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Expression Patterns of Key JAK/STAT Signaling Proteins in Disorders Affecting the Oral Mucosa

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Abstract

The JAK/STAT signaling cascade comprises intracellular proteins through which numerous cytokines and growth factors regulate genes governing cell activation, proliferation, and differentiation. Although disruptions in this pathway have been reported in many inflammatory and autoimmune disorders, studies specifically addressing autoimmune bullous diseases remain scarce. This research aimed to investigate the expression levels of JAK3, STAT2, STAT4, and STAT6 in epithelial lesions from patients with pemphigus vulgaris (PV), bullous pemphigoid (BP), oral lichen planus (LP), and chronic ulcerative stomatitis (CUS), compared with healthy controls. Expression patterns were assessed using immunohistochemistry and immunoblotting techniques. Our results demonstrated a marked upregulation of the selected JAK/STAT proteins in affected oral mucosa, supporting their involvement in disease pathogenesis. Notably, STAT2 expression was not elevated in PV and BP, whereas STAT4 remained unchanged in CUS and LP. These expression differences suggest potential targets for therapeutic intervention.

Keywords: CUS, Lichen planus, Pemphigoid, Pemphigus, JAK/STAT

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Introduction

Janus kinases (JAKs) and signal transducers and activators of transcription (STATs) are key components of a cellular signaling system in animal tissues. This pathway enables various cytokines and growth factors to control genes that regulate cell activation, growth, and differentiation. It is particularly crucial in monocytes and lymphocytes, integrating signals from multiple cytokines and their receptors [1]. Recent evidence points to an important role of JAKs in autoimmune skin conditions, where mediators such as TNF-α, IL-6, IL-4, IFNs, and IL-17 influence Th2 cell differentiation [1, 2].

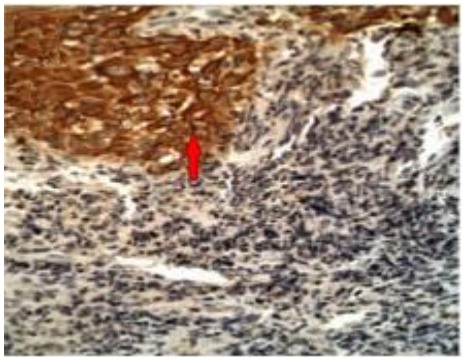
Despite this, little is known about the pathway's role in certain autoimmune mucosal disorders. PV, BP, LP, and CUS exhibit similar clinical manifestations, including blisters and erosions on the skin and oral mucosa, with oral lesions often appearing first. These overlapping features make diagnosis and management challenging. This study therefore aimed to quantify JAK3, STAT2, STAT4, and STAT6 expression in oral lesions from patients and controls, to identify proteins that could serve as disease biomarkers or future therapeutic targets.

Results and Discussion

Immunohistochemistry

In healthy oral mucosa, JAK3 and STAT4 were detected in several cell populations. Across patient samples, JAK3, STAT2, STAT4, and STAT6 were primarily localized to

the cytoplasm and cell membrane. STAT2 levels in PV ($p = 0.58$) and BP ($p = 0.38$) did not differ significantly from controls, while patients with CUS ($p < 0.04$) and LP ($p < 0.02$) exhibited significantly higher STAT2 expression **(Figure 1 and Table 1)**.



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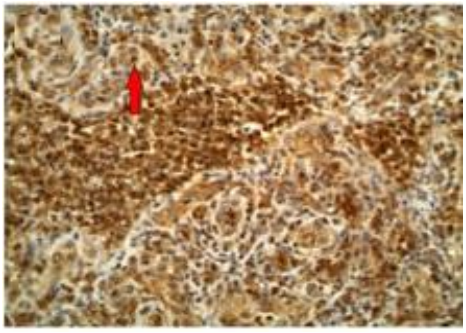

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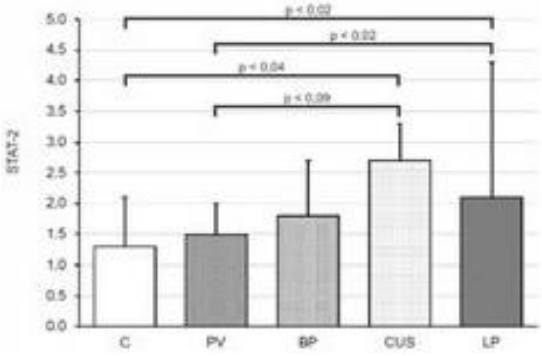

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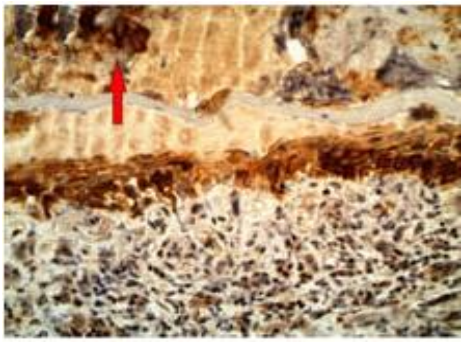

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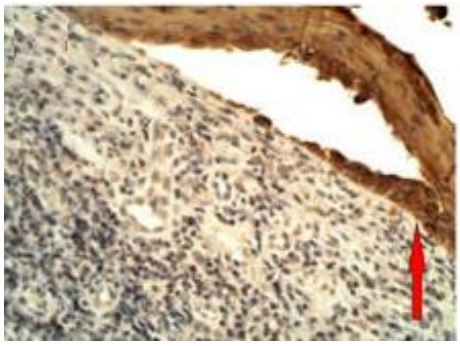

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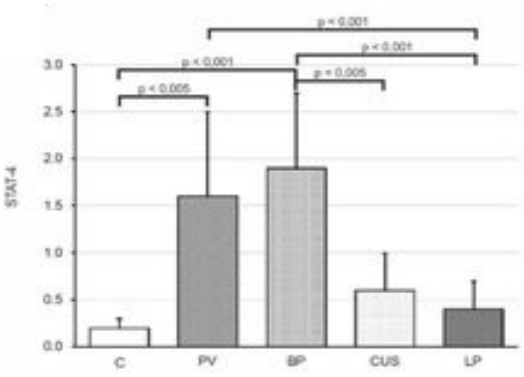

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Figure 1. (a) IHC image highlighting STAT2 positivity in epithelium and surrounding inflammatory cells in chronic ulcerative stomatitis (CUS), 400×. (b) IHC image displaying STAT2 in epithelial layers with inflammatory involvement in lichen planus (LP), 400×. (c) Graph showing differences in STAT2 levels among pemphigus vulgaris (PV), bullous pemphigoid (BP), CUS, LP, and normal mucosa (control group). (d) IHC image of STAT4 staining in epithelium and infiltrate in PV, 400×. (e) IHC image revealing STAT4 in epithelial cells and inflammation in BP, 200×. (f) Graph illustrating variations in STAT4 levels for PV, BP, CUS, LP, and control healthy mucosa.

Table 1. STAT2 expression across study groups. C—control group; BP—bullous pemphigoid; PV—pemphigus vulgaris; LP—lichen planus; CUS—chronic ulcerative stomatitis.

Comparison	Significance	p-value
C vs. PV	NS	0.58
C vs. BP	NS	0.38
C vs. CUS	*	<0.04
C vs. LP	*	<0.02
PV vs. BP	NS	0.48

PV vs. CUS	NS	<0.09
PV vs. LP	*	<0.02
BP vs. LP	NS	0.23
BP vs. CUS	NS	0.13
CUS vs. LP	NS	0.05

*NS = not significant; * = statistically significant

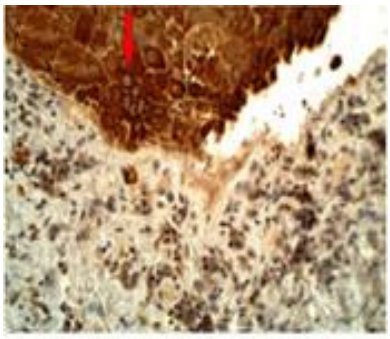
STAT4 protein levels were markedly elevated in patients with pemphigus vulgaris (PV; p = 0.006) and bullous pemphigoid (BP; p = 0.001) relative to the control group (C). In contrast, no significant differences in STAT4 expression were observed in chronic ulcerative stomatitis (CUS; p > 0.06) or lichen planus (p = 0.02) patients when compared to controls **(Figure 1 and Table 2)**.

Table 2. STAT4 expression across study groups. C—control group; BP—bullous pemphigoid; PV—pemphigus vulgaris; LP—lichen planus; CUS—chronic ulcerative stomatitis.

Comparison	Significance	p-value
C vs. PV	*	<0.006
C vs. BP	*	<0.001
C vs. CUS	NS	0.06
C vs. LP	NS	0.2
PV vs. BP	NS	0.45
PV vs. CUS	*	<0.05
PV vs. LP	*	<0.001
BP vs. LP	*	<0.001
BP vs. CUS	*	<0.005
CUS vs. LP	NS	0.18

*NS = not significant; * = statistically significant

Compared to the control group (C), STAT6 protein levels were significantly elevated in PV (p = 0.04), BP (p = 0.02), and LP (p = 0.05) patients, whereas CUS patients did not show a statistically significant change in STAT6 expression (p < 0.49) **(Figure 2 and Table 3)**.



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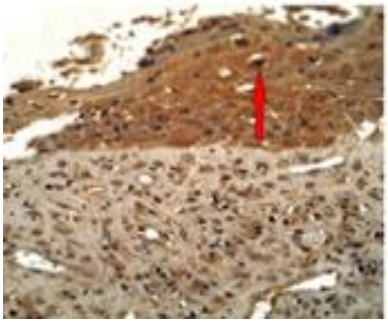

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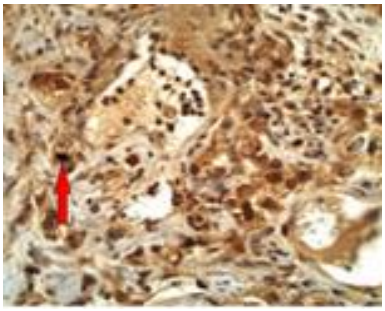

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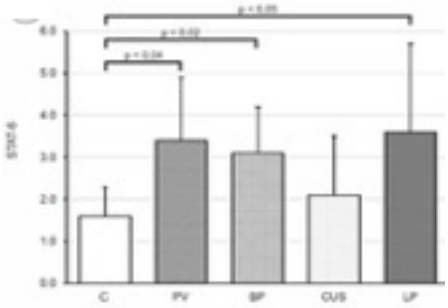

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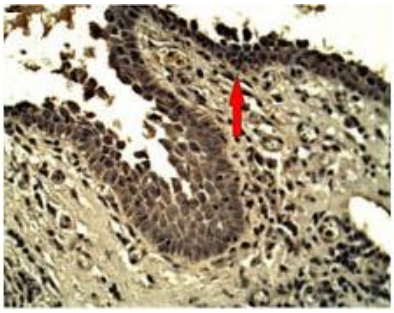
Figure 2. (a) Image from IHC revealing STAT6 presence in the epithelium and nearby inflammatory cells in pemphigus vulgaris (PV), viewed at 400×. (b) IHC image depicting STAT6 localization in epithelial tissue with inflammation in bullous pemphigoid (BP), 400×. (c) IHC image showing STAT6 in epithelium and inflammatory areas in lichen planus (LP), 400×. (d) Graph presenting differences in STAT6 amounts between PV, BP, CUS, LP, and healthy control mucosa.

Table 3. STAT6 expression across study groups. C—control group; BP—bullous pemphigoid; PV—pemphigus vulgaris; LP—lichen planus; CUS—chronic ulcerative stomatitis.

Comparison	Significance	p-value
C vs. PV	*	<0.04
C vs. BP	*	<0.02
C vs. CUS	NS	0.49
C vs. LP	*	<0.05
PV vs. BP	NS	0.62
PV vs. CUS	NS	0.14
PV vs. LP	NS	0.78
BP vs. LP	NS	0.45
BP vs. CUS	NS	0.14
CUS vs. LP	NS	0.13

*NS = not significant; * = statistically significant

Compared with the control group (C), patients with PV, BP, LP, and CUS exhibited significantly increased JAK3 protein expression, with p-values of <0.02, <0.007, <0.04, and <0.03, respectively **(Figure 3 and Table 4)**.



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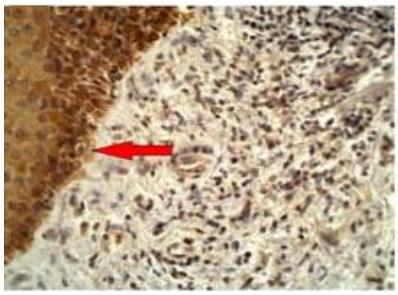

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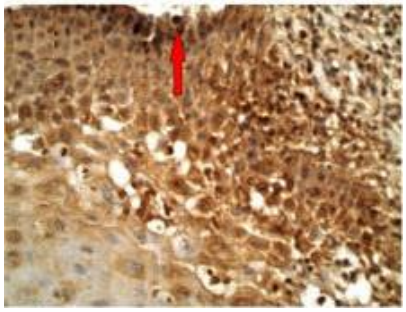

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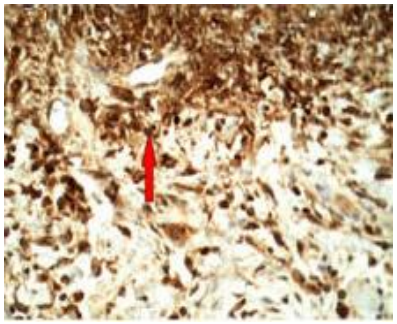

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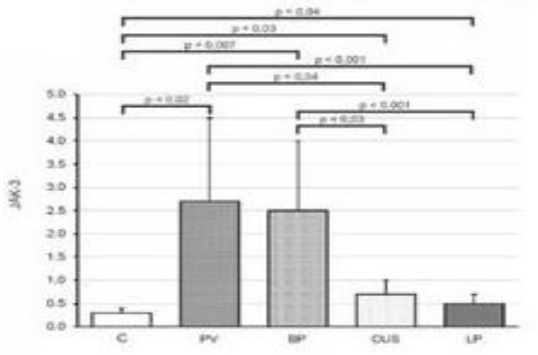

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Figure 3. (a) JAK3 localization within epithelial cells and surrounding inflammatory cells in PV, shown at 200× magnification. (b) JAK3 distribution in BP epithelial tissue with inflammatory infiltration, 400× magnification. (c) Expression of JAK3 in CUS lesions, highlighting epithelial and inflammatory cell staining, 400× magnification. (d) JAK3 detection in LP-affected epithelial tissue and infiltrating immune cells, 400× magnification. (e) Overview comparing JAK3 expression levels among PV, BP, CUS, LP, and normal mucosa (c).

Table 4. JAK3 protein expression in study groups. C—control group; BP—bullous pemphigoid; PV—pemphigus vulgaris; LP—lichen planus; CUS—chronic ulcerative stomatitis.

Comparison	Significance	p-value
C vs. PV	*	<0.02
C vs. BP	*	<0.007
C vs. CUS	*	<0.03
C vs. LP	*	<0.04
PV vs. BP	NS	0.7
PV vs. CUS	*	<0.04
PV vs. LP	*	<0.001
BP vs. LP	*	<0.001
BP vs. CUS	*	<0.03
CUS vs. LP	NS	0.05

*NS = not significant; * = statistically significant

Immunoblotting

Western blot evaluation validated the immunohistochemical observations for proteins involved in the JAK/STAT signaling cascade, revealing a consistently increased JAK3 band intensity in all pathological groups—PV (133.48 ± 0.84; $p < 0.05$), BP (132.21 ± 0.96; $p < 0.05$), CUS (134 ± 1.03; $p < 0.05$), and LP (132 ± 0.89; $p < 0.05$)—relative to the control samples (130.42 ± 1.65; $p < 0.05$), as shown in **Figure 4**.

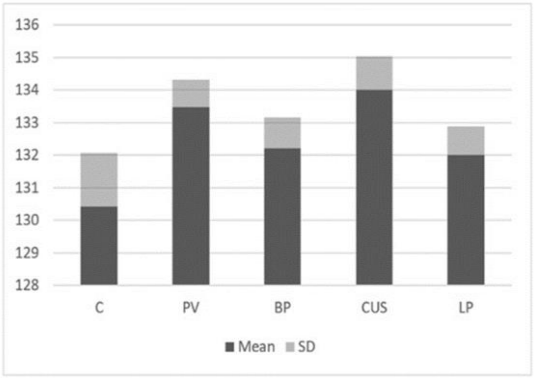

Figure 4. Immunoblotting analysis of JAK3 across study and control groups. Assessment of STAT2 protein levels demonstrated a marked increase in patients with CUS (145.83 ± 0.25) and LP (143.85 ± 3.09) relative to the control group (136.28 ± 2.84; $p < 0.05$), whereas STAT2 expression in PV and BP did not differ significantly from control values, as depicted in **Figure 5**.

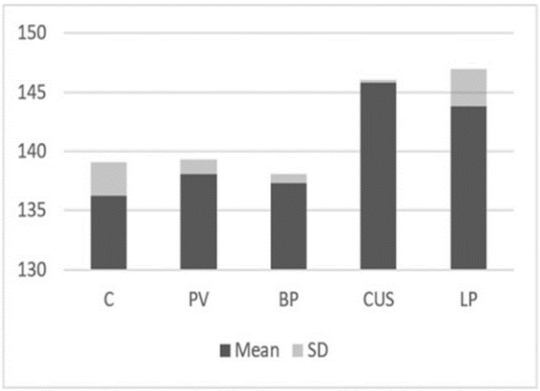

Figure 5. Western blot analysis of STAT2 expression in the patient groups and the control group. STAT4 protein levels, as measured by band intensity, were significantly elevated in patients with pemphigus vulgaris (PV; 138.39 ± 0.84) and bullous pemphigoid (BP; 141.2 ± 0.05) compared to the healthy control group (121.63 ± 1.75; $p < 0.05$). Additionally, statistically significant differences were observed in STAT4 expression between patients with chronic ulcerative stomatitis (CUS) and lichen planus (LP) **(Figure 6)**.

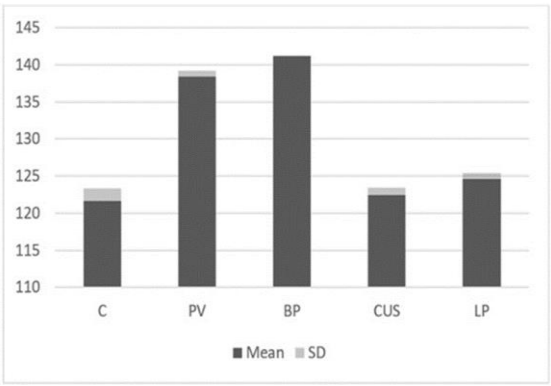

Figure 6. Western blot analysis of STAT4 expression in the patient groups and the control group. STAT6 protein expression was significantly elevated in patients with pemphigus vulgaris (PV; 131.37 ± 2.55), bullous pemphigoid (BP; 129.34 ± 1.37), and lichen planus (LP;

130.56 ± 1.76) compared to the healthy control group (123.48 ± 1.13; $p < 0.05$). In contrast, no statistically significant difference was observed in STAT6 expression between patients with chronic ulcerative stomatitis (CUS) and the control group **(Figure 7)**.

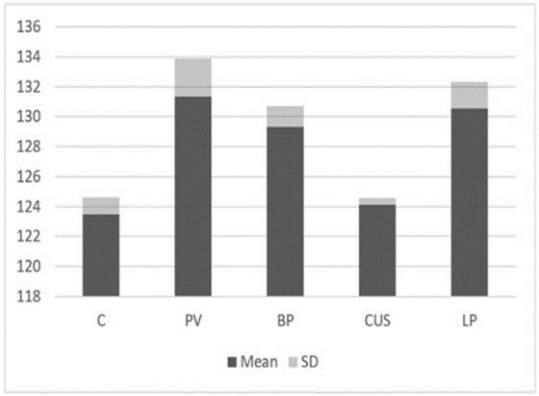

Figure 7. Immunoblot analysis of STAT6 expression in the study groups and the control group.

Nishio *et al*. [3] demonstrated that proteins belonging to the JAK/STAT signaling pathway are detectable in normal human epidermis, suggesting that maintaining immune homeostasis in healthy epidermal tissue requires a baseline level of JAK/STAT activity [3]. By extension, it can be assumed that this signaling cascade also contributes to the physiological function of epithelial cells lining the oral mucosa.

In line with this assumption, our analysis of normal oral mucosal samples revealed constitutive expression of JAK3, STAT2, STAT4, and STAT6, indicating that basal activation of the JAK/STAT pathway is a characteristic feature of healthy oral epithelium.

A growing body of evidence implicates cytokine-mediated JAK/STAT signaling in the development of inflammatory disorders [1, 2]. Many inflammatory skin and mucosal diseases are characterized by T-lymphocyte–driven inflammation accompanied by increased levels of proinflammatory cytokines. Consequently, it is plausible that dysregulation of this pathway contributes to the pathogenesis of disorders such as bullous pemphigoid (BP), pemphigus vulgaris (PV) [2], lichen planus (LP), and chronic ulcerative stomatitis (CUS).

In PV, numerous studies point toward a predominance of Th2-type immune responses, reflected by elevated serum concentrations of IL-4, IL-6, and IL-10 [4–6]. Cytokines including TNF-α, IL-6, IL-15, IL-10, and IL-12 are known to participate in blister formation in pemphigus [6, 7]. Reports on IFN-γ and IL-2 levels are inconsistent, with studies describing increased, decreased, or unchanged concentrations compared with healthy controls [5], underscoring the need for further clarification of the Th1/Th2 imbalance in PV pathogenesis.

Despite these uncertainties, the elevated JAK3 expression observed in our PV samples supports the involvement of this signaling pathway in disease development [5]. Given that JAK3 mediates IL-2 signaling, which is thought to contribute to lesion recurrence in PV [8], JAK3 may serve as a potential marker of disease activity. Moreover, increased serum IL-2 levels reported in PV patients further support the role of JAK/STAT signaling in the mechanisms underlying pemphigus lesions [6].

Previous investigations have consistently shown increased serum levels of TNF-α and IL-6 in PV [9], along with elevated IL-1 expression in lesional tissue [10]. Higher IL-8 concentrations have also been detected in both blister fluid and serum [11]. IL-12 has emerged as another key cytokine in PV etiopathogenesis, with Masjedi *et al*. [12] reporting significantly increased serum IL-12 levels in affected patients [12].

Consistent with these findings, our results demonstrated enhanced STAT4 expression in PV. STAT4 is primarily activated by IL-12, and signaling through STAT4 in response to IL-12, IFN-α, and IFN-β is crucial for Th1 differentiation and IFN-γ production [13].

Recent studies have also documented functional abnormalities in both T- and B-cell populations in PV. Th2-derived cytokines strongly stimulate B cells, promoting autoantibody production [14]. In agreement with this mechanism, we observed markedly increased STAT6 expression in PV lesions compared with controls, suggesting that STAT6 contributes to disease pathogenesis, most likely by facilitating Th2-dependent immune responses.

STAT6 activation is mediated by IL-4 and IL-13. Elevated serum IL-4 levels have been reported in PV patients [14], which may explain the increased STAT6 expression detected in our study.

Cytokines and other inflammatory mediators interacting with the JAK/STAT pathway are also critically involved in BP pathogenesis. The contribution of Th2 lymphocytes in BP is supported by increased levels of Th2-associated cytokines, including IL-4, IL-5, IL-6, and soluble IL-2 receptor [14–16]. Engman *et al*. [17] identified early infiltration of activated CD4+ T cells and eosinophils as a key event in blister formation [17].

Our observation of elevated JAK3 expression in BP lesions is consistent with these data. Examination of the cytokine milieu characteristic of BP reveals a close association with JAK3-dependent signaling, as JAK3 transduces signals from IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [18, 19]. This further substantiates the role of JAK3 in BP etiopathogenesis, particularly given the documented increase in IL-2 concentrations in BP patients [18, 19].

Additionally, we detected increased STAT4 expression in oral mucosal samples from BP patients. The involvement of STAT4 in BP may be linked to Th1-associated immune

responses and interactions with STAT2 signaling. Similar conclusions were reported by Juczynska *et al*. [2], who demonstrated elevated STAT4 expression in cutaneous BP lesions [2].

STAT6 is known to be activated by IL-4 and IL-13 [20]. Rico *et al*. [14] reported increased levels of IL-4, IL-5, and IL-13 in pemphigoid lesions, and our findings of enhanced STAT6 expression indirectly support a role for IL-4–mediated signaling in BP pathomechanisms.

The upregulation of STAT6 observed in BP biopsies may therefore reflect both the dominance of Th2-type immune responses and the characteristic eosinophil-associated cytokine profile that defines this disease [15].

In lichen planus (LP), a pronounced expansion of peripheral Th1 and Th17 lymphocyte populations has been documented compared with healthy subjects [21]. Th17 cells are well known as a major source of inflammatory mediators, including IL-17, IL-17F, IL-21, and IL-26, all of which contribute to sustained tissue inflammation. Cytokines driving both Th1- and Th17-oriented immune responses transmit their signals predominantly through the JAK/STAT signaling cascade [22].

The JAK3 expression pattern identified in our analysis aligns with earlier concepts proposing that JAK3 upregulation occurs mainly within T lymphocytes. These cells are key regulators of inflammatory reactions and play a central role in the etiopathogenesis of LP, as well as in the previously discussed conditions PV and BP.

LP is characterized by a cytotoxic immune process accompanied by the release of numerous inflammatory cytokines, including IL-1, IL-3, IL-6, IL-8, TNF-α, and IFN-γ. Infiltrating $CD8^+$ T lymphocytes within the skin and oral mucosa are primarily responsible for basal keratinocyte destruction, leading to damage of the basal epithelial layer [23, 24].

Our findings demonstrated a marked increase in STAT2 and STAT6 expression within LP lesions. STAT2 plays a critical role in IFN-α– and IFN-β–mediated signaling and is functionally interconnected with STAT1. In this pathway, IFN-α induces STAT1 activation through a STAT2-dependent mechanism, highlighting the coordinated activity of these transcription factors [25]. Given the spectrum of cytokines acting through STAT2- and STAT6-associated pathways, further investigations are needed to clarify the contribution of inflammatory mediators to LP lesion development.

In biopsies obtained from patients with chronic ulcerative stomatitis (CUS), elevated STAT2 and STAT6 expression was also observed. These results suggest that the molecular events leading to erosion formation in CUS may partially overlap with those described in LP. On this basis, involvement of IFN-α and IFN-β in CUS pathogenesis can be hypothesized, although supporting data are currently absent from the literature.

Interestingly, STAT6 expression levels in CUS were comparable to those detected in the control group, which may point toward a predominance of Th1-driven immune mechanisms in this disease entity [26]. Comprehensive immunological studies are therefore required to fully elucidate the pathways responsible for the initiation and progression of CUS lesions.

Materials and Methods

Patients

An initial cohort of 181 individuals treated at the Department of Periodontology and Oral Implantology and the Department of Dermatology and Venereology, Medical University of Lodz, was screened for participation. All patients were evaluated during the active stage of disease, characterized by the presence of erosive or bullous oral lesions at diagnosis. At the time of tissue sampling, none of the participants had received systemic or topical therapy. The study protocol (RNN/132/07/KB) was approved by the Local Ethical Committee of the Medical University of Lodz.

After applying inclusion criteria, the final study population comprised 112 patients with confirmed diagnoses: 28 with PV (mean age 54.4 years), 31 with BP (mean age 67.3 years), 38 with LP (mean age 52.8 years), and fifteen with CUS (mean age 64.6 years). The control group consisted of twenty five healthy volunteers with a mean age of 47.3 years **(Table 5)**.

Table 5. Demographic characteristics and immunohistopathologic findings (increased protein expression compared with the control group). PV—pemphigus vulgaris; BP—bullous pemphigoid; LP—lichen planus; CUS—chronic ulcerative stomatitis; C—control group.

Disease Group	Age (Years)	No. of Patients	Immunopathologic Findings	JAK3	STAT6	STAT4	STAT2
PV	54.4 (45–64)	28	28/28 anti-Dsg3 (1:40–1:320)	+	+	+	-
BP	67.3 (46–89)	31	23/31 anti-BMZ (1:80–1:160), 19/31 anti-NC16a	+	+	+	-
LP	64.6 (51–82)	38	Negative	+	+	-	+
CUS	47.3 (22–61)	15	SES ANA (1:40–1:640)	+	-	-	+
C	54.4 (45–64)	25	Negative	-	-	-	-

The diagnoses of pemphigus vulgaris (PV), bullous pemphigoid (BP), lichen planus (LP), and chronic ulcerative stomatitis (CUS) were established through a combination of patient medical history, clinical examination, and immunofluorescence analyses. In PV patients, direct immunofluorescence (DIF; Euroimmun, Lübeck, Germany) consistently revealed IgG in a network-like pattern along the epithelial structures. Indirect immunofluorescence (IIF; Euroimmun, Lübeck, Germany) on monkey esophagus substrate was positive in all patients, with 12 exhibiting titers of 1:40 and the remaining patients showing titers of 1:320. Additionally, circulating anti-Dsg3 antibodies were detected in every PV patient using the DSG-3 ELISA test (Euroimmun, Lübeck, Germany).

For BP, DIF demonstrated linear deposits of IgG and/or complement component C3 along the basement membrane zone (BMZ) in all cases. The salt-split technique confirmed epidermal binding in artificial blisters. IIF on monkey esophagus substrate revealed circulating IgG antibodies against the BMZ in 23 out of 31 patients, with titers ranging from 1:80 to 1:160, and 19 patients displayed detectable anti-BP180 NC16a autoantibodies (Euroimmun, Lübeck, Germany).

In CUS patients, IIF confirmed the presence of SES-ANA antibodies, with titers between 1:40 and 1:640 (Euroimmun, Lübeck, Germany).

Methods

Protein expression in lesional epithelium was assessed using immunohistochemistry and Western blotting.

Immunohistochemistry

Tissue sections embedded in paraffin were placed on Superfrost slides, deparaffinized, and subjected to heat-induced antigen retrieval using TRS solution (Dako, Glostrup, Denmark) followed by rinsing in distilled water. Endogenous peroxidase was quenched, and sections were incubated with primary antibodies: rabbit polyclonal anti-STAT2 and anti-STAT6, and mouse monoclonal anti-STAT4 and anti-JAK3 (Santa Cruz Biotechnology, Dallas, TX, USA). Immunostaining was visualized with the EnVision-HRP kit (Dako, Carpinteria, CA, USA), followed by hematoxylin counterstaining. Negative controls were included for all antibodies. Activated STAT2, STAT4, and STAT6 typically localize to both cytoplasm and nucleus.

Semiquantitative evaluation

Staining intensity for JAK3, STAT2, STAT4, and STAT6 was evaluated in 5–7 high-power fields per sample by two independent observers. Immunopositive cells were quantified as follows: 0–10% = 0, 10–30% = 1, 30–50% = 2, 50–70% = 3, 70–100% = 4. Staining intensity was classified as 0 = negative, 1 = mild, 2 = moderate, and 3 = strong.

Western blot analysis

Total protein was extracted from frozen tissue samples of PV, BP, LP, and CUS patients, as well as healthy controls, using RIPA buffer supplemented with protease inhibitors (Sigma-Aldrich, St. Louis, MO, USA). Lysates were centrifuged to remove debris, and protein concentrations were determined using the BCA Protein Assay Kit (Pierce, Thermo Scientific, Waltham, MA, USA). Membranes were blocked with non-fat milk in TBST and incubated with mouse primary antibodies (Santa Cruz Biotechnology, Dallas, TX, USA) followed by goat anti-mouse IgG secondary antibodies conjugated to alkaline phosphatase. Bands were visualized using BCIP/NBT substrate (Merck Millipore, Darmstadt, Germany) and analyzed densitometrically with ImageJ 1.34s software (NIH, Bethesda, MD, USA). Results are expressed as mean ± SD.

Statistical analysis

Data were expressed as mean ± SEM. Statistical tests were performed using Statistica v10.0 (StatSoft, Tulsa, OK, USA). Data distribution and variance homogeneity were checked using Levene's test. Group comparisons were performed using ANOVA for Western blot results, unpaired Student's t-test for immunohistochemistry, or Mann–Whitney U test when appropriate. Statistical significance was defined at $p < 0.05$.

Conclusion

Our results suggest that imbalances between Th1 and Th2 lymphocyte subsets contribute significantly to the pathogenesis of PV, BP, LP, and CUS. JAK3 expression was consistently elevated in all lesion biopsies compared with controls, with the highest levels observed in PV and BP. This indicates that JAK3 could serve as a potential biomarker and a target for further research into the pathogenesis of these diseases.

Although studies on lymphocyte subset involvement in CUS remain limited, the increased JAK3 expression observed suggests that Th1/Th2 dysregulation may also contribute to its development. Differential patterns of STAT protein expression were also observed: STAT2 was not elevated in PV and BP, while STAT4 remained unchanged in LP and CUS, suggesting disease-specific pathogenic mechanisms. These findings indicate that JAK/STAT pathway components could serve as markers for specific disorders and inform targeted therapeutic strategies.

Overall, the JAK/STAT signaling pathway represents a promising area of investigation in dermatology. Existing

evidence links it to inflammatory dermatoses, and the development of JAK inhibitors offers a potential avenue for treatment, particularly in autoimmune conditions where conventional therapies are insufficient or associated with complications.

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Conflict of interest: None

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Ethics statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Medical University of Lodz (RNN/42/13/KB 12.03.2013) for studies involving humans.
Informed consent was obtained from all subjects involved in the study.

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