Original Article

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Dynamic transition of pSTAT3 expression demonstrates the highest level in severe oral epithelial dysplasia before downregulation in invasive carcinoma

Rachanis Chokesirikulchai[1], Jintana Pankam[2], Puangwan Lapthanasupkul[3], **Siribang-on Piboonniyom Khovidhunkit[1]**

[1] *Department of Advanced General Dentistry, Faculty of Dentistry, Mahidol University, Bangkok, 10400, Thailand*
[2] *Faculty of Dentistry, Mahidol University, Bangkok, 10400, Thailand*
[3] *Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Mahidol University, Bangkok, 10400, Thailand*

This study aimed to preliminarily evaluate the expression of phosphorylated signal transducer and activator of transcription 3 (pSTAT3) in oral epithelial dysplasia (OED) and oral squamous cell carcinoma (OSCC) in comparison with normal oral mucosa (NOM). Additionally, its potential involvement in the sequential process of oral carcinogenesis was investigated. This study included 75 formalin-fixed, paraffin-embedded tissue specimens, comprising 15 cases each of NOM, mild OED, moderate OED, severe OED, and OSCC. Immunohistochemical analysis was performed to evaluate protein expression. The proportion of positive cells and the staining intensity were semi-quantitatively assessed and recorded as an immunoreactive score (IRS). Comparisons of IRS were conducted among the NOM group, the various grades of OED, and the OSCC group using appropriate statistical analyses. pSTAT3 was found predominantly in the nuclei of epithelial cells, with mild cytoplasmic staining observed to a lesser extent. Immunostaining demonstrated a progressive expansion of positivity from the basal layers in NOM to the superficial epithelial layers in severe OED. Based on the IRS, pSTAT3 expression gradually increased from NOM through the OED groups and declined in the OSCC group. The highest IRS was observed in severe OED compared with NOM (p = 0.002). However, pSTAT3 levels significantly decreased in OSCC compared with severe OED (p = 0.007). pSTAT3 expression progressively increases from NOM to OED, with expansion from basal to full epithelial thickness as the severity of dysplasia increases. These results imply a role of pSTAT3 in early oral carcinogenesis.

Keywords: oral cancer, oral epithelial dysplasia, oral squamous cell carcinoma, pSTAT3

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Introduction

Oral cancer ranks as the sixth most common cancer worldwide, with a five-year survival rate of approximately 50%. Among these, oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies. Its high incidence, late-stage diagnosis, and poor prognosis make OSCC one of the major global health challenges [1, 2]. OSCC often develops from precursor lesions such as oral epithelial dysplasia (OED), which has a risk of malignant transformation [3]. Clinically, both OED and OSCC may present as non-healing ulcers or exophytic growths, which are often asymptomatic in early stages, leading to delayed diagnosis [4]. In spite of advances in surgical and additional therapies, treatment of OSCC still frequently impacts the patient's quality of life,

Corresponding author: Siribang-on Piboonniyom Khovidhunkit
Department of Advanced General Dentistry, Faculty of Dentistry, Mahidol University, 6 Yothi Rd. Ratchathewi, Bangkok, 10400 Thailand
Tel: +66-2200-7853, Fax: +66-2200-7852
E-mail address: siribangon.pib@mahidol.ac.th
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including loss of organ function, mastication, swallowing, and esthetics [5]. Therefore, early identification methods, such as immunohistochemistry, can be valuable diagnostic tools to assess the biological behavior of OED and OSCC, helping to predict malignant progression, optimize prognosis, and improve clinical outcomes.

A recent molecular oncology study has highlighted the role of downstream signaling pathways in oral carcinogenesis [6]. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is mentioned due to its involvement in head and neck carcinogenesis [7]. The signal transducer and activator of transcription 3 (STAT3), in its phosphorylated form (pSTAT3), has been reported to be elevated in OSCC, leading to aberrant cell cycle progression, tumor growth, and survival of tumor cells. Resistance to standard therapies such as chemoradiation has also been associated with aberrant STAT3 signaling due to increasing production of immunosuppressive cytokines. So far, STAT3 has been identified as the most notable STAT family member that plays a role in the development of head and neck cancers [8, 9].

Immunohistochemistry enables in situ assessment of protein expression and activation, helping to clarify the biological behavior of oral lesions [10]. A better understanding of the expression patterns of pSTAT3 may help in identifying high-risk dysplastic lesions and prognostic markers for OSCC, as well as establish potential therapeutic targets for personalized therapies [11].

Since studies on pSTAT3 expression in oral potentially malignant disorders and oral cancer are limited [7, 9], the aim of this study is to investigate pSTAT3 expression in OED and OSCC compared with normal oral mucosa (NOM) using immunohistochemistry and to explore its possible role in the sequential process of oral carcinogenesis.

Materials and methods

Human ethics approval and sample selection

This study was approved by the Faculty of Dentistry/ Faculty of Pharmacy, Mahidol University, institutional review board (COA.No.MU-DT/PY-IRB 2025/066.2209). The ethical guidelines of the Declaration of Helsinki were followed in this study. A total of 60 formalin-fixed paraffin-embedded (FFPE) tissue samples, including 15 cases each of mild OED, moderate OED, severe OED, and OSCC, were retrieved from the archives of the Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Mahidol University, Bangkok, Thailand. The demographic data of participants were collected from the pathology forms sent with the specimens and medical records. Fifteen specimens of NOM were obtained from clinically normal gingival tissue adjacent to the third molar during impacted tooth removal. Only mucosal tissues showing normal epithelium on histopathological evaluation were included as controls. Since NOM samples were retrieved from anonymous participants, there is no demographic data for the samples in the NOM group.

Preparation of tissue sections for immunohistochemistry

All samples were FFPE tissue specimens. The Hematoxylin and Eosin (H&E) stained sections were reviewed by board-certified oral pathologists (P.L.) for the diagnosis of OED and OSCC. For each case, 3 µm thick paraffin sections were cut by a microtome, and the tissue sections were mounted on adhesive glass slides (Matsunami Glass Ind., Osaka, Japan).

Immunohistochemical procedure

In brief, tissue sections were heated in a hot air oven at 65°C for 30 minutes to enhance tissue adhesion and ensure proper attachment to the

slides prior to deparaffinization. The sections were then deparaffinized in xylene twice, followed by rehydration through a graded series of ethanol (100%, 95%, 80%, and 70%), and rinsed in 1X phosphate-buffered saline (PBS). Antigen retrieval was carried out using Tris(hydroxymethyl) aminomethane-ethylenediaminetetraacetic acid (Tris-EDTA) buffer pH 9.0, by heating for 12 minutes. Endogenous peroxidase activity was subsequently blocked with 3% hydrogen peroxide diluted in methanol. After washing with distilled water (dH_2O) and PBS, the tissue sections were outlined with a PAP pen, followed by incubation with the primary antibody overnight at 4°C in a humidified chamber. Phospho-STAT3 (Tyr705) antibody (#9131, Cell Signaling Technology®, Massachusetts, USA) was diluted 1:100 in antibody diluent (S0809, Dako, Santa Clara, USA). The sections were then incubated with the EnVision™ detection system (K5007, Dako, Glostrup, Denmark) for 30 minutes at room temperature. Immunoreactivity was visualized using the Liquid DAB+ Substrate Chromogen System (K5007, Dako, Glostrup, Denmark). The reaction was terminated by rinsing the slides in Phosphate Buffered Saline with Tween-20 (PBST) for 5 minutes followed by 5 minutes of tap water. The sections were counterstained with Mayer's hematoxylin (05-06002/L; Bio-Optica Milano Spa, Milano, Italy) and rinsed in tap water for 10 minutes. Subsequently, the slides were dehydrated through a gradient of ethanol concentrations (70%, 95%, and 100%) for 5 minutes each, cleared in xylene twice, and mounted with mounting medium (Bio-Optica Milano SpA, Milan, Italy). Tissue sections of the lymph node served as positive controls. Sections that had not been treated with the primary antibody served as negative controls.

Immunohistochemistry data analysis

The entire section was initially examined at low magnification to identify the epithelial region. A random starting point was determined, and three to five non-overlapping high-power fields (400x) were selected. Areas with necrosis, artifacts, or tissue folding were excluded. The immunohistochemical staining images were evaluated independently by two investigators (P.L. and R.C). pSTAT3 was predominantly observed in the nuclei of cells. Cytoplasmic staining was also detected with lesser extent. Both positive nuclei and cytoplasmic staining were considered positive. pSTAT3 expression was analyzed using a semi-quantitative scoring system as suggested by Kaemmerer *et al* [12]. The staining intensity was classified as negative (0), weak (1), moderate (2), or strong (3). The percentage of stained cells was scored as 0 (negative), 1 (<10% positive), 2 (10-50% positive), 3 (51-80% positive), or 4 (>80% positive). The immunoreactive score (IRS) was calculated by multiplying the staining intensity score by the percentage of positive cells.

Statistical analysis

This study used the PASW Statistics version 18.0.0 program (formerly SPSS Statistics) to perform the statistical analysis. Descriptive statistics were used to report demographic data, including gender, age, and lesions' location. Normality of the data was assessed using the Shapiro-Wilk test. However, as the data violated the assumption of normality, non-parametric statistics were used. Descriptive statistics are presented as medians and interquartile ranges (IQR: Q1, Q3). Differences in IRS between the five study groups were analyzed using the Kruskal-Wallis test. To find the significant results, post-hoc pairwise comparisons were performed using Dunn's test with *p*-values adjusted using the Bonferroni correction. Inter-rater reliability was performed by a weighted Kappa test ($\kappa = 0.861$).

Results

Participants Characteristics

The study analyzed specimens from 60 participants, including 15 cases each of mild OED, moderate OED, severe OED, and OSCC (Table 1). Approximately half of the participants were female (56.7%). The overall mean age of the participants was 65.02 ± 13.68 years, with the highest mean age observed in the severe OED group (69.40 ± 8.95 years). Regarding anatomical location, the buccal mucosa was the most frequent site in severe OED (66.67%), followed by mild OED (46.67%), whereas the tongue was the primary site for OSCC (46.67%). Among the OSCC cases, nine were well-differentiated, two were moderately differentiated, and one was poorly differentiated; histopathological grading data were unavailable for three cases.

Table 1 General characteristics of the specimens by tissue types

Characteristics	Oral epithelial dysplasia						OSCC (n = 15)	
	Mild (n = 15)		Moderate (n = 15)		Severe (n = 15)			
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Male	5	(33.33)	8	(53.33)	6	(40.00)	7	(46.67)
Female	10	(66.67)	7	(46.67)	9	(60.00)	8	(53.33)
Age range (years)								
≤ 40	-	(0.00)	1	(6.67)	-	(0.00)	2	(13.33)
41 - 50	3	(20.00)	-	(0.00)	-	(0.00)	1	(6.67)
51 - 60	7	(46.67)	5	(33.33)	3	(20.00)	2	(13.33)
61 - 70	2	(13.33)	4	(26.67)	6	(40.00)	3	(20.00)
71 - 80	2	(13.33)	4	(26.67)	5	(33.33)	4	(26.67)
≥ 81	1	(6.67)	1	(6.67)	1	(6.67)	3	(20.00)
Range	49 - 92		36 - 85		54 - 88		21 - 90	
Mean ± SD	61.40 ± 12.29		65.20 ± 12.62		69.40 ± 8.95		64.07 ± 19.04	
Location								
Tongue	-	(0.00)	4	(26.67)	4	(26.67)	7	(46.67)
Buccal mucosa	7	(46.67)	2	(13.33)	10	(66.67)	1	(6.67)
Gingiva	4	(26.67)	5	(33.33)	-	(0.00)	5	(33.33)
Palate	3	(20.00)	3	(20.00)	-	(0.00)	1	(6.67)
Lip	1	(6.67)	-	(0.00)	1	(6.67)	1	(6.67)
Labial mucosa	-	(0.00)	1	(6.67)	-	(0.00)	-	(0.00)

Abbreviations: OSCC, oral squamous cell carcinoma; SD, standard deviation.

Note. Since NOM samples were retrieved from anonymous participants, there are no demographic data for the samples in the NOM group.

IRS for pSTAT3

In our study, all cases of NOM, OED, and OSCC showed positive staining for pSTAT3. The median IRS for pSTAT3 in NOM, OED, and OSCC are shown in Table 2. The IRS values were gradually increased according to the severity of OED and significantly dropped in OSCC. Post-hoc pairwise comparisons using Dunn's test with Bonferroni correction showed that NOM and severe OED differed significantly from one another (p = 0.002). The statistically significant difference of IRS was also retrieved between the severe OED and the OSCC group (p = 0.007).

Table 2 IRS for pSTAT3 in OED and OSCC

	n	Median	IQR [Q1, Q3]	p-value
NOM	15	1.98[a]	[1.17, 3.64]	0.001
Mild OED	15	3.20	[2.00, 4.84]	
Moderate OED	15	5.60	[1.92, 8.00]	
Severe OED	15	6.12[ab]	[4.68, 8.56]	
OSCC	15	2.04[b]	[0.94, 5.44]	

Abbreviations: IRS, immunoreactive score; NOM, normal oral mucosa; OED, oral epithelial dysplasia; OSCC, oral squamous cell carcinoma; IQR, interquartile range.
a indicates significant difference at p =0.002; b indicates significant difference at p =0.007 based on Dunn's post-hoc test with Bonferroni correction.

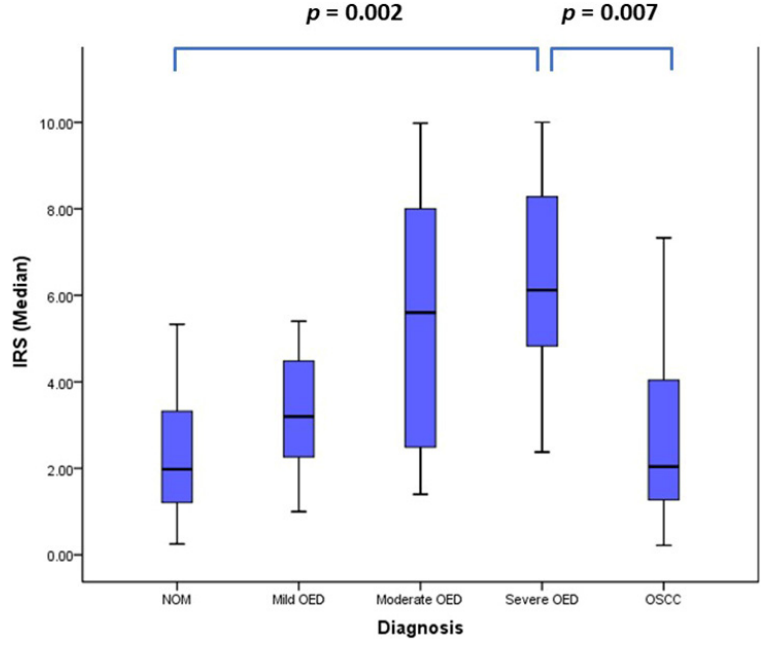

Figure 1 Comparison of IRS across diagnostic groups. Box plot represents the median, interquartile range, and range. Statistical analysis was performed using the Kruskal-Wallis test and Dunn's post hoc test.
Abbreviations: NOM, normal oral mucosa; OED, oral epithelial dysplasia; OSCC, oral squamous cell carcinoma

Pattern of pSTAT3 Immunostaining

In NOM, pSTAT3 positivity was restrictedly observed in the nuclei of basal and parabasal epithelial cell layers, with a greater number of positive cells and stronger staining intensity in mild OED compared with NOM. In moderate OED, increased nuclear staining was observed in the superficial epithelial layers. In severe OED, nuclear staining was even more prominent across all epithelial layers. Moreover, across all OED groups, a number of cells exhibited mild cytoplasmic staining.

In contrast, the OSCC specimens demonstrated less frequent nuclear staining with less intensity compared with the OED groups. Furthermore, cytoplasmic staining was rarely observed in OSCC.

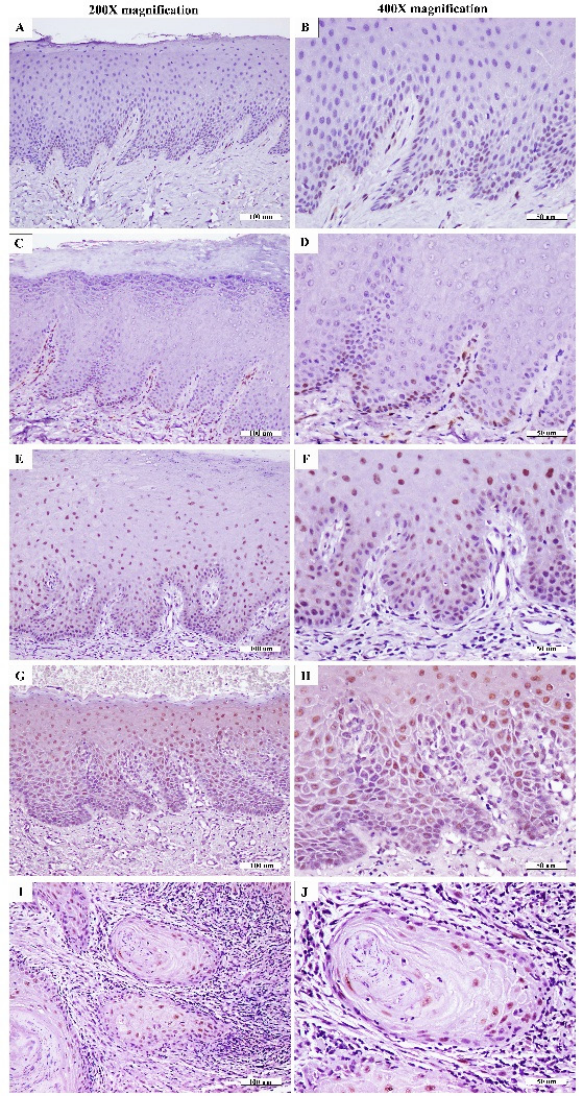

Figure 2 Representative images of immunostaining for pSTAT3. A (200 X) and B (400 X): In NOM, the nuclear staining is found in the basal and some of parabasal cell layers. C (200 X) and D (400 X): In mild OED, a larger number and stronger intensity of positive cells compared to NOM. E (200 X) and F (400 X): In moderate OED, positive immunostaining is observed from the basal to the superficial layer of cells. G (200 X) and H (400 X): In severe OED, the nuclear staining is prominent in all layers of epithelial cells. I (200 X) and J (400 X): In OSCC, less frequent nuclear staining with milder intensity was observed in the tumor cells compared with the OED groups.

Discussion

Our study demonstrates a clear gradient of pSTAT3 nuclear localization corresponding to the severity of OED. In normal oral mucosa, pSTAT3 expression was mostly confined to the basal and parabasal layers. However, as the tissue progressed from mild to severe OED, a distinctive upward extension of nuclear staining into the superficial layers was observed, particularly in severe dysplasia, where pSTAT3 exhibited prominent nuclear expression across all epithelial layers. These findings are consistent with the observations of Monteiro *et al*., who reported that while nuclear localization of pSTAT3 is present in the basal cell layer during early dysplastic stages, its distribution becomes increasingly widespread throughout the epithelium as the grade of dysplasia worsens [13]. This change in nuclear localization suggests that activation of STAT3 signaling may be an early molecular driver in the transition from NOM to OED. Our results also support the study by Fasanaro *et al*., which identified nuclear pSTAT3 as a critical marker of malignant potential [14]. They highlighted that nuclear accumulation, rather than cytoplasmic presence, is the key event that triggers transcription of oncogenic genes. Furthermore, a similar pattern was observed in actinic cheilitis reported by Cury *et al*. where nuclear pSTAT3 became increasingly noticeable as OED progressed [15]. Although mild cytoplasmic staining was observed in some cases, nuclear staining remains the most significant indicator of the role of the pSTAT3 pathway in lesion progression. For clinical application, although pSTAT3 is not currently a standalone diagnostic marker, its nuclear localization, which reflects active STAT3 signaling, may help support the grading of OED and provide adjunctive information in borderline cases.

While nuclear pSTAT3 is typically expected to increase with cancer progression, our study observed a decrease in nuclear pSTAT3 levels in OSCC compared to OED. This suggests that pSTAT3 may reach its peak activity during the early stages of malignant transformation. Wu *et al*. explained the activation of negative feedback loops, in which proteins such as Suppressor of Cytokine Signaling 3 (SOCS3) are induced by STAT3 to shut down its own signaling in head and neck cancer [16]. The observed decline in pSTAT3 expression in OSCC compared with severe OED may, in part, be explained by activation of negative feedback regulators such as SOCS3. STAT3 activation is known to transcriptionally induce SOCS3, which functions as a classical negative feedback inhibitor of the JAK/STAT pathway [17,18]. SOCS3 binds to JAK kinases and cytokine receptors, including gp130, thereby inhibiting further STAT3 phosphorylation and attenuating downstream signaling [18]. In the context of sustained STAT3 activation during the dysplastic stage, prolonged pathway stimulation may lead to compensatory upregulation of SOCS3, ultimately dampening STAT3 activity in established carcinoma. This regulatory feedback mechanism may contribute to the reduced pSTAT3 levels observed in OSCC and further supports the concept that STAT3 activation plays a stage-specific role in malignant transformation rather than serving as a continuous driver of tumor progression.

Furthermore, a decline in nuclear pSTAT3 levels may indicate a process called ‘pathway switch’ in late-stage oral cancer transformation. While pSTAT3 may be involved as an early driver of oral cancer, studies by Tan *et al*. demonstrated that advanced tumors rely on the PI3K/AKT pathway rather than the JAK/STAT pathway, allowing malignant transformation even when pSTAT3 levels decline [19].

According to the current study, the non-linear expression of pSTAT3, which we observed at the highest level in OED and a decline in OSCC, is also reported in other types of cancer. For instance, a study in breast cancer by Wang *et al*. revealed that high nuclear pSTAT3 expression was actually associated with smaller tumor size and lower histological grade, with levels frequently decreasing as the cancer became more invasive or metastatic [20]. A similar trend was reported in cervical cancer by Walch-Ruckheim *et al*., who observed that while nuclear pSTAT3 levels increased significantly from normal tissue to high-grade cervical intraepithelial neoplasia, these levels decreased in invasive squamous cell carcinoma lesions [21]. Furthermore, Hashimoto *et al*. found that STAT3 activation was significantly greater in low-grade than in high-grade tumors in colorectal cancer [22].

STAT3 may also act as a gatekeeper of the malignant transformation. During the dysplastic stage, particularly in severe OED, epithelial cells are exposed to strong proliferative and inflammatory stimuli. Activation of the JAK/STAT3 pathway at this stage promotes increased cellular proliferation, resistance to apoptosis, enhanced survival signaling, and maintenance of a pro-inflammatory microenvironment. Consequently, pSTAT3 may function as a critical facilitator of malignant transformation by enabling dysplastic cells to overcome normal growth control mechanisms. However, once sufficient genetic and epigenetic alterations accumulate and cells progress to invasive carcinoma, tumor cell survival and progression may no longer depend predominantly on STAT3 signaling. Therefore, STAT3 activation may be essential for the transitional phase of malignant transformation rather than for sustaining the fully established malignant phenotype.

Unlike Tyr705, Ser727 phosphorylation results in the localization of STAT3 predominantly in mitochondria, where it regulates the electron transport chain activity [23]. While nuclear Tyr705 phosphorylation is the conventional marker of STAT3 transcriptional activity, STAT3 can also undergo Ser727 phosphorylation and translocate to the mitochondria. In this non-canonical context, mitochondrial STAT3 has been shown to regulate components of the electron transport chain and oxidative phosphorylation, contributing to metabolic adaptation and plasticity in invasive tumors [24]. Accordingly, the observed reduction in nuclear pSTAT3 in OSCC may not necessarily indicate loss of STAT3 function but could instead reflect a shift in subcellular localization that supports the metabolic demands of an invasive phenotype.

Current strategies to inhibit STAT3 oncogenic activity primarily target upstream kinases. As described by Geiger *et al*., STAT3 in head and neck cancer is typically hyperactivated by growth factor receptors such as the epidermal growth factor receptor (EGFR) [8]. Consequently, agents like Cetuximab (an EGFR inhibitor) and Ruxolitinib (a JAK inhibitor) have been used to indirectly suppress downstream STAT3 signaling [25]. Qureshy *et al*. demonstrated that Ruxolitinib is effective in tumors with high level of pSTAT3 than in those with a lower level [26]. However, Picon and Guddati suggested that EGFR blockade alone may be insufficient, as tumors can develop resistance through alternative signaling pathways, highlighting the need for more precise therapies [27].

To overcome these resistance mechanisms, a recent study suggested a shift toward direct STAT3 inhibitors [28]. A major advancement is TTI-101, a specific inhibitor targeting the STAT3 SH2 domain, which was reported by Tsimberidou *et al*. in a Phase I clinical trial to be safe and to demonstrate preliminary antitumor activity [29]. The development of direct STAT3 inhibitors suggests that our findings may have potential

clinical implications. In cases of severe OED that can be adequately managed by surgical excision, the use of STAT3 inhibitors may not be necessary. However, in patients with widespread lesions or those with a high recurrence rate in whom repeated surgical intervention is not feasible, such inhibitors could be considered as a potential adjunctive approach. Since our study observed that nuclear pSTAT3 peaks during OED before potentially declining in carcinoma, this dysplastic phase represents the optimal therapeutic window. Targeting the pathway when pSTAT3 is at its highest intensity, during OED, may effectively block the "rate-limiting" step of tumorigenesis, which may potentially prevent the transition to invasive carcinoma [30].

Although with some clinical significance, we acknowledge the limitation of this study in that the number of samples was low, which may limit the generalizability of the findings. In addition, the use of gingival tissue from the removal of third molar may introduce a potential anatomical confound. Further studies with larger cohorts and matched locations of oral tissue are required to validate and extend the present results.

Conclusion

The nuclear localization of pSTAT3 is a dynamic, non-linear event in the progression of oral carcinogenesis. pSTAT3 expression peaks significantly during severe OED before declining in invasive OSCC. This expression pattern suggests that pSTAT3 functions as one of the early oncoproteins of malignant transformation. Moreover, the expression of STAT3 observed in the dysplastic phase may help identify a potential therapeutic window. Targeting pSTAT3 at its peak stage in dysplastic lesions represents an opportunity to effectively prevent the transformation from premalignant lesions to carcinoma.

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