PASI: Psoriasis area and severity index, FUT8: Fucosyltransferase 8

FUT8 upregulation has been observed in several malignancies. The epidermis of psoriatic skin is distinguished by higher expression of FUT8.[21]

TGF-β is a multipotent cytokine responsible for regulating cellular growth and differentiation, maintaining and enhancing the inflammatory response, and producing proinflammatory mediators such as interleukin-17 (IL-17) and IL-22 in psoriasis.[3]

TGF-β1 promotes angiogenesis, vasodilatation, and fibroblast growth, all of which are observed in the early stages of psoriasis. There is compelling evidence that the overexpression of latent TGF-β1 in the epidermis is closely linked to skin inflammation resembling psoriasis.[9]

FUT8 was expressed in 76.7% of normal skin biopsies in the epidermis, and according to reports, FUT8 has a physiological role in healthy skin and significantly affects cellular proliferation and differentiation.[22] In mammals, the fucosylation of glycoconjugates is associated with numerous biological activities, such as blood antigens and cell adhesion.[23]

Comparable findings were demonstrated by Blander et al.,[24] who reported that certain FUT in T lymphocytes in normal skin were markedly elevated. Kelel et al.[21] also reported that in human cells, FUT8 facilitates the transfer of the guanosine diphosphate-L-fucose moiety to the innermost GlcNAc structure of an N-linked glycan via an alpha-1,6 linkage, including skin. Additionally, other studies have demonstrated that FUT8 is widely expressed in mammalian tissues, including skin.[22]

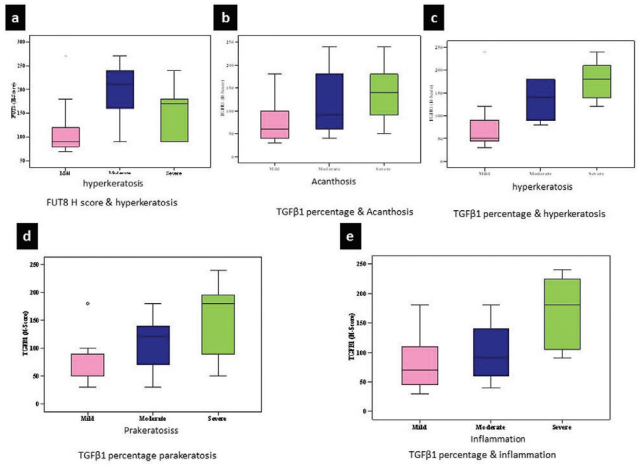

Figure 6. Significant relationship between mean H-score of FUT8 in the epidermis of lesional skin and hyperkeratosis (H=7,643, $P = 0.022$). (a) Statistically significant relationship between mean percentage of positive cells of TGF-β1 in epidermis of lesional skin and acanthosis (H=6,453, $P = 0.040$) (b), hyperkeratosis (H=14,286, $P = 0.001$) (c), parakeratosis (H=7,473, $P = 0.024$) (d), and inflammation (H=8,108, $P = 0.017$) (e)

TGF-β1: Transforming growth factor-beta: FUT8: Fucosyltransferase 8

Upon comparing lesional psoriatic skin (epidermis) to both normal and perilesional epidermis, FUT8 expression was considerably higher, and this overexpression could provide proof of its involvement in the etiology of illness. Similar to these results, Kelel et al.[21] documented the upregulation of FUT8 expression in the epidermis of individuals with psoriasis. Furthermore, the authors reported that the proliferation of cells in the lesional epidermis was linked to FUT8 overexpression. FUT8 expression was detected in the epidermis of all perilesional skin biopsies in the current study and was significantly higher than that in control skin. The evidence indicated that pathological changes in psoriasis were also seen in perilesional skin, as reported by Micali et al.[25] who stated that although the capillaries in lesional skin appear to be more dilated, tortuous, and elongated, their density is comparable to that of uninvolved skin. Slight epidermal hyperplasia, punctiform spongiotic areas with involvement of the stratum basale and around the subpapillary blood vessels, and mild inflammatory reaction with an increase in the number of macrophages, mast cells, and lymphocytes were also observed in the perilesional skin of psoriasis patients.[26]

The findings of this study revealed a significant positive correlation between PASI scores and FUT8 expression in lesional skin (epidermis). Kelel et al.[21] also reported that FUT-8 regulated cyclin expression significantly in cells of the epidermis of patients with psoriasis and was correlated with the severity of the disease in order that the epidermal growth factor receptor signaling pathway upsurges keratinocyte proliferation.

The results of this investigation revealed a statistically significant correlation between hyperkeratosis and FUT8 expression. Similar results were reported by Ito et al.[27] who found that skin with ichthyosis showed altered N-glycan profiles compared with normal skin, and these findings indicated reduced activities of N-acetylglucosaminyltransferase II and FUT8. The biological function of N-glycans in keratinization was proposed based on altered N-glycan structures in hyperkeratotic skin and the fucose-labeled glycoproteins from keratinocytes in psoriasis lesions may be linked to abnormal development of the psoriatic epidermis.[28]

Regarding the dermis of the studied psoriatic cases, FUT8 was also found to be significantly expressed in the dermis of the studied cases, which may be attributed to the role of FUT8 in inflammation. Liu et al.[29] reported that during a diversity of pathological procedures, like a response to inflammation, altered fucosylated structures frequently appeared. Fujii et al.[30] discovered that T-cell-mediated intestinal inflammation was prevented in FUT8-deficient mice, and under colitic conditions, FUT8-/- mice produced fewer inflammatory

cytokines. Additionally, because T-cell antigen receptor-related glycoproteins in the lipid raft fraction did not accumulate as well in FUT8-deficient T-cells, these cells responded to inflammatory stimuli with reduced sensitivity.

The present investigation identified a statistically significant correlation between itchiness and FUT8 expression. Puan et al.[31] reported that FUT6 (another member of the FUT family) deficiency exhibits a reduced itch sensitivity due to basophil affection. Indeed, Zou et al.[28] reported a strong correlation between N-glycan indicators and psoriasis clinical indices.

Moreover, our investigation of the correlation between FUT8 expression in the epidermis and smoking revealed a significant association. This correlation can be elucidated by evidence that supports the pivotal role of smoking in stimulating the generation of reactive oxygen species, leading to inflammation and the development of cancer.[32] As a cytoprotective measure against excessive reactive oxygen species, the body's antioxidant response is believed to enhance the synthesis of FUT8 mRNA, perhaps leading to an increase in core fucose.[33] However, FUT8 activity was reduced in mice exposed to cigarette smoke, indicating that a long smoking duration is key to such changes.[34]

According to this study, 40% of normal skin biopsies (epidermis) exhibited TGF-β1. TGF-β1 was reported to play a physiological role in normal skin. Fibroblasts and epithelial cells are responsible for tissue secretion in a specific, function-, and context-dependent manner.[35] TGF-β1 is involved in skin formation. It promotes the production of extracellular matrix components and/or proliferation in cultures of skin-derived fibroblasts.[36]

Similar findings were demonstrated by Ghosh et al.[37] who stated that TGF-β was present in normal dermal fibroblasts. Differential expression of TGF-β is observed in almost all skin component cells. In the context of a healthy human epidermis, basal cellular layer expression of TGF-β3 predominates; however, TGF-β1 expression is also present. Therefore, it has been proposed that this is both required and constitutive for epithelial homeostasis.[11]

As per the current study, lesional psoriatic skin (epidermis) significantly expressed more TGF-β1 than either normal or perilesional skin (epidermis). This overexpression could provide proof of TGF-β1 involvement in the pathogenesis of psoriasis. Likewise, Li et al.[38] found that in transgenic mice, keratinocyte-targeted overexpression of TGF-β1 in cell type induces pathological changes in which keratinocytes show phenotypical and molecular alterations similar to psoriasis.

Furthermore, cases with psoriasis and normal control subjects had a statistically significant difference in genetic polymorphism of the *TGF-β1* gene at codon 10 with susceptibility to psoriasis in a section of Egyptian cases.[9]

Ahmed et al.[39] established that the *TGF-β1* gene's codon 10 and 25 polymorphisms may enhance a person's vulnerability to psoriasis. However, they do not appear to affect the disease's severity or its serum level. Moreover, Doi et al.[40] reported that the psoriatic epidermis exhibits a significant decrease in TGF receptors, and this reduction in signaling of TGF-β is explained by the TGF-β's role in enhancing epidermal proliferation of keratinocytes as TGF-β1 is a strong inhibitor of keratinocyte growth. Additionally, these results confirm the distinct functions of various TGF-β1 codons, which should be considered in experimental studies of targeted therapy.

Upon studying TGF-β1 expression in perilesional skin, the current research exhibited its expression in 73.3% of perilesional skin biopsies (in the epidermis), and its expression was significantly higher than that in normal skin. Similar to these results, Owczarczyk-Saczonek et al.[41] reported the high expression of TGF-β in perilesional psoriatic patients. This can be explained by the pathological changes detected in perilesional skin, which are also caused by psoriasis.[25]

Regarding the expression of TGF-β1 in dermal inflammatory cells, the expression was statistically significant. Abdou et al.[42] reported similar results and stated that this may be due to the role of TGF-β1 in inflammation.

Regarding the histopathological data of lesional skin, the present study reported a statistically significant relationship between TGF-β1 expression and hyperkeratosis and parakeratosis. Similarly, Sellheyer et al.[43] reported that the skin of mice expressing different TGF-β1 constructs revealed hyperkeratosis. Liarte et al.[11] reported that on intensified TGF-β expression, reactive hyperkeratosis and parakeratosis develop.

Moreover, TGF-β1 and FUT8 levels in the lesional and perilesional skin of the studied psoriatic cases were significantly positively correlated. The association between the TGF-β receptor complex pathway and FUTs was aberrantly expressed in non-small-cell lung cancer, and human peroxisome assembly factor 2 inhibited TGF-β signaling and cell migration.[44]

The biological processes mediated by TGF-β receptors may be significantly impacted by core fucosylation. FUT8 showed higher regulation throughout TGF-β induced epithelial-mesenchymal transition (EMT) in breast cancer cells, and the overexpression of FUT8 changed the core-fucosylated N-glycans on targets on the surface of the cell, namely, TGF-β RI and RII complexes trying to advance binding of ligand and stimulating downstream of signaling.[45]

These processes facilitate the transformation of epithelial phenotypes into mesenchymal ones with enhanced migratory and invasive capability in breast cancer cells, which may result in distal lung metastasis. The transcriptional level of FUT8 may be partially regulated by elevated mRNA levels of FUT8 in TGF-β-induced EMT.[45] Therefore, the collaboration between TGF-β1 and FUT8 could play a role in psoriasis.

Study limitations

This study had a small sample size and was conducted at a single center; thus, further multicentric longitudinal studies are warranted for further assessment of the role of FUT8 and TGF-β1 in psoriasis.

Conclusion

Increased levels of FUT8 and TGF-β1 in psoriasis are directly related to disease severity and to each other, indicating their roles in the development and advancement of psoriasis. Additionally, implementing targeted therapy for FUT8 and TGF-β1 may prove beneficial in the management of psoriasis. The key strengths of this work lie in its uniqueness as one of the few studies that examined the expression of FUT8 and TGF-β1 in psoriasis and compared their levels in lesional and perilesional skin with normal skin.

Ethics

Ethics Committee Approval: This study was approved by the Menoufia University Faculty of Medicine Research Ethics Committee (approval number and date: 8/2021 DERMA 13).

Informed Consent: Every participant signed a written informed consent form before initiating the research work.

Authorship Contributions

Concept: W.A.S., A.H.M., A.S.H., Design: W.A.S., A.H.M., A.S.H., Data Collection or Processing: W.A.S., A.H.M., Y.I.E., Analysis or Interpretation: W.A.S., A.S.H., Literature Search: W.A.S., A.H.M., Y.I.E., A.S.H., Writing: W.A.S., A.H.M., Y.I.E., A.S.H.

Conflict of Interest: The authors declared that they have no conflict of interest.

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