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# INTEGRATED TRANSCRIPTOMIC AND IMMUNOHISTOCHEMICAL PROFILING OF INFLAMMATORY BIOMARKERS FOR EARLY PREDICTION OF ORAL EPITHELIAL DYSPLASIA PROGRESSION

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## ABSTRACT

Oral epithelial dysplasia represents a clinically important precursor to oral squamous cell carcinoma, yet conventional histopathological grading alone cannot reliably identify lesions that will progress. This comprehensive review examines the value of integrating transcriptomic and immunohistochemical profiling of inflammatory biomarkers for earlier and more accurate risk prediction. Evidence was synthesized across studies addressing molecular progression, cytokine and chemokine signaling, immune-cell infiltration, immune-checkpoint activity, epithelial stress responses, stemness, stromal remodeling, metabolic adaptation, and epithelial–mesenchymal transition. Transcriptomic approaches reveal dysregulated gene-expression programs linked to inflammation, proliferation, immune suppression, and malignant transformation, while immunohistochemistry confirms protein expression and preserves spatial relationships within epithelial and stromal compartments. Biomarkers involving p53, Ki-67, p16, hypoxia-inducible factor 1 alpha, heat-shock proteins, programmed death ligand 1, E-cadherin, vimentin, survivin, podoplanin, and cancer stem-cell markers show potential for distinguishing biologically active dysplasia from more stable lesions. No single marker currently provides sufficient predictive accuracy for routine clinical use. Multimarker models combining molecular signatures with histological grade, lesion phenotype, anatomical site, and patient-related factors appear more clinically relevant. Standardized protocols, prospective multicentre cohorts, longitudinal validation, spatial transcriptomics, multiplex immunohistochemistry, and digital pathology are needed to translate integrated biomarker profiling into personalized surveillance, targeted biopsy, and earlier intervention. Such integration may reduce delayed diagnosis, unnecessary treatment, and uncertainty in clinical decision-making.

**KEYWORDS:** Inflammatory biomarkers, Immunohistochemistry, Oral epithelial dysplasia, Risk prediction, Transcriptomic profiling

## 1. INTRODUCTION

OED is a critical step in the multistep process of development of OSCA and occurs in a subset of clinically defined OPDs, including leukoplakia, erythroplakia, OSMF, and some lichenoid lesions. The oral cancer burden includes these disorders, as these can remain, recur, or become malignant even after they have been identified and treated. The significance of oral leukoplakia is related to its high prevalence, the possibility of transformation in different individuals, and the possible different biological behavior of the various types of lesions. Malignant transformation is strongly dependent on clinical phenotype, anatomical site, degree of dysplasia, and patient-related factors, and thus the need for a more precise estimation of the risk of early transformation (Pimenta-Barros et al., 2025).

The histopathologic manifestation of OED is architectural and cytologic changes that include disrupted epithelial maturation, disordered proliferation, and genomic instability. Diagnosis is made based on the following features: irregular stratifications of the epithelium, loss of polarity of the basal cells, excessive mitotic activity and an abnormal number of mitoses, nuclear pleomorphism, dyskeratosis, and disturbed keratinization. There are usually two types of grading systems for use in determining the severity of the dysplasia: either the lesion is classified as mild, moderate, or severe dysplasia, or a low-risk/high-risk classification system is used. While these approaches continue to play a pivotal role in clinical decision-making, there is interobserver variability, sampling limitations, and lack of uniformity in the distribution of dysplastic changes, which limit reproducibility and precision of prognosis (Ranganathan & Kavitha, 2019). Histological grading is then a crucial morphological assessment, but it is not sufficient to fully reflect the molecular diversity that will determine whether or not the individual lesion will be stable or will progress.

The biological course of OED is a result of a series of genetic, epigenetic, transcriptomic, and microenvironmental changes. Some of the most thoroughly studied molecular markers of progression are regions of loss of heterozygosity in

the genome, indicating that genomic instability may be able to detect high-risk lesions before the onset of clinical disease (Rao et al., 2018). There have also been some successes with identifying different molecular patterns in dysplasia in non-smokers, which indicates that not all cases of dysplasia can be explained by conventional exposure-based models, and that precision-risk assessment should consider biologically distinct patient subgroups (Rock et al., 2018). OED, therefore, is not a homogeneous pathological process, but rather a spectrum of lesions with varying molecular courses.

Current diagnostic adjuncts such as autofluorescence, vital staining, optical imaging, and other non-invasive technologies could enhance the visibility of the lesions, as well as the selection of biopsy sites; however, these are not yet sufficient to predict malignant progression on their own (Yang et al., 2018). These are also the challenges that are posed by proposed tissue, salivary, and blood markers, which frequently rely on small, cross-sectional, or methodologically divergent studies. Few candidates have been sufficiently validated over time using a longitudinal approach or demonstrated to be reproducible and routinely used in clinical practice in an attempt to identify prognostic markers in oral leukoplakia (Villa et al., 2019). Evaluation of dysplasia-associated biomarkers also suggests that none is uniformly predictive in populations, laboratories, or lesion category (Rivera et al., 2020).

Oral inflammation is now well known to have a significant role in the pathogenesis of oral carcinogenesis. Chronic inflammatory signals may lead to oxidative stress, DNA damage, proliferation of epithelial cells, angiogenesis, remodeling of the stroma, and immune evasion. Clinically, cytokines, chemokines, immune-checkpoint molecules, macrophage polarization, lymphocyte distribution, and stress-response proteins could offer valuable information regarding the dysplasia-to-invasive-carcinoma transition. Oral PMDs are caused by dynamic interplay between epithelial changes, environmental factors, host immunity, and local tissue microenvironment, suggesting the potential for inflammatory biomarkers to be investigated together as an integrated approach (Kumari et al., 2022).

Transcriptomic profiling allows for an assessment of the patterns of gene expression, signaling pathways, and immune-related programs, while immunohistochemistry allows for the confirmation of protein expression with retention of spatial information in the epithelial and stromal compartments. Combining these will grant the possibility to overcome these drawbacks of either platform by enabling the association of molecular activity to tissue localization and histopathology context. This might help to differentiate between stable and progressive lesions, detect stable biomarker panels, and enhance predictive value over traditional grading. There is a need for a more transparent integration of existing evidence to identify a consistent inflammatory signature associated with progression, validation of these signatures, and the potential to incorporate them into clinically relevant risk stratification models. This review summarizes the transcriptomic and immunohistochemical studies of inflammatory markers in OED, highlighting the importance of the accurate identification of markers at the earliest possible stage, methodological integration, and the clinical application of this data to personalized surveillance and management.

**Objectives of the review:**

- To identify inflammatory biomarkers associated with oral epithelial dysplasia progression.
- To evaluate integrated transcriptomic and immunohistochemical profiling approaches.
- To assess their predictive value for risk stratification and early intervention.

## 2. Biological Continuum from Normal Oral Epithelium to Invasive Carcinoma

Normal oral epithelium progresses to invasive oral squamous cell carcinoma through molecular, cellular, and microenvironmental changes that occur in a multistep biological process. The early epithelial changes may present clinically as Oral potentially malignant disorders and histopathologically as architectural disturbance, cytological atypia, and grades of dysplasia. The changes do not happen in a consistent manner, and lesions that look alike may have different clinical courses. The molecular signature from the transcriptomic analysis showed a higher probability of distinguishing the lesions with a higher probability of progression, which implies that the molecular signature can be used in addition to the histological assessment to distinguish the lesions (Sathasivam et al., 2021).

In this spectrum, the dysplastic epithelial cells become hyperproliferative, resistant to apoptosis, genomically unstable, and dysfunctional with respect to differentiation. Regulatory non-coding RNAs could play a role in these alterations by altering genes related to the regulation of inflammation, cell-cycle control, invasion, and malignant transformation. Salivary microRNAs are thus being explored as easily accessible markers that would reflect molecular abnormalities in oral potentially malignant disorders (Maheswari et al., 2018).

There are also changes at the protein level that appear before the onset of invasion. Proteomic changes in oral mucosa have also been used for label-free profiling to identify differentially expressed proteins related to cellular stress, metabolism, cytoskeletal organization, and tumor development, suggesting that these changes could be used to identify precancerous lesions that are more likely to develop into cancer (Sharma et al., 2023). The use of parallel evaluation of biomarkers, a combination of noninvasive sampling and lesion-specific molecular confirmation, could facilitate early detection. The paired salivary and tissue analysis of P90-associated biomarkers has proven its potential in the identification of oral leukoplakia and its characterization of biological status (Wan et al., 2024). The biological stages of progression from normal oral epithelium to proteomic alterations are shown in Figure 1.

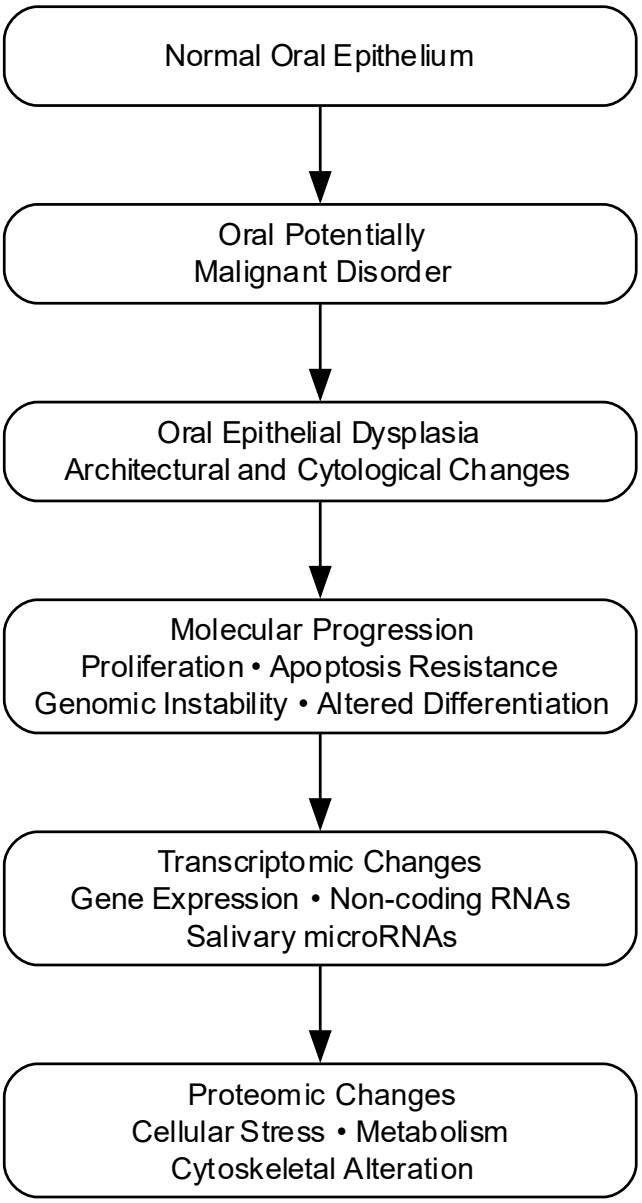


**Figure 1. Biological Progression from Normal Oral Epithelium to Proteomic Alterations**

**3. Inflammation-Driven Mechanisms in Oral Epithelial Dysplasia Progression**

Chronic inflammation is responsible for the progression of oral epithelial dysplasia through the generation of a microenvironment that fosters genomic instability, abnormal proliferation, stromal remodeling, and immune escape. Ongoing exposure to inflammatory mediators can lead to activation of signaling pathways of oxidative stress, angiogenesis, EMT, and apoptosis resistance. The processes are interlinked with the traditional clinicopathological risk factors, suggesting that the process of malignant transformation is not solely determined by histology grade. Multivariable prediction models with demographic, clinical, and pathological parameters have been shown to provide better estimation for malignant transformation and recurrence, which is an argument for the incorporation of molecular and inflammatory parameters in future risk-stratification systems (Mahmood et al., 2023).

Spatial heterogeneity of immune-cell infiltration and differences in protein expression between epithelial and stromal compartments are also features of the inflammatory microenvironment. Quantitative immunohistochemical assessment helps to minimize subjectivity by quantifying the intensity, distribution, and localization of the markers. Even though there are difficulties in oral leukoplakia diagnosis, automated image-analysis systems like the OralImmunoAnalyser show that segmentation and classification algorithms can help standardize the evaluation of oral leukoplakia and enhance the repeatability of different observers, as discussed by Al-Tarawneh et al., 2024.

Clinically related lesions also might have distinct inflammatory and molecular programs, as suggested by transcriptomic evidence. Leukoplakia and proliferative verrucous leukoplakia have different gene-expression signatures, which indicate different biological pathways and progression risks, even though the clinical features seem to be the same (Pérez-Sayáns et al., 2026). The process of malignant transformation is thus a synergistic interaction of transformations of epithelial cells, cytokine networks, immune suppression, changes in the extracellular matrix, and activation of the stromal cells. This multilevel analysis of these molecular and microenvironmental drivers might help to detect high-risk lesions earlier and might also provide an explanation for the variable outcomes of OPDs in terms of either stable or malignant progression

(V et al., 2026). To summarize, the inflammation-related mechanisms involved in the progression of oral epithelial dysplasia (OED) are shown in Figure 2.

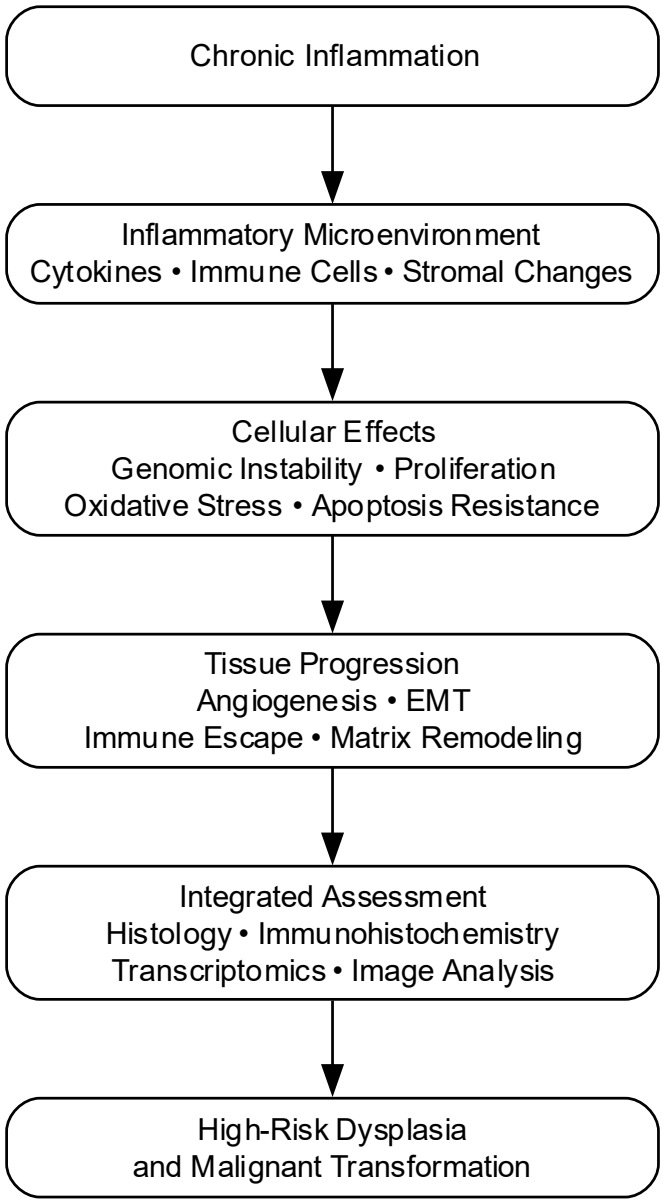


**Figure 2. Inflammation-Driven Mechanisms in Oral Epithelial Dysplasia Progression**

**4. Transcriptomic Signatures Associated With Progressive Oral Dysplasia**

The transcriptomic changes observed during the progression of oral epithelial dysplasia are indicative of a coordinated response in epithelial signaling, inflammatory regulation, stromal activity, and immune surveillance. The dysplastic microenvironment does not passively accompany the process of carcinogenesis but is an active player in its process, including fibroblasts, remodeling of the extracellular matrix, changes in blood vessels, recruitment of immune cells, and soluble mediators. These components modulate proliferation, apoptosis resistance, angiogenesis, invasion, and immune evasion programs of gene expression that play a role in the progression of OPDs to invasive carcinoma (Deng et al., 2022). Changes in transcription and production of proteins in dysplastic tissue may be reflected in changes in inflammatory proteins in saliva. Patients suffering from OPDs have been found to have variations of salivary cytokines, matrix-associated proteins, and acute-phase mediators, thus making it possible to develop a measurable molecular signature that stems from the inflammatory processes taking place in the oral cavity beyond the lesion (Dikova et al., 2019). Oral cancer studies of salivary cytokines have also shown consistent changes in inflammatory mediators, and they could potentially be used in noninvasive biomarker panels, but the sampling of these studies, the assays used, and the diagnostic thresholds are not always consistent, so it is not easy to directly translate these findings into practice (Chiamulera et al., 2021).

Other progressive lesions can also exhibit changes in immune-cell infiltration and checkpoint function, regulated by transcription. It is found that the two mechanisms of immune activation and suppression can coexist in the early transformation process in oral lesions, as increased T-cell infiltration and increased expression of immune-checkpoint molecules are found in both premalignant and malignant oral lesions (Surendran et al., 2022). A combination of transcriptional profiles from epithelial cells with inflammatory markers in saliva and immune measurements in tissues

could thus provide important biological signatures for progression. This type of profiling combination may be useful to differentiate transient inflammatory processes from a continued process of carcinogenesis and aid in early classification of dysplastic lesions with high malignant potential. Based on this information, there are some indicators of dysplasia progression that are suggested and summarized in Table 1.

**Table 1. Molecular and Transcriptomic Features Associated With Oral Epithelial Dysplasia Progression**

| Biomarker domain | Representative markers or approaches | Biological significance | Potential clinical application | In-text citation |
|---|---|---|---|---|
| Transcriptomic signatures | Differential gene-expression profiles | Identify molecular programs associated with stable and progressive lesions. | Molecular classification of high-risk oral potentially malignant disorders | (Sathasivam et al., 2021) |
| Salivary microRNAs | miRNA expression panels | Reflect dysregulation of proliferation, apoptosis, inflammation, and invasion. | Noninvasive screening and longitudinal monitoring | (Maheswari et al., 2018) |
| Tissue proteomics | Differentially expressed mucosal proteins. | Detect alterations in metabolism, cytoskeletal regulation, and cellular stress. | Identification of lesions predisposed to malignant transformation | (Sharma et al., 2023) |
| Paired saliva–tissue biomarkers | P90-associated proteins | Connect noninvasive salivary signals with lesion-specific tissue changes | Combined detection and biological characterization of oral leukoplakia | (Wan et al., 2024) |
| Multivariable prediction models | Clinical and histopathological variables | Integrate multiple determinants of malignant transformation and recurrence. | Personalized risk estimation and surveillance planning | (Mahmood et al., 2023) |
| Automated immunohistochemical analysis | Image segmentation and classification algorithms | Standardize marker quantification and reduce observer variability | Reproducible digital assessment of oral leukoplakia | (Al-Tarawneh et al., 2024) |

**5. Cytokine and Chemokine Networks as Predictive Biomarker Systems**

The oral microenvironment is a complex network that involves communication between dysplastic epithelial cells that are dysplastic, immune cells, stromal cells, and vascular elements, all of which are regulated by cytokine/chemokine networks. Ongoing inflammatory signals can lead to the recruitment of leukocytes, proliferation of epithelial cells, neovascularisation, remodelling of the extracellular matrix, and immune suppression. High-grade oral epithelial dysplasia has been shown to have specific patterns of inflammation in terms of immune-cell composition and altered gene expression, suggesting that inflammatory markers may be markers of biologically aggressive lesions rather than of nonspecific tissue irritation (Flores-Hidalgo et al., 2024).

The checkpoint pathways are tightly related to immune regulation mediated by cytokines. The expression of programmed cell death protein 1 and programmed death ligand 1 was detected to be increased in both stages of oral leukoplakia and oral squamous cell carcinoma, indicating a progressive decrease in the ability of the tumor to produce antitumor immune responses during the malignant development of oral leukoplakia (Greeshma et al., 2023). These alterations can be accompanied by cytokine-induced T-cell exhaustion and loss of cytolytic activity, which could lead to the expression of these checkpoints as a part of the predictive inflammatory panels.

Macrophages also regulate the cytokine and chemokine profiles in oral potentially malignant disorders. They impact the inflammatory persistence, tissue repair, angiogenesis, and immune escape, depending on their phenotype and spatial distribution. From the available evidence, it is suggested that macrophage polarization may be changing to a more tumor-supportive activation state during progression, but the substantial variation in markers and scoring systems for macrophages in tumor samples, as well as in the classification of lesions, hampers direct comparisons across studies (Sutera et al., 2025).

A complex and dynamic interplay between antitumor surveillance and protumor inflammation is reflected by the broader immune microenvironment. Thus, integrated measurement of cytokines, chemokines, checkpoint proteins, and immune-cell populations is likely to have a better predictive value than individual biomarkers. This multi-dimensional profiling approach might support in detecting dysplastic lesions that represent ongoing immune remodeling and are moving towards malignant transformation (Ali et al., 2025). The inflammatory and immune-microenvironment biomarkers for oral dysplasia are summarized in Table 2.

**Table 2. Inflammatory and Immune-Microenvironment Biomarkers in Dysplastic Oral Lesions**

| Biomarker domain | Representative markers or cells | Role in progression | Predictive relevance | In-text citation |
|---|---|---|---|---|
| Inflammatory microenvironment | Cytokines, fibroblasts, immune cells, extracellular matrix | Promotes proliferation, angiogenesis, stromal remodeling, and immune evasion | Distinguishes biologically active lesions from stable dysplasia | (Deng et al., 2022) |
| Salivary inflammatory proteins | Cytokines and acute-phase proteins | Reflect local inflammatory activity within oral potentially malignant disorders. | Noninvasive detection of inflammatory dysregulation | (Dikova et al., 2019) |
| Salivary cytokines | IL-6, IL-8, TNF-related mediators | Indicate persistent immune activation and carcinogenesis-associated inflammation. | Candidate components of salivary biomarker panels | (Chiamulera et al., 2021) |
| T-cell infiltration | CD4-positive and CD8-positive lymphocytes | Represents simultaneous immune activation and immune dysfunction | Assessment of evolving antitumor immunity | (Surendran et al., 2022) |
| Immune checkpoints | PD-1 and PD-L1 | Suppress cytotoxic immune responses and facilitate immune escape | Identification of immunologically high-risk lesions | (Greeshma et al., 2023) |
| Macrophage polarization | Tumor-associated macrophage phenotypes | Supports chronic inflammation, angiogenesis, tissue remodeling, and immune suppression | Characterization of progression-supportive microenvironments | (Sutera et al., 2025) |

**6. Immunohistochemical Markers of Epithelial Inflammation and Cellular Stress**

Oral epithelial dysplasia marks the site of tissue-based evidence of biological changes that occur during the process of its development, as shown by immunohistochemical markers of epithelial inflammation and cellular stress. Changes in expression of cell-cycle regulators may be early signs of loss of growth control before development of invasive carcinoma. The decreased or imbalanced expression of p16 and p27 has been reported in the dysplastic and malignant oral epithelium, suggesting their potential in detecting the dysregulated cell cycle and cancer progression (Thambiah et al., 2018).

The expression of p53 and Ki-67 can also be used to determine the proliferative activity and the genomic stress. The levels of immunoreactivity for these markers increased with increasing histopathologic grades of oral leukoplakia, indicating that p53 abnormalities in the accumulation and proliferation of epithelial compartments increase with a greater degree of dysplasia (Suwasani et al., 2018). Evaluation by both their morphology and biology may thus be more informative than morphology alone.

Another aspect of epithelial stress is related to hypoxia signaling. Hypoxia-inducible factor 1 alpha (HIF1A) is a transcription factor that regulates various adaptations to hypoxia, and is involved in angiogenesis, metabolic reprogramming, survival, and invasion. The greater the amount of expression, the more dysplastic it becomes, and the more dysplastic it is, the more malignant it becomes; hence, hypoxic adaptation can start as a premalignant process and can progress with malignant transformation (Patel et al., 2019).

Heat-shock proteins are a marker of cellular response to oxidative, inflammatory, and proteotoxic stress. The expression of heat shock protein 70 is increased in dysplastic and malignant oral tissues, indicating its protective function, which may be beneficial for the survival of the epithelium in unfavorable microenvironmental conditions (Priyanka et al., 2019). Therefore, a combined assessment of cell-cycle, proliferation, hypoxia, and stress-response markers may be helpful for the identification of biologically unstable lesions with high progression potential. The immunohistochemical markers of epithelial inflammation and cell stress are highlighted in Figure 3.

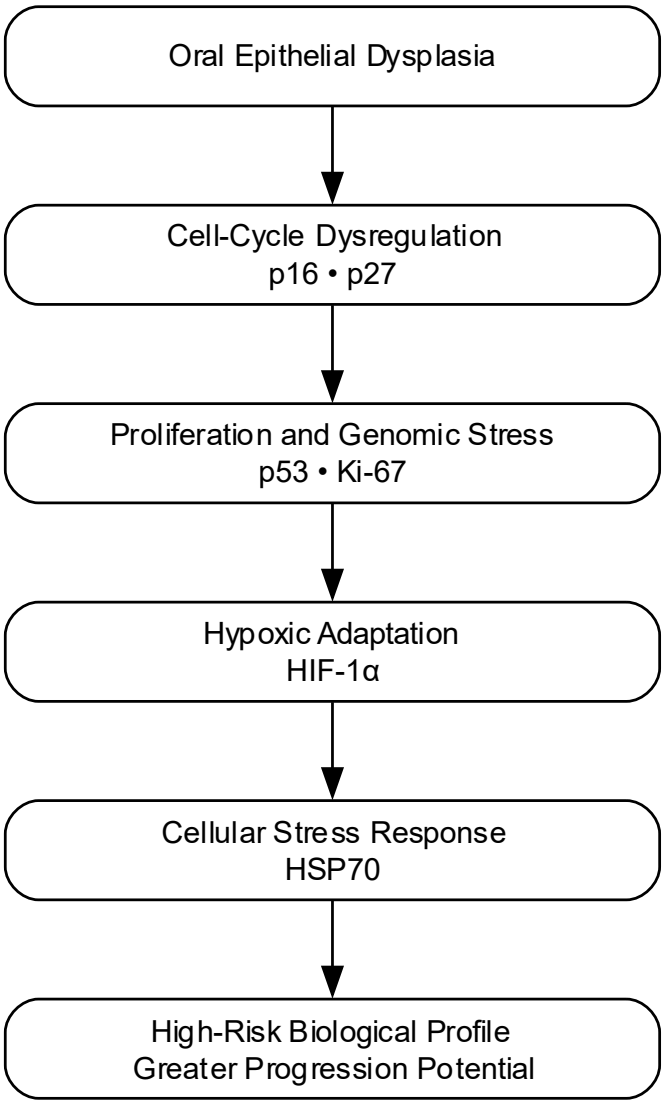


**Figure 3. Immunohistochemical Markers of Epithelial Inflammation and Cellular Stress**

**7. Stemness-Associated Alterations Within the Dysplastic Microenvironment**

Dysplastic oral microenvironment not only is altered due to inflammatory and stromal changes but also results from epithelial subpopulations with increased proliferative capacity, self-renewal, and resistance to differentiation. Changes in expression of p16, p53, and Ki-67 indicate disturbance of cell cycle regulation, genomic surveillance, and control of proliferation. As they become increasingly abnormal in expression in dysplastic and malignant oral lesions, there is a suggestion that expansion of unstable epithelial clones starts before the onset of invasive carcinoma (Yadav et al., 2019). Transcription factors related to stemness can also help to select epithelial cells that can maintain the persistence of the lesion and its malignant progression. SOX2 and OCT4 have been found to be highly expressed in oral epithelial dysplasia and oral squamous cell carcinoma, and their expression is associated with changes in WNT5A signaling. The expression of these markers correlates with the self-renewal, diminished differentiation, cellular plasticity, and invasive behavior, indicating the emergence of stem-like phenotypes in premalignant development (Vijayakumar et al., 2020).

Another regulator associated with embryonic development, maintenance of stem cells, and tumorigenesis is spalt-like transcription factor 4. The immunohistochemical expression of the disease from the dysplastic epithelium to the carcinoma that is growing is also an indication of its potential to detect lesions that have enhanced malignant potential and progressive molecular deregulation (Kulkarni et al., 2020).

Other markers of cancer stem cells show changed expression in oral dysplasia and carcinoma, such as ALDH1, Bmi1 and OCT4. The co-expression could suggest that they are associated with populations of epithelium with higher treatment resistance, survival, and ability for clonal expansion (Rao et al., 2020). Consequently, a combination of proliferation, cell-cycle disruption, and stemness markers may be useful in characterizing the dysplastic microenvironment and differentiating between active and clinically latent morphologically similar lesions. The immunohistochemical markers of proliferation, stress, stemness, and metabolism are highlighted in Table 3.

**Table 3. Immunohistochemical Markers of Proliferation, Stress, Stemness, and Metabolic Adaptation**

| Marker group | Representative markers | Main biological process | Expression pattern or implication | In-text citation |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Cell-cycle regulation | p16 and p27 | Cell-cycle control and growth suppression | Dysregulated expression accompanies progression from dysplasia to carcinoma | (Thambiah et al., 2018) |
| Proliferation and genomic stress | p53 and Ki-67 | DNA-damage response and epithelial proliferation | Increasing expression is associated with higher dysplasia grades | (Suwasini et al., 2018) |
| Hypoxic adaptation | HIF-1α | Angiogenesis, metabolic reprogramming, and survival | Progressive elevation suggests early adaptation to hypoxia | (Patel et al., 2019) |
| Cellular stress response | HSP70 and HSP27 | Protection against oxidative and proteotoxic stress | Increased expression may enhance survival of altered epithelial cells | (Priyanka et al., 2019; Ramalingam et al., 2022) |
| Cancer stemness | SOX2, OCT4, ALDH1, Bmi1, and SALL4 | Self-renewal, plasticity, and resistance to differentiation | Higher expression may identify persistent and aggressive epithelial clones | (Vijayakumar et al., 2020; Rao et al., 2020; Kulkarni et al., 2020) |
| DNA repair | ERCC1 | Nucleotide excision repair | Altered expression may reflect impaired repair capacity during early invasion | (Kulkarni et al., 2020) |
| Metabolic adaptation | GLUT-1 | Glucose transport and energy metabolism | Increased expression supports survival under high metabolic demand | (Patlolla et al., 2020) |
| Apoptosis resistance | Survivin | Inhibition of programmed cell death | Progressive elevation may indicate biologically aggressive dysplasia | (Ghritlahare et al., 2022) |

**8. Stromal Remodeling, DNA Repair, and Metabolic Adaptation in Early Malignant Transformation**

The process of oral epithelial dysplasia consists of the evolution of epithelial changes along with the stroma. Myofibroblasts are activated stromal cells that synthesize extracellular-matrix components, growth factors, cytokines, and proteolytic enzymes that can promote epithelial proliferation and invasion. They are progressively found in normal oral mucosa, dysplastic areas, and in oral squamous cell carcinoma, suggesting that the activation of the stromal compartment occurs even before the occurrence of an overt malignancy and may reflect a microenvironment that is conducive to malignant progression (Shete et al., 2020).

Genetically unstable epithelial cells are also enhanced in their survival due to defective responses to DNA damage. Excinuclease repair cross-complementation group 1 is involved in repairing lesions in DNA that are induced by carcinogens, and in the nucleotide excision repair process. Changes in ERCC1 expression in the transition from premalignant change to invasion (ductal or glandular invasion) suggest that the repair capacity is altered as well when moving from a premalignant state to an invasive cancer (Kulkarni et al., 2020).

Progressive oral carcinogenesis is also illustrated by the identification of myofibroblasts by alpha-smooth muscle actin and vimentin. Up-regulation of the expression of these markers indicates fibroblast activation, and the development of a contractile phenotype resulting in matrix reorganization, tissue stiffness, and tumor-supportive signaling (Mahajan et al., 2020).

Another aspect of the biologically active dysplasia is metabolic adaptation. Increased energetic demands and hypoxia: glucose transporter 1 (GLUT1) is involved in glucose uptake. It has been found to rise from dysplastic epithelium to OSCC in its expression, indicating early metabolic reprogramming which could help in cell survival and proliferation (Patlolla et al., 2020). Thus, a composite evaluation of stromal markers, repair and metabolic markers may be more helpful in the diagnosis of lesions that are in a state towards malignant transformation. During progression, there is a remodeling of stromal cells, an impairment of DNA-repair processes, and a metabolic adaptation as shown in Figure 4.

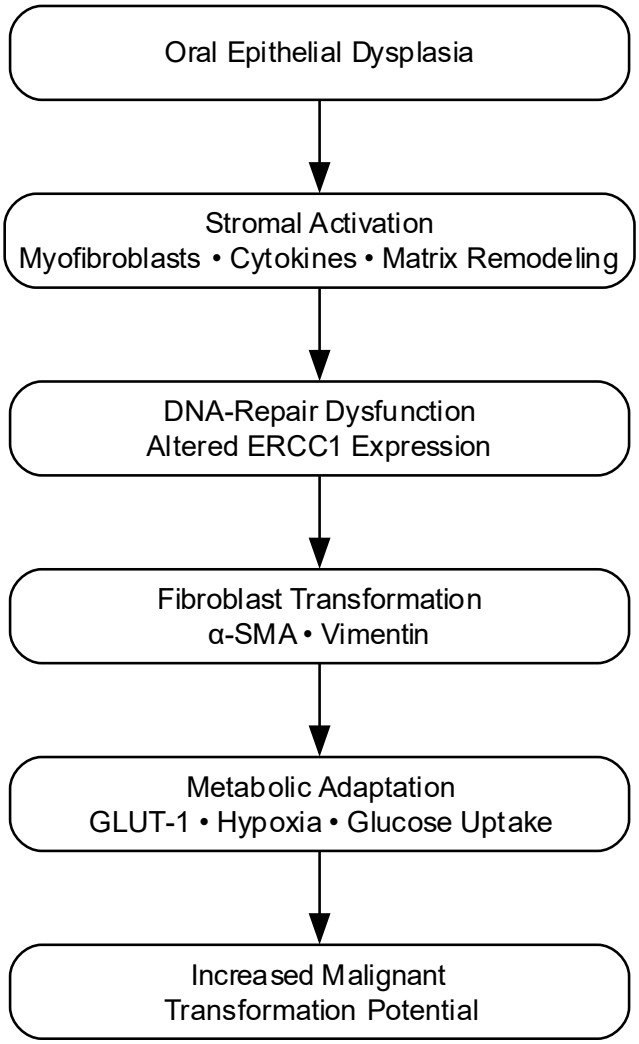


**Figure 4. Stromal Remodeling, DNA-Repair Dysfunction, and Metabolic Adaptation in Oral Dysplasia**

**9. Integration of Transcriptomic and Immunohistochemical Biomarker Profiles**

The goal of integrated biomarker profiling is to link molecular activity to expression in the tissue, localization of the active molecules, and histopathological progression. Both immunohistochemical markers and transcriptomic data could be used to identify specific biological processes in the dysplastic epithelium, and the regulatory networks that underlie the changes in the dysplastic epithelium. The expression of another microtubule-regulating protein, Stathmin, which is involved in cell division, motility, and cytoskeletal instability, is increased in the grades of oral dysplasia, suggesting a possible alteration in microtubule dynamics during progressive epithelial transformation (Vadla et al., 2021).

Other pathways associated with the virus or stemness may be responsible for the molecular heterogeneity of oral epithelial dysplasia as well. Immunohistochemical evaluation of human papillomavirus-associated proteins and cancer stem-cell markers has revealed that there are different patterns of expression among dysplastic lesions, which may identify a set of different biological subgroups based on virus exposure, self-renewal capacity, and failure to differentiate (Thankappan et al., 2021). Characterization of these lesions by transcriptome analysis could help to determine if the patterns of proteins observed are associated with particular gene expression programs and/or progression risks.

Stromal markers give clues to additional information in addition to epithelial abnormalities. Raised myofibroblast expression in dysplasia and carcinoma is indicative of the activation of surrounding connective tissue and may be a sign of extracellular-matrixremodelling, cytokine production and tumour-supportive signalling (Pinisetti et al., 2021). Further evidence of loss of epithelial adhesion and acquisition of mesenchymal properties comes from the loss of epithelial–mesenchymal transition markers. A decrease in E-cadherin levels and an increase in vimentin levels in all the dysplasia grades indicate progressive cellular plasticity and an invasive potential (Puneeta et al., 2022).

Transcriptomic signatures and immunohistochemical panels containing cytoskeletal, stemness, stromal and epithelial–mesenchymal markers might thus result in better biological classification, validate molecular results at a cellular level and better identification of dysplastic lesions of greater malignant potential.

**10. Clinical Evidence, Validation, and Predictive-Model Performance**

For candidate biomarkers, there is a need for evidence that expression is consistent between the different grades of dysplasia and correlates with malignant progression. Heat-shock protein 27 is responsible for cellular stress tolerance, cytoskeletal stability, apoptosis resistance, and signaling for survival. The progressive rise of its immunohistochemical

expression in oral epithelial dysplasia to oral squamous cell carcinoma holds promise as a prognosticator, but needs to be further validated in a longitudinal study before clinical use (Ramalingam et al., 2022).

Survivin is an IAP that is linked to increased cell growth and programmed cell death resistance. The earlier the control of apoptosis fails, the earlier the expression of survivin increases in the process of oral cancer development. A multimarker model that assesses its role could be developed to identify biologically aggressive dysplasia (Ghritlahare et al, 2022).

The expression of podoplanin has also been studied as a marker of changes in cellular motility, lymphatic interaction, and invasive potential. It is suggested that its overexpression in oral leukoplakia and OSCCs may aid in separating the advanced epithelial transformation from the less serious abnormalities (Srinivasan et al., 2023). Complementary information might be provided by immune and adhesion-related markers. CD138 is a marker of epithelial differentiation and cell adhesion, while CD43 is mainly expressed by leukocytes and inflammatory cells. Oral leukoplakia has differential expression of these molecules, which may be used to characterise disruption of the epithelia and immune involvement of the dysplastic microenvironment, respectively (Akkaloori et al., 2023).

Clinico-pathological factors and validated biomarkers of stress responses, apoptosis, invasion, differentiation and inflammation should be included in reliable predictive models. Their performance should be evaluated in terms of sensitivity, specificity, discrimination, calibration, reproducibility and external validity in independent longitudinal cohorts before they are used in routine clinical practice. The biomarker validation process for prediction of oral epithelial dysplasia progression is shown in Figure 5.

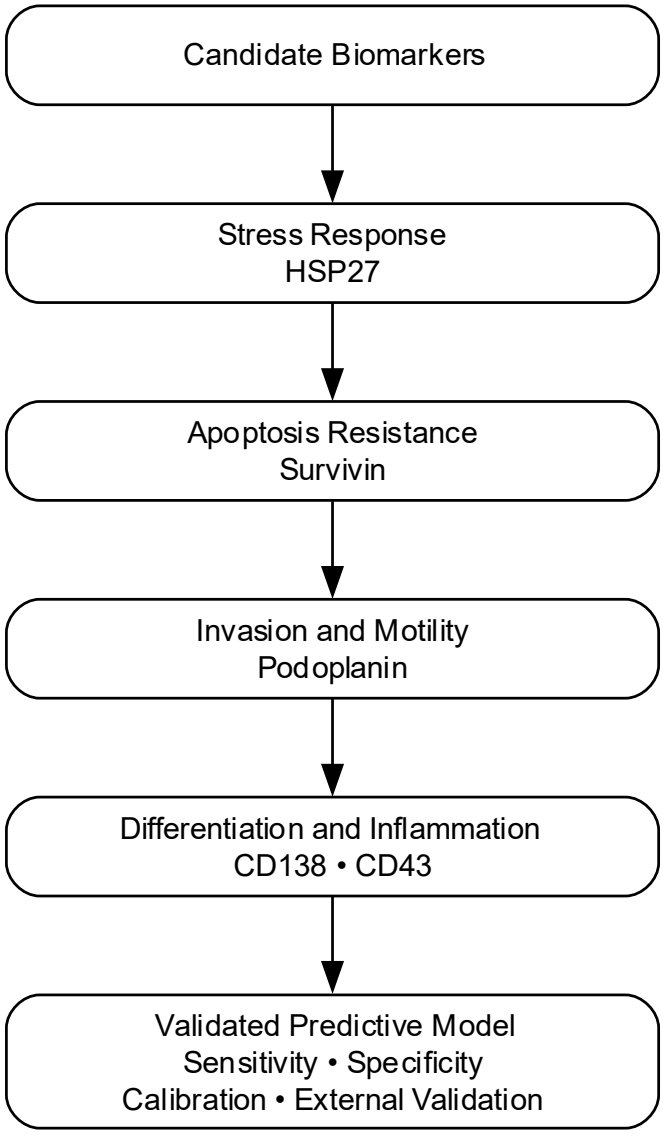


**Figure 5. Immunohistochemical Biomarker Validation Framework for Predicting Oral Epithelial Dysplasia Progression**

**11. Translation Into Risk Stratification and Clinical Surveillance**

Reproducible biomarkers that can help to refine the classification of risk beyond the traditional histopathological grading would be useful in the translation of biomarker research into clinical surveillance. Immunohistochemical markers of proliferation, apoptosis, genomic instability, inflammation, adhesion and epithelial–mesenchymal transition have been promising as markers to differentiate low and high risk for oral epithelial dysplasia. To be clinically useful, they must be

standardized in staining protocols, scoring, as well as threshold definitions and validation of the results in independent populations (Zdrojewski et al., 2024).

Notably, E-cadherin is important since loss of epithelial adhesion is a key element of the early stages of malignant transformation. The decreasing expression of the membrane in grades of dysplasia and OSCC suggests a progressive loss of integrity of the epithelium and increased invasiveness. However, when combined in multimarker panels, it could be useful to better detect lesions that are morphologically not too severe, but have more biologically advanced changes (Kani et al., 2025).

Cellular plasticity before true invasion may be identified by the presence of early EMT markers and further aid in risk stratification. Changes in expression of E-cadherin, vimentin, N-cadherin, transcription repressors, and corresponding proteins have been reported to correlate with dysplastic progression, but there is currently methodological variability that prevents direct comparisons and clinical standardization (Rivera-Reza et al., 2026).

A clinically applicable framework needs to be a combination of histological grade, lesion localization, clinical phenotype, patient risk, transcriptomic signatures, and validated immunohistochemical markers. This might enable risk-stratification of patients, planning of biopsy sites, planning of surveillance intervals, and earlier treatment of lesions with molecular progression. Multicentre studies with longitudinal endpoints are needed to define well-validated thresholds, to evaluate incremental predictive value and to determine if the use of a biomarker assay for surveillance would benefit patients. Profiling, which is designed to assess both the probability of developing clinical disease and the risk of progression, is provided in Table 4.

**Table 4. Integrated Biomarkers for Clinical Risk Stratification and Surveillance**

| Biomarker or approach | Biological interpretation | Proposed clinical use | Current limitation | In-text citation |
|---|---|---|---|---|
| E-cadherin and vimentin | Loss of epithelial adhesion and acquisition of mesenchymal characteristics | Detection of early epithelial–mesenchymal transition | Variable antibodies, scoring systems, and cutoff values | (Puneeta et al., 2022) |
| Myofibroblast markers | Stromal activation and extracellular-matrix remodeling | Identification of a tumor-supportive stromal environment | Limited longitudinal evidence linking expression to transformation | (Pinisetti et al., 2021) |
| Stathmin | Microtubule instability, proliferation, and cellular motility | Recognition of dysplastic lesions with increased proliferative activity | Requires validation in larger, independent cohorts | (Vadla et al., 2021) |
| Podoplanin | Cellular migration, invasion, and lymphatic interaction | Differentiation of advanced leukoplakia from lower-risk lesions | Predominantly cross-sectional evidence | (Srinivasan et al., 2023) |
| CD138 and CD43 | Epithelial adhesion and inflammatory-cell activity | Combined assessment of epithelial disruption and immune involvement | Uncertain prognostic thresholds and limited reproducibility | (Akkaloori et al., 2023) |
| Immunohistochemical biomarker panels | Combined proliferation, apoptosis, inflammation, and adhesion markers | Improved grading and risk classification beyond morphology alone | Lack of standardized panels and external validation | (Zdrojewski et al., 2024) |
| E-cadherin-based assessment | Progressive loss of membranous adhesion | Identification of lesions approaching invasive transformation | Should not be used independently of histopathology | (Kani et al., 2025) |
| Early epithelial–mesenchymal transition panels | E-cadherin, N-cadherin, vimentin, and transcriptional repressors | Early detection of cellular plasticity and invasive potential | Considerable methodological heterogeneity | (Rivera-Reza et al., 2026) |

## 12. Limitations and Future Directions

However, the available evidence is small, retrospective, has varying definitions of malignant progression, varying follow-up periods, and varying lesion classifications. There are limitations to comparability between studies due to variations in tissue preservation, transcriptomic platforms, antibody selection, staining protocols, scoring systems, and thresholds for biomarkers. Most investigations are "cross-sectional" and test individual markers to see if they are predictive of transformation themselves. Other factors, such as limited external validation, incomplete adjustments for tobacco use, alcohol use, anatomical site and dysplasia grade, and under-representation of diverse populations further decrease generalizability.

Long-term clinical outcomes should be emphasized in future studies, and prospective multicentre studies with standardized diagnostic criteria and uniform handling of biospecimens should be prioritized. Interactions between the epithelium, immune and stromal compartments might be better understood using integrated spatial transcriptomics, single-cell sequencing, digital pathology and multiplex immunohistochemistry. The candidate panels should be independently validated, calibrated and compared with the conventional histological grading. Clinical models that integrate molecular signatures, immunohistochemical markers, and clinicopathological features are required to aid in personalised surveillance, targeted biopsy and early intervention.

## 13. CONCLUSION

The integrated transcriptomic and immunohistochemical profiling could be a potentially useful approach to better predict the progression of oral epithelial dysplasia. Although conventional histopathological grading is still important, it has some drawbacks as it is based on random sampling, interobserver variability, and underrepresentation of the molecular heterogeneity of the tumor. Transcriptomic analysis may help detect the inflammatory pathways, the cytokine networks, the activity of immune checkpoints, the epithelial stress response, and the interactions of stromal cells, while immunohistochemical analysis can detect the expression of proteins and maintain the spatial relationships among proteins in the dysplastic tissue. Data collected from epithelial, immune, metabolic, stemness, and microenvironmental markers suggest that there is no single reliable marker to predict the routine clinical outcome. A combination of molecular signatures and histological grade, lesion phenotype, anatomical site, and patient's risk factors is more likely to yield clinically meaningful stratification in multimarker models. Standardisation of tissue processing, validation of the scoring thresholds, long-term follow up and external validation in a variety of multicentre cohorts will be required for translation to practice. New techniques, such as spatial transcriptomics, multiplex immunohistochemistry, single-cell analysis and digital pathology, could provide further subclassification of lesions. A well-validated comprehensive biomarker system has the potential to facilitate individualized surveillance, timely intervention, better identification of high-risk individuals for malignant transformation and to minimize overtreatment of stable disease.

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