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Original Article

Investigating GILZ and SGK-1 in Oral Lesions: Biomarker Potential in Malignant Transformation

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ABSTRACT

Glucocorticoid-induced leucine zipper (GILZ) and serum/glucocorticoid-regulated kinase-1 (SGK-1) are key proteins induced by glucocorticoids. Recent research has highlighted that cortisol can be locally produced in the oral mucosa, potentially influencing the tissue expression of GILZ and SGK-1. Both proteins have been implicated in the pathogenesis of various cancers; however, their expression patterns in potentially malignant oral lesions, such as epithelial dysplasia, and in malignant lesions like squamous cell carcinoma (SCC) remain largely unexplored. This study aimed to investigate the hypothesis that the expression profiles of GILZ, SGK-1, and the phosphorylated (active) form of SGK-1 (pSGK-1) differ between epithelial dysplasia and SCC. To test this, archived paraffin-embedded biopsy samples underwent immunohistochemical analysis to determine tissue localization and expression of the target proteins. Histopathological evaluation using hematoxylin and eosin staining classified the samples into mild-to-moderate dysplasia, severe dysplasia, or SCC, with benign keratosis serving as a control. Immunohistochemistry revealed that all tissue types expressed SGK-1 and pSGK-1. SGK-1 was predominantly cytoplasmic, whereas pSGK-1 localized mainly to the cell membrane. In contrast, GILZ showed primarily nuclear staining across all samples. Semi-quantitative analysis indicated that GILZ expression was elevated in epithelial dysplasia but decreased in SCC to levels comparable to benign keratosis. Conversely, SGK-1 and pSGK-1 expression were reduced in SCC compared with benign keratosis or dysplastic tissues. Overall, although the immunostaining patterns of GILZ, SGK-1, and pSGK-1 did not clearly distinguish epithelial dysplasia from SCC, the differences in subcellular localization and expression suggest that these proteins may have distinct functional roles in dysplastic versus malignant oral lesions compared with benign keratosis.

Keywords: Squamous cell carcinoma, Human, GILZ, Leukoplakia, SGK-1, Immunohistochemistry

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Introduction

Glucocorticoids are well-established for their immunosuppressive actions and are commonly applied in conditions marked by abnormal immune regulation [1]. In cancer, their effects vary considerably and are influenced by multiple factors, including the type of tumor, levels of glucocorticoid receptor expression, and characteristics of the tumor microenvironment [2]. Consequently, glucocorticoids can either support or hinder tumor development through a range of mechanisms, some of which are summarized in **Figure 1**. For example, they are used to trigger apoptosis in lymphohematopoietic cancers, whereas in solid tumors, they often serve as supportive therapy to reduce chemotherapy- and radiotherapy-induced side effects [2-4].

Emerging evidence, however, indicates that glucocorticoids may contribute to the progression of epithelial malignancies. Mechanisms include blocking apoptotic pathways, dampening immune surveillance,

boosting tumor cell metabolism, and promoting chemoresistance [4-6] **(Figure 1)**. Clinically, patients with oral squamous cell carcinoma (SCC) receiving glucocorticoids or other immunosuppressants exhibit more aggressive disease, with cervical lymph node involvement, extracapsular spread, and increased risk of distant metastasis [7].

Although the adrenal glands are the main source of circulating glucocorticoids, steroid metabolism also occurs locally in tissues such as the colon, skin, and oral mucosa [8-10]. Cortisol levels in tissues are regulated by 11-β-hydroxysteroid dehydrogenases (11-β-HSD1 and 11-β-HSD2), where 11-β-HSD1 activates cortisone to cortisol, and 11-β-HSD2 reverses this process. Key aspects of glucocorticoid regulation in oral tissues are summarized in **Figure 1** [10, 11]. Notably, reduced 11-β-HSD2 expression in oral SCC underscores the potential significance of local glucocorticoid synthesis in oral tissue pathologies [10, 11].

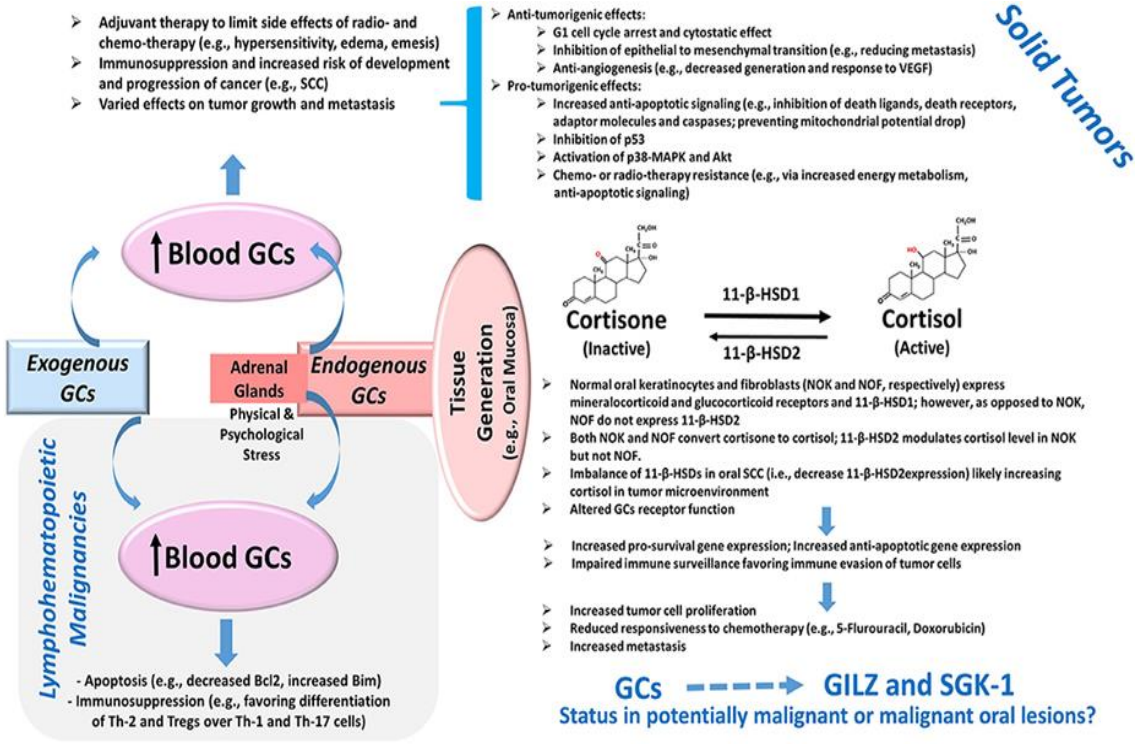


Figure 1. Glucocorticoids and Cancer.

Glucocorticoids (GCs), whether administered therapeutically or produced endogenously by the adrenal glands, elevate systemic GC levels and influence tumor biology. In lymphohematopoietic cancers, GCs exert beneficial effects by promoting apoptosis—partly through modulation of Bcl-2 family proteins—and by regulating immune responses via T-helper (Th) cells and regulatory T cells (Tregs). Conversely, in solid tumors, adjuvant GC therapy can have complex effects on tumor progression and metastasis, mediated through multiple mechanisms summarized in **Figure 1** [2-6]. Recent findings indicate that several tissues, including the oral mucosa, possess an intrinsic GC system. Cortisol is locally generated from cortisone by 11-β-hydroxysteroid dehydrogenase type 1 (11-β-HSD1) and can be converted back to cortisone by 11-β-HSD2. Reduced 11-β-HSD2 expression in oral squamous cell carcinoma (SCC) likely increases local cortisol availability, enhancing glucocorticoid receptor (GR)-mediated signaling. This may activate survival pathways, diminish immune surveillance, and contribute to larger tumor size, chemoresistance, and higher metastatic potential [10, 11]. Importantly, GCs strongly induce glucocorticoid-induced leucine zipper (GILZ) and serum/glucocorticoid-regulated kinase-1 (SGK-1), proteins implicated in tumorigenesis; however, their roles in potentially malignant or malignant oral lesions remain unexplored and are addressed in this study.

Most GC effects are mediated at the transcriptional level via the glucocorticoid receptor, with GILZ and SGK-1—encoded by TSC22d3 and SGK1, respectively—being prominent targets whose expression is markedly increased in response to GCs [1, 12, 13]. Both proteins perform diverse physiological functions, and their dysregulation has been linked to multiple diseases, including cancer [1, 2, 14]. Nevertheless, the expression of GILZ and SGK-

1 in premalignant or malignant oral lesions has not yet been determined.

Oral potentially malignant disorders (OPMDs) include lesions such as leukoplakia, presenting as white, non-scrapable patches of the oral mucosa, and erythroplakia, which manifests as solitary red lesions [15-18]. These lesions are clinically assessed and subsequently evaluated histologically to identify the presence and severity of epithelial dysplasia, carcinoma in situ, or invasive SCC. SCC is the most frequent oral malignancy and often develops from leukoplakia or erythroplakia [16-19]. Clinically, SCC may appear as white, red, mixed, non-healing ulcerative, or mass-like lesions, and histologically, poorly differentiated tumors are associated with rapid growth and early metastasis.

This study investigates the expression patterns of GILZ, SGK-1, and its phosphorylated, active form (pSGK-1) in human oral tissue specimens presenting as leukoplakia, ulcerative, or mass lesions, subsequently classified as epithelial dysplasia or SCC. The investigation is particularly significant given that the oral mucosa can generate cortisol locally [10, 11] **(Figure 1)**. Immunohistochemical profiling and semi-quantitative analysis of these proteins in dysplastic and malignant lesions were compared with benign keratosis tissues, which served as controls.

Materials and Methods

The research made use of stored, formalin-fixed paraffin-embedded tissue blocks from patients who had earlier been seen at the Oral and Maxillofacial Pathology Section within the Department of Oral Biology and Diagnostic Sciences at the Dental College of Georgia. All patient-identifying information had been stripped from these samples before they were accessed for the study. These individuals had originally come in because of visible oral abnormalities. After clinical examination, biopsies were taken and examined microscopically, resulting in the following diagnoses: mild or moderate dysplasia of the epithelium (N= 3), severe epithelial dysplasia (3 cases), and invasive squamous cell carcinoma (N=5). As a comparison group, five biopsies showing only benign keratinizing lesions without dysplasia were included.

The project was classified as exempt by the institutional review board. **Table 1** lists the age, sex, lesion location, and original clinical diagnosis for each participant.

Table 1. Patient and lesion characteristics for the cases included in this investigation (SCC = squamous cell carcinoma).

Category	Case ID	Age	Gender	Race	Location of Lesion	Initial Clinical Impression
Benign keratosis (controls)	C1	50	Male	African-American	Lateral tongue	Hyperkeratosis
	C2	64	Female	African-American	Posterior maxillary gingiva	Hyperkeratosis
	C3	75	Female	Unknown	Posterior mandibular gingiva	Hyperkeratosis
	C4	53	Male	Caucasian	Retromolar pad	Tobacco-related keratosis
	C5	57	Female	Caucasian	Mandibular gingiva	Hyperkeratosis (dysplasia not excluded)
Mild-to-moderate dysplasia	D1	51	Male	Caucasian	Floor of mouth	Lesion associated with smokeless tobacco use
	D2	70	Female	Caucasian	Lateral tongue	Leukoplakia
	D3	44	Female	Caucasian	Buccal mucosa	Leukoplakia
Severe dysplasia	D4	71	Female	Caucasian	Lateral tongue	Leukoplakia; suspicion of squamous cell carcinoma
	D5	63	Male	Caucasian	Floor of mouth	Dysplastic lesion; suspicion of SCC
	D6	66	Male	Caucasian	Ventral tongue	Leukoplakia; suspicion of SCC
Squamous cell carcinoma	S1	59	Female	Caucasian	Floor of mouth	Squamous cell carcinoma
	S2	64	Male	Caucasian	Floor of mouth	Squamous cell carcinoma
	S3	77	Female	Caucasian	Mandibular gingiva	Squamous cell carcinoma
	S4	51	Male	African-American	Lateral tongue	Squamous cell carcinoma
	S5	91	Female	Caucasian	Palate	Squamous cell carcinoma

Tissue blocks embedded in paraffin were sectioned to 5 µm thickness and mounted onto glass slides for analysis. Slides were deparaffinized using a Leica Auto-Stainer XL (Leica, Wetzlar, Germany), and antigen retrieval was conducted with a citric acid-based unmasking solution (Vector Laboratories, Burlingame, CA, USA). Endogenous peroxidase activity was blocked by incubating the sections in 0.3% hydrogen peroxide for 30 minutes at room temperature. Sections were then rinsed and incubated in a blocking solution consisting of 2.5% horse serum, 1% bovine serum albumin, and 0.5% Triton X-100 for at least one hour to reduce non-specific binding.

Primary antibodies were diluted in the same blocking solution (GILZ: 1:100; SGK-1: 1:100; pSGK-1: 1:50) and applied to the tissue sections overnight at room temperature. The antibodies included mouse monoclonal anti-GILZ (LS-B4313, LifeSpan Biosciences, Seattle, WA, USA), rabbit monoclonal anti-SGK-1 (ab32374, Abcam, Cambridge, UK), and rabbit polyclonal anti-pSGK-1 (Ser422, Invitrogen, Waltham, MA, USA; catalog 44-1264G). After primary incubation, slides were washed in phosphate-buffered saline and treated with horseradish peroxidase-conjugated secondary antibodies (Vector Laboratories, Burlingame, CA, USA) for one hour. Signal detection was carried out using 3,3′-diaminobenzidine (DAB) with the ImmPACT DAB Substrate Kit (Vector Laboratories), followed by hematoxylin counterstaining and coverslipping. Human mammary tissue served as a positive control for antibody validation. Histopathological evaluation was performed on adjacent sections stained with hematoxylin and eosin (H&E).

Quantitative analysis of immunohistochemical staining was performed using ImageJ Fiji software based on a previously described approach [20]. This method involves separating DAB staining from background through image deconvolution, measuring the mean gray intensity normalized to nuclear staining, and calculating the fraction of tissue area showing positive staining, providing a semi-quantitative assessment of protein expression.

Statistics

Semi-quantitative results are presented as mean ± standard error of the mean (SEM) for each experimental group. Statistical comparisons were performed using analysis of variance (ANOVA), followed by Newman–Keuls post hoc testing to determine significant differences between groups, with a threshold of $p < 0.05$.

Results and Discussion

Table 1 outlines the main characteristics of the participants whose biopsy samples were analyzed in this study. Representative tissue morphology, as assessed by hematoxylin and eosin (H&E) staining, is illustrated in **Figure 2a**. Immunohistochemical detection of the target proteins is shown in **Figures 2b and 3**, with each figure presenting 200× magnification images from three individual specimens per group. For a more detailed view of cellular and staining patterns, **Figure 4** provides 400× magnification images from a single biopsy categorized as severe epithelial dysplasia.

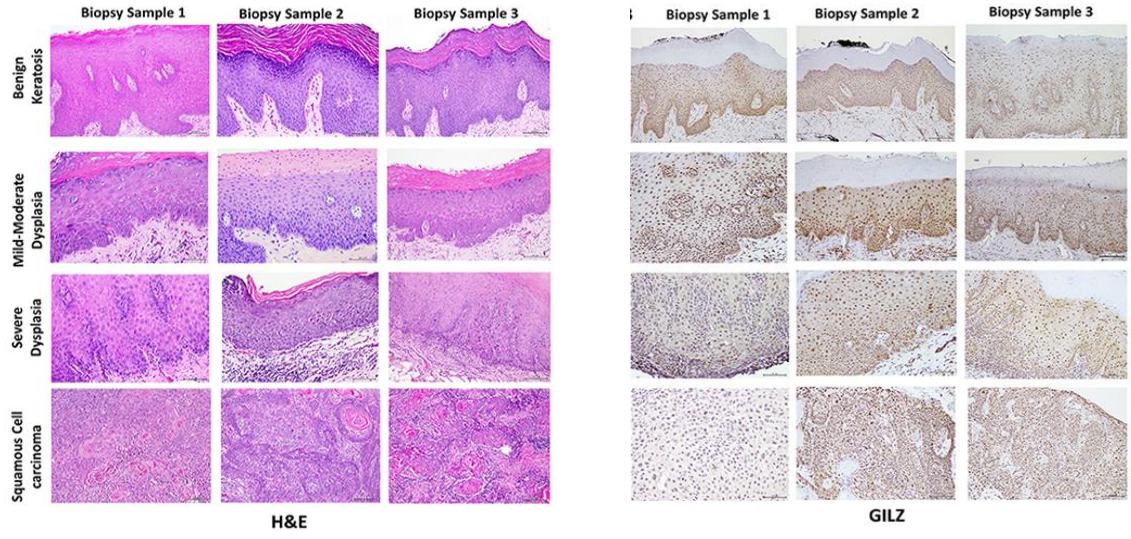
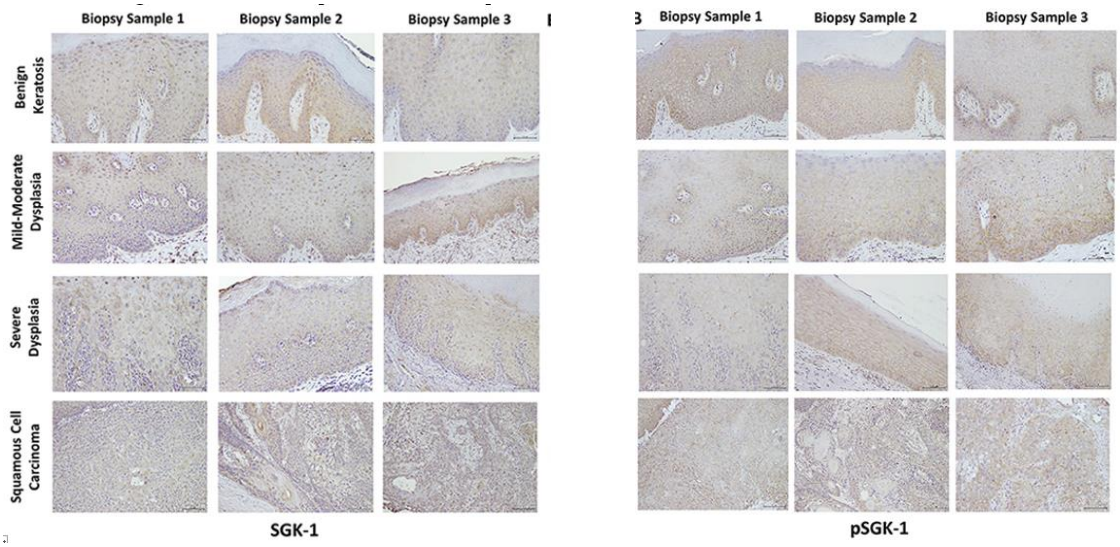


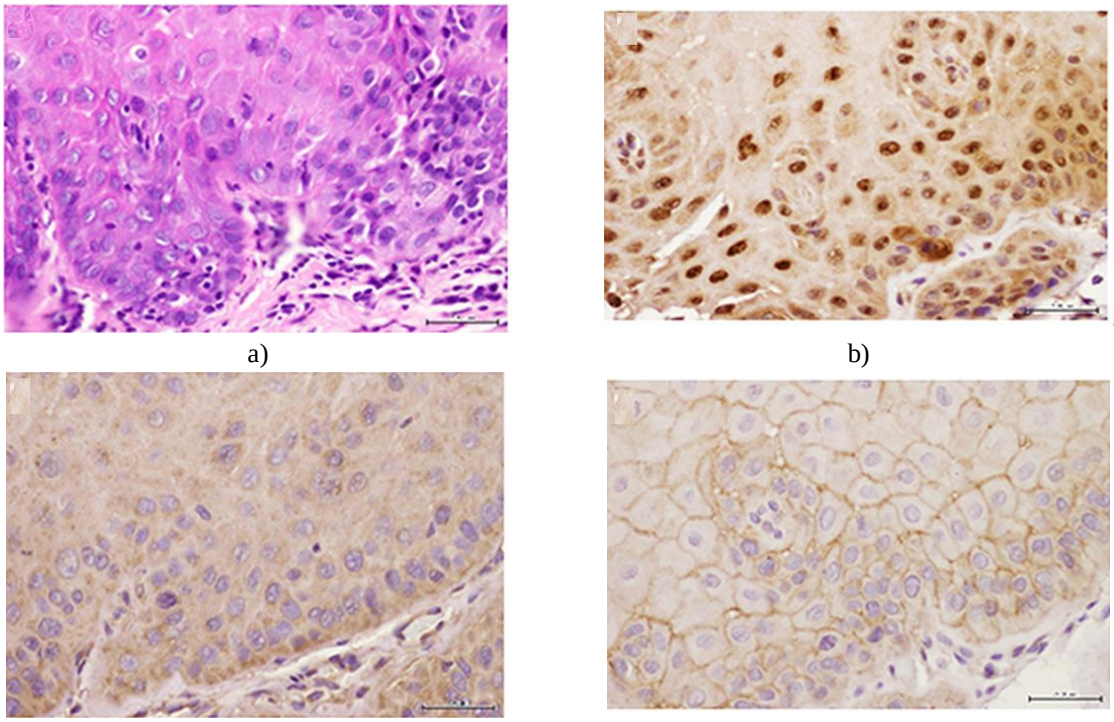
Figure 2. (a) Hematoxylin and eosin (H&E) staining of tissue sections from three subjects per group at 200× magnification. (b) Nuclear immunostaining for glucocorticoid-induced leucine zipper (GILZ) is shown across

the full epithelial thickness in benign keratosis, mild-to-moderate dysplasia, and severe dysplasia, whereas in malignant lesions, GILZ-positive nuclei are present throughout the tumor epithelium (200×).



a) b)

Figure 3. (a.b) Immunohistochemical detection of SGK-1 and phosphorylated SGK-1 (pSGK-1) in oral tissue specimens from three subjects per group at 200× magnification. (A) SGK-1 shows strong cytoplasmic staining and variable nuclear localization across the full epithelial thickness in benign keratosis, mild-to-moderate dysplasia, and severe dysplasia, although some individual cells lack detectable staining. Squamous cell carcinoma samples also exhibit prominent cytoplasmic staining with occasional nuclear positivity throughout the malignant epithelium. (b) pSGK-1 demonstrates intense cell membrane staining without nuclear involvement in benign keratosis, mild-to-moderate dysplasia, and severe dysplasia across the epithelial layers. In SCC specimens, pSGK-1 staining is consistently localized to the cell membrane of malignant epithelial cells (200×).



a) b)

c) d)

Figure 4. Representative images are shown for (a) GILZ, (b) hematoxylin-eosin, (c) pSGK-1 and (d) SGK-1, (d) for one case of severe epithelial dysplasia ×400.

Histopathology

Figure 2a presents the histological features of the tissue specimens across all study groups. In the non-dysplastic samples, subject 1 displayed hyperparakeratosis with acanthosis, whereas the other two showed hyperorthokeratosis. Among the mild-to-moderate dysplasia group, epithelial abnormalities were confined to the basal one-third to one-half of the epithelium, with hyperkeratosis present in all cases. Severe dysplasia samples exhibited more extensive changes, affecting at least three-quarters of the epithelial thickness, also accompanied by hyperkeratosis **(Figures 2a, 4a)**. In contrast, squamous cell carcinoma specimens revealed invasive keratinizing epithelium with features such as individual cell keratinization and keratin pearl formation. Histologic grading of these tumors ranged from well-differentiated to moderately differentiated carcinomas.

Glucocorticoid-induced leucine zipper immunohistochemistry

GILZ immunostaining was observed in the nuclei across the entire epithelial thickness in benign keratosis samples, as well as in tissues exhibiting mild-to-moderate and severe dysplasia **(Figures 2b, 4b)**. Similarly, squamous cell carcinoma specimens demonstrated strong nuclear GILZ positivity throughout the malignant epithelial cells **(Figure 2b)**.

Serum-glucocorticoid-regulated kinase-1 and psgk-1 immunohistochemistry

In benign keratosis, as well as in mild-to-moderate and severe dysplasia, SGK-1 immunostaining was predominantly cytoplasmic, with variable nuclear positivity observed throughout the full thickness of the epithelium **(Figures 3a, 4c)**. Some individual cells, however, did not display detectable staining. Squamous cell carcinoma specimens similarly exhibited strong cytoplasmic SGK-1 staining, accompanied by occasional nuclear positivity across the malignant epithelium **(Figure 3a)**.

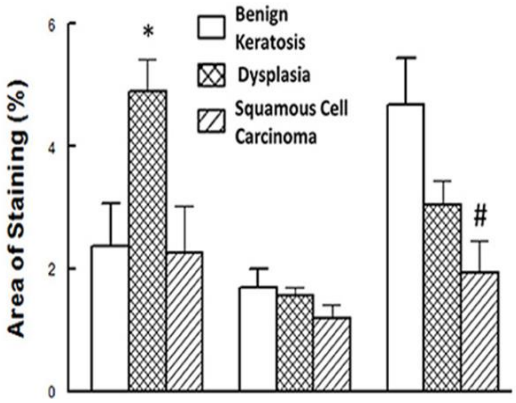
For pSGK-1, benign keratosis and dysplastic specimens showed intense staining confined to the cell membrane, without nuclear localization, throughout the epithelial layers **(Figures 3b, 4d)**. Likewise, squamous cell carcinoma samples demonstrated membrane-restricted pSGK-1 staining throughout the malignant epithelial cells **(Figure 3b)**.

Staining profile of stromal cells

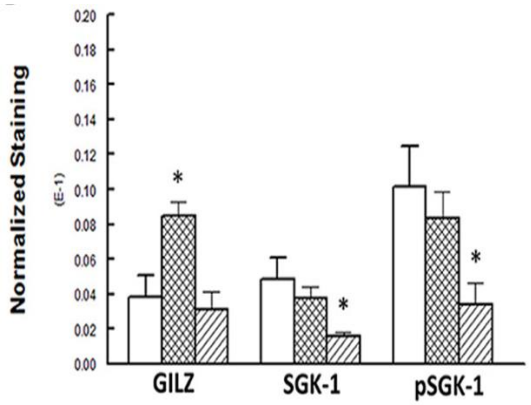
The stromal compartment of the tissue sections comprised fibroblasts, infiltrating white blood cells, vascular wall cells, and muscle cells. It should be noted that not all sections contained every stromal component, nor was staining consistently observed for each protein across all cell types in every category. Overall, analysis of the immunostaining patterns indicated that GILZ and SGK-1 did not differentiate among stromal elements, as most cell types exhibited detectable staining, although muscle cells showed weaker signal. For pSGK-1, positive staining was observed in white blood cells and vascular wall cells across all specimens, but muscle cells consistently lacked staining. Interestingly, fibroblasts in benign keratosis and dysplastic specimens—though fewer in number compared with carcinoma cases—also displayed pSGK-1 positivity.

Semi-quantitative analysis

Figure 5 summarizes the semi-quantitative evaluation of protein expression across the study groups. For this analysis, data from mild-to-moderate and severe dysplasia were combined. As shown in panel A, dysplastic tissues exhibited a significantly larger GILZ-positive area compared with benign keratosis and squamous cell carcinoma (SCC), while pSGK-1 staining was notably decreased in SCC relative to benign keratosis. Panel B displays DAB intensity normalized to nuclear count, following the method described previously [20]. This analysis confirmed that GILZ levels were significantly elevated in dysplastic lesions compared with both benign and malignant tissues. In contrast, SGK-1 and pSGK-1 levels were significantly lower in SCC specimens than in either benign keratosis or dysplastic samples.



a)



b)

Figure 5. (a) Displays the percentage of tissue area exhibiting positive staining for the target proteins. (b) Shows staining intensity normalized to the number of cell nuclei. Values represent mean ± standard error of the mean across cases (n = 5–6 samples per diagnostic category, as detailed in the Methods section). *p < 0.05 versus both other groups combined. #p < 0.05 versus the benign keratosis (control) group only.

This study provides insights into the subcellular localization and expression patterns of GILZ, SGK-1, and its phosphorylated form, pSGK-1, in potentially malignant and malignant oral lesions. GILZ was predominantly nuclear, whereas SGK-1 localized mainly to the cytoplasm and pSGK-1 to the cell membrane. Although these distinct subcellular localizations do not appear to distinguish between dysplastic and malignant oral lesions or their stromal components, semi-quantitative analysis suggests that GILZ expression is regulated differently from SGK-1 and pSGK-1 in these tissues. To the best of the authors' knowledge, this is the first study to document the localization and expression of these two major glucocorticoid-responsive proteins in oral tissue from human subjects with heterogeneous demographics, presenting with potentially malignant and malignant lesions. These findings gain added significance in light of evidence supporting a tissue-specific glucocorticoid system in the oral mucosa [10, 11] **(Figure 1)**.

Inflammation is a key driver in initiating malignant transformation and promoting tumor progression and metastasis. Inflammatory cells infiltrating tumors constitute an important component of the tumor microenvironment, influencing both tumor growth and aggressiveness. Importantly, pathways mediating inflammation, immune regulation, and tumor initiation often overlap [2]. For instance, NF-κB and AP-1 regulate genes involved in cancer cell proliferation and survival [21-23], and NF-κB can interfere with p53, thereby potentially promoting tumorigenesis [24]. Since GILZ inhibits NF-κB and AP-1 transcriptional activity, it may suppress tumor growth through downregulation of pro-inflammatory cytokines. However, GILZ-mediated immunosuppression could also facilitate tumor development, suggesting that, like glucocorticoids, GILZ may exert context- and cell type-dependent pro- or anti-tumor effects [2] **(Figure 1)**. For example, GILZ inhibits Ras-dependent signaling, contributing to dexamethasone-induced antiproliferative effects in activated T lymphocytes and antioncogenic activity in Ras-transformed NIH-3T3 cells [25]. Conversely, cytoplasmic GILZ expression in ovarian cancer—but not in normal ovarian epithelium or benign tumors—suggests a role in promoting proliferation, with in vitro studies showing that GILZ enhances Akt phosphorylation and activity [26]. In estrogen-responsive MCF-7 breast cancer cells, estrogen suppresses GILZ expression [27]. In dormant murine melanoma cells, GILZ signaling reactivates the cell cycle and tumor growth, whereas repression of GILZ induces cellular quiescence [28]. High GILZ levels are associated with reduced response to cyclopamine in lung cancer, a Hedgehog pathway inhibitor [29], although GILZ may also reduce invasiveness of lung epithelial cancer cells by inhibiting hypoxia-inducible factor-1α [30]. GILZ overexpression can enhance mitochondrial oxidative phosphorylation, promoting cell proliferation [31]. Moreover, drugs targeting MAPK pathways in thyroid cancer upregulate the long-GILZ (L-GILZ) isoform, which exhibits anti-proliferative and anti-oncogenic effects, in part by sequestering NF-κB in the cytoplasm [32]. In the present study, GILZ staining was consistently nuclear across all specimens, with dysplastic lesions showing elevated expression, which declined in squamous cell carcinoma. The mechanisms underlying this differential expression remain unclear, though they likely reflect the complex and context-dependent roles of GILZ in tumor biology [2].

SGK-1, a member of the serine-threonine kinase family, was first identified through screening for glucocorticoid-inducible transcripts in a rat mammary tumor cell line [13]. It operates downstream of PI3K and shares structural and functional similarities with Akt, including overlapping substrate specificity and pro-survival activity upon phosphorylation [33-35]. SGK-1 has been implicated in multiple human cancers, including breast, tongue, head and neck, ovarian, prostate, multiple myeloma, and non-small cell lung carcinoma [36-43], where its expression or activity contributes to invasiveness, metastasis, and treatment resistance [37, 44–46]. Consequently, SGK-1 has emerged as a potential therapeutic target [47], with the inhibitor SI113 shown to induce cell death in colon carcinoma cells, enhance paclitaxel sensitivity [48],

and reduce hepatocarcinoma growth in vitro and in vivo [49]. Downregulation of SGK-1 mRNA also increases sensitivity to chemotherapy and impairs migration in breast and hepatocellular carcinoma cells [50]. In the current study, SGK-1 was largely cytoplasmic, whereas pSGK-1 was localized to the cell membrane. While the precise mechanisms for this differential localization remain uncertain, prior studies suggest that SGK-1 phosphorylation at Ser422 occurs in the perinuclear membrane in a context- and cell type-dependent manner [51]. Notably, both SGK-1 and pSGK-1 levels were reduced in squamous cell carcinoma compared with benign and dysplastic lesions, particularly for pSGK-1, the active form, suggesting a possible adaptive mechanism to limit tumor growth and highlighting potential relevance for SGK-1-targeted therapies [47].

The use of archived human biopsy samples offers both advantages and limitations. Historically, archived specimens have facilitated discoveries such as the link between smoking and lung cancer, the identification of BRCA1/2 genes, and advances in breast cancer research [52]. Limitations include the retrospective design, single-institution sample origin, small sample size, and incomplete clinical data, including lesion progression and comorbidities. For this study, the relatively limited number of cases is acknowledged; however, random case selection and the heterogeneity of demographics, lesion sites, and clinical impressions mitigate some of these constraints.

Conclusion

In conclusion, despite the small sample size, the findings demonstrate differential subcellular localization and expression of glucocorticoid-regulated proteins GILZ and SGK-1 in potentially malignant and malignant oral lesions. Given the complexity of their roles in tumor biology and the presence of a local glucocorticoid system in oral mucosa, further investigation into the mechanisms and functional contributions of these proteins may enhance understanding of the pathogenesis of oral epithelial dysplasia and squamous cell carcinoma.

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Ethics Statement: None

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