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Tumor Markers and Their Significance in Oral Dysplasia

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Abstract

Oral epithelial dysplasia (OED) denotes precancerous alterations in oral tissue, signalling potential malignancy. Not all cases of OED lead to oral squamous cell carcinoma (OSCC). The chances of progression depend on the severity of the dysplasia. Severe cases are more likely to progress, while mild cases can stay the same or improve. Individual immune responses, genetic factors, and environmental exposures (e.g., tobacco and alcohol) impact the likelihood of progression, leading to diverse outcomes in each OED case. Tumor markers, whether produced by the tumor or as a response to its presence, play a crucial role in diagnosing cancer and evaluating the extent of the tumor. In OED, these markers are

critical for identifying high-risk patients, allowing early detection, timely intervention, and potentially improved treatment outcomes. However, the underutilization of these markers in predicting OED prognosis highlights the need for their more effective integration into clinical practice.

Incorporating these markers into clinical practice can enhance OED prognosis and management, ultimately benefiting individuals at risk for oral cancer.

Keywords: Oral squamous cell carcinoma, prognosis, treatment outcomes, epithelial-mesenchymal transition, cancer stem cells, Matrix Metallo Proteinases, Angiogenesis, oxidative stress, oncogenes.

Introduction

Oral epithelial dysplasia (OED) is a histopathological term used to identify a precancerous state within the oral epithelial tissue, now recognized as potentially malignant disorders. Its important to emphasize that not all cases of OED develop into oral squamous cell carcinoma (OSCC). [1] OED is defined as an epithelial tissue in which the prevalence of OSCC is higher than in its healthy counterpart. [2] The progression of OED into OSCC is a multifaceted process influenced by several factors. Not all instances of OED evolve into cancer due to various reasons including the degree of dysplasia, with severe dysplasia posing a higher risk of progression. In contrast, mild dysplasia may remain stable or regress. The individual's immune response is critical, as it can detect and eliminate precancerous cells. Genetic factors and environmental exposures, such as tobacco and alcohol, also impact the likelihood of progression.[1] Regular monitoring and timely management of OED, along with lifestyle choices, contribute to preventing its transformation into cancer. Each case of OED is unique, and its variability further contributes to the diverse outcomes observed in patients with this condition.

Tumor markers are substances that are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign conditions that can aid in the diagnosis of cancer and the assessment of tumor burden. [3, 4] Utilizing tumor markers in the prognosis of oral epithelial dysplasia is critically significant for the identification of high-risk patients. This, in turn, facilitates early detection, timely intervention, and the potential improvement of treatment outcomes and survival rates.

Nevertheless, the underutilization of these markers in predicting OED prognosis underscores the imperative for their more effective integration into clinical practice. Numerous studies have examined various immunohistochemical markers that are utilized to evaluate the malignant transformation of OED into OSCC. Several research studies have investigated a range of immunohistochemical markers that are employed to assess the progression of OED to OSCC.

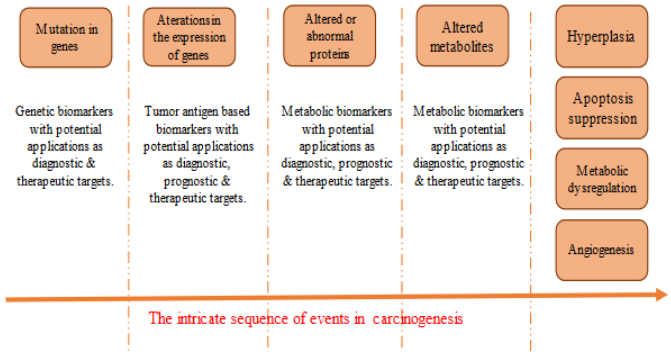

Figure- 1: The role of tumor markers in understanding and detecting carcinogenesis.

Ki-67

In 1983, Johannes Gerdes and colleagues introduced the monoclonal antibody Ki-67 (Antigen Kiel 67) as a marker for actively dividing cells. Ki-67 is effective in assessing cell proliferation, with advantages including resistance to external influences, minimal residual

staining, and specific nuclear expression during the cell cycle. Its valuable for evaluating the histologic grades of OED and OSCC, overexpressed in premalignant and malignant lesions.

Ki-67's positive cell fraction correlates withdisease progression, with high-risk OED showing deeper proliferation into the basal layer compared to low-risk OED. [5, 6]

PCNA

Proliferating cell nuclear antigen (PCNA) is a pivotal protein crucial for DNA replication and repair processes. Acting as a cofactor for DNA polymerase delta, it plays a fundamental role in maintaining genomic stability. Additionally, PCNA serves as a reliable molecular marker for cell proliferation, with elevated expression during the G1 and S phases of the cell cycle. In OED, heightened PCNA levels indicate an increased cell proliferation index, creating a favourable environment for the accumulation of genetic alterations and potential cancer development. Consequently, monitoring PCNA expression emerges as a valuable prognostic tool for OED, signifying the potential for malignant transformation and emphasizing the necessity for sustained patient follow-up to identify any indications of possible malignancy. [7]

Cyclin D1

Oral carcinogenesis often involves disruptions in cell cycle control. Cyclin-dependent kinases (CDKs) and their inhibitors play a pivotal role in regulating the cell cycle. There are eleven cyclins, including D1-3 and E, which interact with CDK 4/6 and CDK 2, respectively, controlling the G1/S phase transition. Cyclin D1, located on chromosome 11q13, is a key regulator of the G1 phase. OED may exhibit molecular anomalies leading to cyclin D1 overexpression. [8-10] Cyclin D1 expression in oral dysplasia ranges from weak to strong in mild to moderate cases, predominantly in the middle layer. Severe dysplasia exhibits strong expression across all layers, particularly increased in basal and parabasal layers. [11]

P27

The p27 gene is part of the kinase inhibitor protein family and inhibits CDKs. Initially, it was known for limiting G1 cyclin-CDK complexes, controlling cell proliferation. However, p27's role in carcinogenesis goes beyond proliferation control. Tumor p27 levels don't always align with the proliferative index, and subcellular localization, like cytoplasmic localization, can be a negative prognostic factor. Changes in p27 expression are tied to cell dynamics in OED, occurring before invasive stages of oral tumorigenesis. [12-16]

P21

Although p21 serves as a critical cyclin-dependent kinase inhibitor essential for cell cycle regulation, its precise role in OED remains elusive. Numerous investigations into p21 expression in both OED and OSCC present conflicting findings, with some studies indicating decreased levels in comparison to normal oral mucosa, while others report increased expression. This variability suggests a multifaceted and context-dependent role for p21 in OED and OSCC. One plausible explanation for reduced p21 expression could be linked to the inactivation of the p53 tumor suppressor pathway. As a downstream target of p53, p21 expression is induced by p53 in response to DNA damage or stress signals, potentially resulting in decreased expression if p53 function is compromised in OED and OSCC. Conversely, elevated p21 expression in these conditions may be attributed to the activation of alternative pathways governing p21 expression. Examples include the Akt/mTOR pathway, which some studies propose as a contributor to increased p21 expression in OSCC.

Additionally, cell cycle phase accumulation, particularly in the G1 phase, has been suggested as a factor associated with heightened p21 expression in OED and OSCC. The intricate dynamics of p21 in these conditions underscore the need for further research to unravel the underlying mechanisms and assess the potential utility of p21 as a diagnostic or prognostic marker. [17]

MDM2

MDM2 (Murine double minute 2), an oncogene, acts as a negative regulator of the p53 tumor suppressor pathway, frequently compromised in OED and OSCC. MDM2's role involves promoting p53 degradation through ubiquitination and subsequent proteasomal breakdown, potentially contributing to p53 inactivation in OED and OSCC. Studies on MDM2 expression in these conditions present conflicting findings, with some reporting increased expression compared to normal oral mucosa and others finding no significant difference. The relationship between MDM2 expression and clinical outcomes remains unclear. Recent research suggests a potential therapeutic role for MDM2 in cancer treatment. Anti-MDM2 antisense oligonucleotides have shown promising in vitro and in vivo activities against various human cancer models, inducing p21 regardless of p53 status. However, the complex role of MDM2 in OED and OSCC requires further investigation to unravel dysregulation mechanisms and assess its potential as a diagnostic, prognostic marker, or therapeutic target. [17]

p53

P53, also known as tumor protein 53, plays a crucial role in maintaining cellular balance, and its mutations are often linked to factors such as alcohol and tobacco use. Various studies have established a positive connection between p53 expression and tumor progression. However, it's worth noting that overexpression of this protein can be influenced by the location of lesions, being more common in areas with high sun exposure. Additionally, the presence of p53 protein is absent in squamous cell carcinomas but is observed in patients who have undergone immunosuppressive treatments, like organ transplant recipients. This suggests that the immune system also regulates the expression of this protein. In premalignant oral lesions, increased p53 expression typically correlates with the degree of epithelial dysplasia, indicating an elevated risk of malignant transformation. Many research teams have concluded that in the case of premalignant oral lesions, the level of p53 expression directly correlates with the risk of developing squamous cell carcinoma, even after long-term monitoring of these lesions' progression. [18-20] Immunohistochemical patterns correlated with P53 mutations and high SCC risk, emphasizing the need for improved diagnosis beyond WHO classification. [21]

Her2

The human epidermal growth factor receptor-2/neu (ErbB) protein, a member of the tyrosine kinase receptor family, plays a crucial role in cellular growth and differentiation. Dysregulation of HER-2/neu is associated with uncontrolled cell cycle, resistance to apoptosis, invasiveness, chemo-resistance, and angiogenesis. Overexpression of HER-2/neu has been linked to poor clinical outcomes in various cancers, including breast, ovarian, osteosarcoma, endometrial, salivary, and gastric carcinomas.

Studies on HER-2/neu in OSCC show variable and discordant results, with incidence ranging from 0 to 40%. Targeted therapies against HER-2/neu have shown efficacy in breast, gastric, and lung cancers. [22] Evaluating HER-2/neu expression in OPMDS and OSCC will help identify a potential biomarker for specific immunotherapy against OSCC, suggesting a valuable avenue for further clinical investigation.

Rb

The retinoblastoma (Rb) tumor suppressor gene regulates cell cycle progression and differentiation through its protein product, Retinoblastoma tumor suppressor protein (pRb). pRb acts as a regulator at the G1-S restriction point, inhibiting growth in mid G1-S phase. Mutations lead to functional pRb inactivation and failure of tumor suppression. In oral cancer, there is evidence of dysfunctional Rb protein pathways. In oral cancer, abnormal Rb protein types or reduced Rb production may lead to low availability of functional pRb. Rb plays a crucial role in terminal differentiation, influencing cell cycle withdrawal and gene modulation for a differentiated phenotype. [23]pRb is considered a tumor suppressor protein rather than a specific molecular marker. Tumor suppressor proteins, like Rb, play a crucial role in regulating cell cycle progression and preventing the development of tumors. This protein is not typically used as a diagnostic marker in the same way as specific molecular markers but is studied for its involvement in cancer development and progression.

Stathmin

Stathmin plays a crucial role in regulating the microtubule cytoskeleton by influencing microtubuledynamics. It facilitates the depolymerization of microtubules and inhibits the polymerization of tubulinheterodimers. This depolymerization process involves sequestering free tubulin dimers or directlyinducing microtubule catastrophe. Numerous studies on stathmin indicate its frequent overexpression. in various human cancers, highlighting its close correlation with cancer cell differentiation, TNMclassification, and lymph node metastases. The observed overexpression of stathmin is linked tosustained cancer cell proliferation, underscoring its significance in tumorigenesis and tumordevelopment. Stathmin serves as a valuable oncobiological marker and a potential molecular target forcancer therapy. [24]

S100

The S100 protein family, with its diverse distribution in the cytoplasm and cell organelles, plays amultifaceted role in cellular functions, largely attributed to its calcium-binding properties. In thecontext of oral epithelial dysplasia, S100's functions include regulation of cell proliferation, celldivision, Ca2+ homeostasis, structural organization of membranes, dynamics of cytoskeletonconstituents, cell growth, motility, survival, enzyme activation, protection from oxidative damage, andinvolvement in protein phosphorylation and secretion. While intracellularly, S100 controls the cellcycle, extracellularly, it acts as a cytokine binding to receptors like RAGE and TLRs. In cancer,dysregulation of S100 proteins is linked to differentiation, with varied expressions observed indifferent members of the S100 family. Notably, S100A14 has been implicated in modulating theexpression of MMP1 and MMP9 in invasive tumor cells of OSCC, providing insights into its potentialrole in the prognosis of OED.[25]

P16

P16, or MTS1 (multiple tumor suppressor 1), is a tumor suppressor that interacts with p21, CDK, andPCNA. It regulates cell proliferation, differentiation, and apoptosis independently of p53. In OSCCcases originating from precursor lesions, about 24% show mutations in the gene responsible for p16production. [26,27]Post-transplant immunosuppressed patients exhibit p16 overexpression inpremalignant and malignant lesions. Methylated p16 might serve as a marker for malignancy and isfound in premalignant lesions and neighbouring epithelium. Moreover, p16 overexpression may beassociated with an infectious cause related to human papillomavirus (HPV) [28]

EGFR

Cytogenetic analysis in head and neck tumors reveals oncogene activation, tumor suppressor geneinactivation, and growth factor expression, including EGF, TGF-α, TGF-β, and FGF, along with EGFRreceptors. EGFR, overexpressed in oral cancers, has become a promising target for monoclonalantibody therapy. Its high expression is linked to tumor size, metastasis, and survival. Exploringmutations in the EGFR 2 gene can provide insights into its overexpression in oral cancer.

Tumors withhigh EGFR expression respond better to chemotherapy, possibly due to increased proliferative activity.Early overexpression of TGF-α in oral carcinogenesis, along with EGFR, may indicate moreaggressive tumors. [29, 30]

Survivin

Survivin, a member of the inhibitor of apoptosis (IAP) protein family, holds significance in cancer dueto its role in regulating mitosis and apoptosis. Highly expressed in various malignancies, includingOSCC, survivin is associated with aggressive disease and poor clinical outcomes. Studies on survivingene polymorphisms indicate their potential utility in disease prognosis and diagnosis, influencingtumor aggressiveness and patient survival. Survivin's differential expression in cancer cells, coupledwith its involvement in key cellular pathways, positions it as a promising target for therapeuticinterventions. In the context of OED, survivin's intricate role and potential as a diagnostic or prognosticmarker necessitate further investigation. [31]

HIF-1α

In oral carcinogenesis, HIF-1α plays a pivotal role in orchestrating various pathways that contribute toa more aggressive tumor phenotype, characterized by metastases and the promotion of epithelialmesenchymal transition (EMT). HIF-1α is a central transcription factor involved in the metabolicadaptation of cancer cells, particularly in the shift from oxidative phosphorylation to glycolysis. Thestabilization of HIF-1α, both under hypoxic and normoxic conditions, is associated with alterations inglucose and glutamine metabolism, leading to increased energy consumption for enhanced tumor cellproliferation. Additionally, HIF-1α upregulates key proteins such as carbonic anhydrase IX (CA IX),hexokinase 2 (HK2), and various proton exchangers, contributing to the acidification of the tumormicroenvironment. The lowered extracellular pH serves as a driving force in the early stages of EMT,further promoting cancer aggressiveness. Numerous studies have highlighted the prognosticsignificance of HIF-1α expression in OSCC, suggesting its potential utility as an independentprognostic marker for patient outcomes. [32]

GLUT1 & HK2

Glucose metabolism is essential for cellular energy production, and its dysregulation is associated with tumorigenesis. Glucose transporters (GLUTs) facilitate glucose entry into cells, and hexokinases (HKs), particularly HK-II, are key enzymes in glycolysis. In OED progression, the overexpression of GLUT-1 and HK-II is observed, contributing to the Warburg effect, a phenomenon where cancer cells favor glycolysis for energy production. This heightened glycolytic activity is crucial for the increased energy demands of rapidly proliferating malignant tumors. Aberrant expression of GLUT-1 and HKII is linked to invasion and metastasis in head and neck cancers, including OED. Furthermore, their abnormal expression is associated with the hypoxic tumor microenvironment. Inhibition of GLUT-1 and HK-II has shown promise in improving the treatment efficacy of malignant tumors, suggesting a potential

novel therapeutic strategy for head and neck cancers, including OED. [33]

β-catenin

In oral epithelial dysplasia, β-catenin's dynamic subcellular localization serves as a pivotal factor inunderstanding the progression towards oral cancer. There is an intriguing pattern where dysplastic oralkeratinocytes exhibit high nuclear accumulation of β-catenin, contrary to the cytoplasmicpredominance observed in oral carcinoma. Unlike some malignancies, mutations in Wnt/β-cateninpathway components are not prevalent in oral carcinogenesis. Instead, the overproduction of Wntligands, notably Wnt3a, emerges as a potential explanation for aberrant pathway activation. Thisheightened Wnt/β-catenin activity, facilitated by increased Wnt ligand release, may contribute to theproliferation of dysplastic cells. Moreover, epigenetic silencing of Wnt inhibitors and the potentialinvolvement of pathways like PI3K-Akt and EGFR warrant further exploration. Understanding theintricate role of β-catenin in dysplasia could offer insights into prognosis and therapeutic interventionsfor oral precancerous lesions. [34]

PTEN

PTEN (Phosphatase and tensin homologue deleted on chromosome 10) is a tumor suppressor generather than a direct marker. As a tumor suppressor gene, PTEN encodes a protein that plays a criticalrole in regulating cell growth, proliferation, and survival by inhibiting the PI3K/AKT signalingpathway. PTEN acts as a phosphatase, dephosphorylating phosphatidylinositol triphosphate (PIP3),which leads to the activation of AKT (Protein kinase B). The loss or inactivation of PTEN function isoften associated with various cancers, including OSCC, and is implicated in tumorigenesis. In thiscontext, PTEN serves as a marker for dysregulation of the PI3K/AKT pathway and a potential indicatorof malignant transformation of OED. [35]

Matrix Metallo Proteinases

Matrix metalloproteinases (MMPs) degrade the extracellular matrix during tumor progression. Highlevels of MMP-1, MMP-2, and MMP-9 in severe dysplasia are linked to poor prognosis. Notably,MMP-2, normally absent in healthy mucosa, increases with dysplasia. MMP-9 shows promise as aprognostic marker in oral cancer, with elevated levels in lesions with malignant potential. However,its role as a reliable biomarker requires additional research. [36]

Vimentin

Vimentin, traditionally a mesenchymal structural protein, now regulates cellular functions, impactingmigration, signalling, adhesion, and tumor metastasis. Overexpression, notably in OSCC, correlateswith unfavourable outcomes. Molecular markers' localization at invasive fronts holds significantprognostic value. Abnormal vimentin expression strongly links to tumor invasion and metastasis, withlimited exploration in precancerous lesions, except for its confirmation in hyperkeratotic oral mucosallesions. [37-40]

E-cadherin

E-cadherin, a 120-kDa glycoprotein, facilitates cell adhesion and inhibits proliferation in epithelialtissues. Decreased E-cadherin expression is linked toaggressiveness and poor outcomes in variouscarcinomas. In OED, reduced E-cadherin predicts higher disease risk, invasion, and a worse prognosis,making it a vital prognostic biomarker.[41-43] In a study by Nagiredla Puneeta et a lin oral dysplasia,E-cadherin expression decreases progressively from mild (90%) to severe (70%). Notably, there is asignificant

shift from membranous to cytoplasmic localization with increasing dysplasia severity. [44]

Bcl-2

Cancer arises when mutations disrupt the regulation of apoptosis and cell survival mechanisms. Theseprocesses are controlled by various gene sets, with the Bcl-2 family being prominent. This familyincludes both pro- and anti-apoptotic members that share sequence homology in their Bcl-2 homologydomains. Bcl-2, initially identified in human follicular non-Hodgkin's B-cell lymphomas, is a proto-oncogene. The Bcl-2 protein, weighing 26 kDa, is found in the nuclear envelope, endoplasmicreticulum, and the outer mitochondrial membrane, encoded by chromosome 18q21. Bcl-2's role inprolonging cell survival can lead to the accumulation of additional mutations in other tumor suppressorgenes and oncogenes, contributing to clonal progression. [45-48]

c-myc

The c-myc gene plays a pivotal role in promoting transcription and cellular proliferation throughcyclin-dependent kinase initiation. In HNSCC, C-Myc influences EMT by altering adhesion proteinsand inducing MMPs, notably MMP-9. The progression of HNSCC is further influenced by thecollaboration of C-Myc with genes like cyclin D1 and hypoxia-inducible factor (HIF)-related genessuch as VEGF. The BCL2 gene, known for its role in inhibiting cell death through the Bcl-2 protein,parallels c- myc in cancer development. [49]

Fascin

Fascin, an up-regulated actin cross-linking protein in various carcinomas, crucially influences theprognosis of OED. Primarily expressed in motile cells, it orchestrates the organization of cellularprotrusions, contributing to cell migration and the progression of carcinomas. In oral cancer, fascin'stight bundling of F-actin and early up-regulation play a pivotal role in the transition from normalepithelium to invasive OSCC, underscoring its significance as a prognostic marker for OED. [50]

COX-2/PGE2

COX-2/PGE2 plays a crucial role in oral epithelial dysplasia. In this context, inflammation induced byCOX-2/PGE2 stimulates the division of initiated tumour cells, inhibits cell death, and promotesangiogenesis, allowing the tumour to grow. This process involves the production of cytokines, ROS,and activation of transcription factors like NF-κB and STAT3. Ultimately, COX-2/PGE2 contributesto the progression of OED through multiple mechanisms, including oxidative stress, immunesuppression, and angiogenesis. [51]

VEGF

Solid tumors, constrained to 1–2 mm^3 without ample blood supply, necessitate angiogenesis forgrowth, invasion, and metastasis. [52] In the oral cavity, 10–20% of dysplastic lesions progress tocarcinomas. [53] Studies reveal increased vascularity from normal oral mucosa to invasive carcinomaduring dysplasia progression. Significantly, a robust association between tumor angiogenesis and theprogression of OSCCs is noted. Vascular endothelial growth factor (VEGF) assumes a crucial role infostering angiogenesis across various tumor types, with numerous studies extensively exploring itsinvolvement in the context of oral dysplasia and cancers. [54-57]

CK19

CK19 expression varies in oral conditions like normal, hyperplasia, dysplasia, and OSCC acrossstudies. Unlike some reports, normal oral mucosa shows CK19 in both keratinized and nonkeratinizedepithelium. Focal epithelial hyperplasias display inconsistent CK19 expression in association withinflammation. Dysplasia

challenges the expected progressive increase, with a decline in mild andmoderate cases and a significant rise in severe dysplasia. OSCC's CK19 expression is inconsistent indifferent studies. These findings highlight CK19's complex role in oral conditions. Further explorationof CK19 as a prognostic marker in oral epithelial dysplasia is warranted, considering the variationsobserved. [58-61]

CD44

CD44, implicated in cancer cell migration, is cleaved by MT1-MMP. TGF-B induces MT1-MMP.CD44 is a CSC marker in head and neck SCC, contributing to drug resistance and EMT. CD44'spleiotropic role includes interaction with hyaluronate, fibronectin, and collagen, crucial for cell-cell/matrix interactions, migration, and tumor progression. The EMT process is vital for variousphysiological processes and correlates with the invasive behavior of cancers like head and neck SCC.[62]

SOX2

SOX2, implicated in OSCC, exhibits varied expression in OPMDs like leukoplakia. Its overexpression,observed in OPMDs, suggests a potential role in OSCC pathogenesis. However, conflicting findingsassociate SOX2 with both poor and improved prognosis in OSCC, necessitating further explorationfor accurate prognosis in oral epithelial dysplasia.[63]

CD133

CD133, also known as Prominin-1, has emerged as a pivotal marker with significant implications inthe prognosis of OED, OSCC and other malignancies. CD133, characterized by an N-terminalextracellular domain, five transmembrane domains, and an intracellular cytoplasmic tail withfunctional tyrosine kinase sites serves as a surface marker for Cancer Stem Cells (CSCs). Originallyidentified as a hematopoietic stem cell marker (Ravindran and Devaraj, 2012), CD133 has evolvedinto a key CSC marker for solid tumors, encompassing breast, gastric, pulmonary, hepatic, prostate,pancreas, and thyroid cancers. In the context of OED, CD133's significance lies in its ability to identifyand characterize CSCs, which play a crucial role in tumor initiation and progression. Its presence as amarker suggests a potential association with the aggressiveness and prognosis of OSCCs. As CD133is linked to distinct cytoplasmic interactions and possesses tyrosine kinase sites, it likely participatesin intricate signalling pathways that influence the behavior of cancer cells. [64]

OCT 4

The OCT4 gene (octamer binding transcription 4), essential for regulating early-stage growth anddevelopment, undergoes decreased expression following cell differentiation and maturation. In OSCC,positive OCT4 immunohistochemical expression is linked to significantly inferior overall survivalrates. Particularly, the prognosis becomes notably unfavourable in cases of triple-positive OSCC(OCT4/NANOG/CD133), underscoring the adverse impact of these combined markers on outcomes.[65]

NANOG

NANOG, a key regulator in the development and progression of OSCC, emerges as a significant factorin the prognosis of OED. NANOG expression is notably absent in normal tissue but is significantly upregulated in OSCC, especially in cases with nodal metastases, suggesting its potential as aprognostic biomarker. Immunohistochemical analysis of NANOG usually reveals positive staining ina substantial proportion of OSCC cases, displaying a cytoplasmic pattern distinct from the nuclearpattern observed in germ-cell tumors. While the significance of these different staining patterns

remains unclear, their presence in dysplastic epithelium adjacent to OSCC further emphasizes the roleof NANOG in tumor development. Despite its crucial role in OSCC, the regulation of NANOGexpression is not fully understood. The positive correlation between NANOG and mRNA levels ofselected protein regulators (AGR2, KLF4, NOTCH1, OCT4, and SOX2) in tumor tissue samplesunderscores their influence on NANOG expression in OSCC. [66]

BAX

Bax (Bcl2 associated x protein), identified as a pro-apoptotic member of the Bcl-2 protein family, playsa critical role in governing programmed cell death or apoptosis. Specifically implicated in the intrinsicpathway of apoptosis, activated by cellular stresses such as DNA damage and oxidative stress, Baxundergoes a structural alteration and relocates to the mitochondria. There, it facilitates the release ofcytochrome c and other pro-apoptotic factors, initiating caspase activation and eventual cell demise.

In the context of OED, a decline in Bax expression signifies potential dysregulation in apoptosismechanisms, hindering the elimination of genetically damaged cells and escalating the risk ofmalignant transformation. Several studies propose that this reduction in Bax expression is pivotal inthe onset and advancement of oral cancer, underscoring its significance in understanding theunderlying mechanisms influencing the transformation of oral epithelial cells.[7]

Laminin and fibronectin

In OSCC, variations in laminin and fibronectin isoforms play a crucial role in cellular processes suchas adhesion and motility. The basement membrane (BM) composition changes during cellularmaturation, with fetal oral squamous epithelium containing laminin chains α2, α3, α5, β1, β2, β3, γ1,and γ2, while adult normal oral squamous epithelium comprises α3, α5, β1, β3, γ1, and γ2. Adulthyperproliferative, dysplastic, and carcinomatous lesions show re-expression of laminin α2 and β2chains. OED and OSCC exhibit BM breaks, correlating with malignancy grade. In the invasion front, laminin-5 chains α3 and γ2 are found outside the BM, suggesting laminin-5 as animmunohistochemical marker for invasion and indicating a guiding role in OSCC invasion. Oncofoetalfibronectins, specifically ED-B fibronectin, are expressed in the stromal compartment, particularly inareas of desmoplasia where stromal myofibroblasts contribute to the fetal extracellular matrix milieu.Overall, OSCC demonstrates a fetal extracellular matrix conversion involving both tumor cells andrecruited stromal myofibroblasts. [67]

Conclusion

OED serves as a critical precursor to OSCC. The significance lies in tumor markers, which arepowerful tools for identifying high-risk OED patients and facilitating timely intervention. However,the underutilization of these markers underscores a missed opportunity for predicting OED prognosis.

Their effective integration into clinical practice is essential. Embracing tumor markers can transformOED management, offering a lifeline to individuals at risk of developing oral cancer, emphasizing thevital role they play in early detection and improved outcomes.

Table 1

Markers based on their roles in evaluating the progression of OED to OSCC.

Marker	Low-Risk Patients	High-Risk Patients
Proliferation Markers		
Ki-67	Decreased	Increased
PCNA	Decreased	Increased
Cell Cycle Regulation		
Cyclin D1	Decreased	Increased
P27	Increased	Decreased
P21	Increased/ Decreased	Increased/ Decreased
MDM2	Decreased	Increased
P53	Decreased	Increased
HER2	Decreased	Increased
Rb	Decreased	Increased
Stathmin	Decreased	Increased
S100	Decreased	Increased

Genetic and Molecular Markers		
p16	Increased	Decreased
EGFR	Increased	Decreased
Survivin	Increased	Decreased
HIF-1α	Increased	Decreased
GLUT-1	Increased	Decreased
HK2	Increased	Decreased
β-catenin	Increased	Decreased
PTEN	Increased	Decreased
Matrix Metalloproteinases Enzymes		
MMP 1	Decreased	Increased
MMP 2	Decreased	Increased
MMP 9	Decreased	Increased
Epithelial-to-Mesenchymal Transition (EMT) Markers		
Vimentin	Increased	Decreased
E-cadherin	Increased	Decreased
c-myc	Increased	Decreased
Fascin	Increased	Decreased
Cell Adhesion and Migration		
Bcl2	Decreased	Increased
Angiogenesis and Inflammation Markers		
COX-2/PGE2	Increased	Decreased
VEGF	Increased	Decreased
VEGF	Increased	Decreased
Differentiation and Tumor Initiation		
CK19	Decreased	Increased
Cancer Stem Cell Markers		
CD44	Increased	Decreased
SOX2	Increased	Decreased
CD133 (Prominin 1)	Increased	Decreased
OCT4	Increased	Decreased
NAN0G	Increased	Decreased
Pro-apoptotic Markers		
P53	Increased	Decreased
BAX	Increased	Decreased
Matrix Proteins		
Laminin	Decreased	Increased
Fibronectin	Decreased	Increased
* These markers collectively aid in evaluating the prognosis and risk of malignant transformation in OED, with each category playing a distinct role in the assessment.		

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