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International Journal of Histopathol Interpret

Review Article

The Intersection of Genetic and Molecular Biology in Oral Potentially Malignant Disorders: Identifying Key Biomarkers and Pathways for Clinical Intervention

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How to cite: ***Hema Shree K.,The Intersection of Genetic and Molecular Biology in Oral Potentially Malignant Disorders: Identifying Key Biomakers and Pathways for Clinical Intervention. Int J Histopathol Interpret 2024; 13(2):1-9.***

DOI: ***https://doi.org/10.56501/intjhistopatholinterpret.v13i2.1133***

Received:18/06/2024 *Accepted:25/06/2024* *Web Published:26/07/2024*

Abstract

Oral Potentially Malignant Disorders (OPMDs) and oral cancer, as an intricate interplay of genetic and molecular factors, have been a central area of study. Researchers have sought to delineate key biomarkers and pathways for potential clinical intervention. The understanding of these genetic and molecular factors is crucial for informed decision-making and patient care. Studies have demonstrated that OPMDs create a field of specific abnormalities known as 'oral field cancerization,' wherein genetically altered cells can predispose to malignancies in multiple oral cavity areas. Molecular investigations have revealed both overexpressed and underexpressed genes in precancerous oral lesions, shedding light on the involvement of oncogenic pathways and proinflammatory conditions in the progression of oral cancer. Furthermore, bioinformatics analyses have brought to the fore crucial genes, such as IRF4, CCR7, TNFRSF17, CD27, and S1PR4, which play substantial roles in oral squamous cell carcinoma and may serve as prognostic markers and potential therapeutic targets. The integration of genetic risk scores with environmental factors has demonstrated promise in identifying high-risk individuals for oral squamous cell carcinoma, underscoring the significance of early screening and intervention strategies to mitigate the incidence of oral cancer. A thorough comprehension of these alterations is essential for prompt evaluation, prognosis, and the creation of focused treatments. This article delves into the genetic and molecular profiling of OPMDs, emphasizing key biomarkers, pathways, and the clinical implications of these discoveries.

Keywords: biofilm, oral squamous cell carcinoma, microbiome, dysbiosis, inflammation

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INTRODUCTION

The high death rate and frequent detection of advanced stages of the disease make oral cancer a significant global public health problem. This underscores the vital necessity for early detection and intervention. It is noteworthy that the idea of "oral field cancerization" has been demonstrated to be crucial in the development of oral cancer from potentially malignant conditions. This emphasizes how crucial it is for high-risk individuals to have routine screens and molecular testing [1, 2]. By being proactive in regular screenings, we can identify potential issues early and take necessary preventive measures. Molecular studies focusing on gene expression profiles in premalignant oral lesions have identified essential genes and pathways involved in the progression to oral cancer, offering insights into potential therapeutic targets and diagnostic biomarkers for early intervention [3]. Consequently, researchers aim to improve treatment strategies and patient outcomes by scrutinizing the molecular mechanisms, prognostic markers, and therapeutic targets associated with oral squamous cell carcinoma, focusing on personalized and targeted interventions [4].

The formation of OPMDs is influenced by a complex interplay of genetic and environmental variables within the mouth cavity. Despite the challenges, genetic and molecular profiling offers a promising approach to understanding the underlying mechanisms of these disorders and improving clinical outcomes [5]. This potential should inspire and motivate us in our research and clinical practice, driving us to further explore and utilize these tools to benefit our patients.

GENETIC ALTERATIONS IN OPMDS

Genetic alterations are known to impact the development of OPMDs significantly. Gene mutations controlling DNA repair, programmed cell death, and cell development are frequently involved in these alterations. A key factor in the advancement of OPMDs is the inactivation of tumour suppressor genes, such as TP53. A higher likelihood of malignant transformation is associated with TP53 gene mutations, which are frequently found in a variety of OPMDs [6]. The loss in TP53 function affects the normal control of cell proliferation and cell death, resulting in the buildup of genetic mutations and tumour formation. Oncogenes like RAS and MYC that are activated also have a role in the unchecked cell growth observed in OPMD infections. The transformation of pre-malignant cells into invasive cancer is aided by aberrant signaling pathways created when certain oncogenes are mutated or overexpressed [7].

CELL CYCLE REGULATION

Changes in genes controlling the cell cycle have a major role in the onset and progression of potentially malignant oral illnesses (OPMDs). The gene CDKN2A, which produces the tumour suppressor protein p16^INK4a, is one of the most important of these proteins [8]. Cyclin-dependent kinase 4 and 6 (CDK4/6) are mostly inhibited by the p16^INK4a protein, which is vital for controlling the cell cycle. These kinases bind to cyclin D1 and phosphorylate the protein that makes up retinoblastoma (RB). This process releases transcription factors called E2F, which propel a cell through the G1 phase to the S phase, which is the stage of the cell cycle where DNA replication takes place [8]

By blocking CDK4/6 and keeping cells in the G1 phase, p16^INK4a functions as a checkpoint in regular cellular processes to prevent unchecked cell division. Before cell division occurs, this checkpoint function ensures genomic stability by facilitating repair of DNA and other regulatory mechanisms. On the other hand, p16^INK4a function may be lost in OPMDs due to changes in the CDKN2A gene [9]. This loss eliminates the inhibitory regulation on CDK4/6, which leads to uncontrolled cell cycle progression, uncontrolled phosphorylation of RB, and continuous release of E2F. In patients with OPMDs, cell cycle

dysregulation is largely caused by the loss of p16^INK4a function [9]
Unchecked cell cycle progression increases the likelihood of accumulating genetic mutations, as the standard regulatory mechanisms that would typically halt the cycle for DNA repair are bypassed. The likelihood that OPMDs will develop into OSCC, is increased by the unchecked proliferation and genetic instability that are characteristics of malignant transformation [10]

The cell cycle deregulation in OPMDs is largely caused by overexpression of cyclin D1, along with the loss of p16^INK4a function. As cyclin D1 is encoded by the CCND1 gene, which forms complexes with CDK4/6, it plays a crucial role in advancing the cell cycle through the G1 phase into the S phase [11] Overexpression of cyclin D1, often observed in OPMDs, leads to excessive activation of CDK4/6. This heightened activation further phosphorylates RB beyond normal regulatory levels, pushing the cell cycle forward irrespective of cellular checkpoints [12]

Cyclin D1 overexpression can occur due to gene amplification, increased transcription, or other post-transcriptional modifications that enhance its stability and activity. In the context of OPMDs, elevated levels of cyclin D1 are associated with increased cell proliferation, reduced sensitivity to growth-inhibitory signals, and evasion of apoptosis, all of which contribute to the malignant potential of these lesions [13]

The interplay between p16^INK4a inactivation and cyclin D1 overexpression highlights a critical axis of cell cycle regulation disruption in OPMDs. This dysregulation promotes uncontrolled cellular proliferation and fosters an environment conducive to additional genetic alterations and tumorigenic processes [14]. For instance, cells with compromised p16^INK4a function and elevated cyclin D1 are more likely to evade cellular senescence, a state of irreversible growth arrest that acts as a barrier to malignant transformation [15].

Furthermore, the dysregulation of the cell cycle in OPMDs affects various downstream signaling pathways and cellular processes. One possible explanation for the chromosomal instability frequently seen in these disorders is that the abnormal stimulation of E2F target genes results in the transcription of genes involved in the replication of DNA, repair, and mitosis [16]. This instability can drive the clonal evolution of cells, leading to the emergence of more aggressive and invasive phenotypes.

From a clinical perspective, the alterations in CDKN2A and CCND1 serve as valuable biomarkers for diagnosing and prognosis of OPMDs. Loss of p16^INK4a expression, detectable by immunohistochemistry, is a marker of increased malignant potential and is often used to identify high-risk lesions.[17] Similarly, overexpression of cyclin D1 can be assessed through various molecular techniques, providing insights into the proliferative status and aggressiveness of the lesion [11].

Understanding cell cycle dysregulation in OPMDs also opens avenues for targeted therapeutic interventions. For example, CDK4/6 inhibitors, which have shown efficacy in other cancers, could be explored as potential treatments for OPMDs with p16^INK4a loss or cyclin D1 overexpression. By restoring control over the cell cycle, these inhibitors may reduce cellular proliferation and prevent the progression of OPMDs to invasive cancer [9].

DNA REPAIR GENES

Defects in DNA repair genes, such as BRCA1 and BRCA2, significantly contribute to genomic instability in oral potentially malignant disorders (OPMDs). Because of their functions in homologous recombination repair—a precise process that fixes DNA double-strand breaks—these genes are essential for preserving genomic integrity. When BRCA1 or BRCA2 functions are compromised, the efficiency of DNA repair is

drastically reduced, leading to the persistence of DNA damage [18]. This impaired DNA repair mechanism allows for the accumulation of mutations and chromosomal abnormalities, enhancing the malignant potential of the affected cells. The continuous build-up of genetic alterations can drive the progression of OPMDs towards malignancy, increasing the risk of developing oral squamous cell carcinoma. The heightened genomic instability caused by these defects not only promotes tumorigenesis but also contributes to the heterogeneity and aggressiveness of the resulting cancers, posing significant challenges for diagnosis, prognosis, and treatment [19]

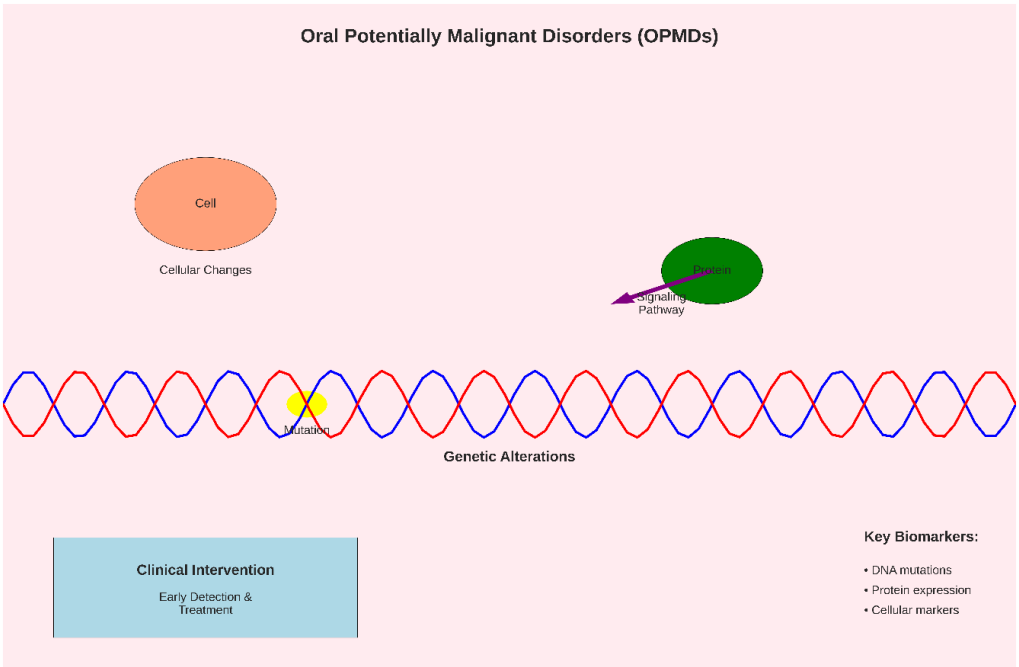

Figure 1. Genetic Alteration in OPMDs

EPIGENETIC MODIFICATIONS

Epigenetic modifications are important in the development of OPMDs in addition to genetic abnormalities. Gene expression is influenced by epigenetic modifications, which do not alter the DNA sequence. These modifications include histone modifications, DNA methylation, & regulation by non-coding RNA [20]

i. DNA Methylation

DNA methylation anomalies, such as hypermethylation of tumor suppressor gene promoters, are common in OPMDs. Certain genes, including MGMT and CDKN2A, become repressed due to hypermethylation, which aids in the loss of their tumor suppressor properties and encourages the development of cancer [21]

ii. Histone Modifications

Histone alterations including methylation, acetylation, & phosphorylation are essential for chromatin remodeling and gene expression. Histone-modifying enzyme dysregulation, including that of histone methyltransferases and deacetylases (HDACs), has been linked to OPMDs. These changes affect gene expression in cell division, proliferation, and apoptosis [22].

iii. Non-Coding RNAs

Non-coding RNAs, such as microRNAs and longer non-coding RNAs (lncRNAs), are becoming increasingly important in controlling gene expression in OPMDs. Dysregulation of specific miRNAs, such as miR-21 and miR-31, has been linked to the pathogenesis of OPMDs. These miRNAs can act as oncogenes or tumor suppressors, modulating key signaling pathways and cellular processes [22]

MOLECULAR PATHWAYS IN OPMDS

Several molecular pathways are dysregulated in OPMDs, contributing to their malignant potential. Understanding these pathways provides insights into the mechanisms driving the progression of OPMDs and identifies potential therapeutic targets.

i. PI3K/AKT/mTOR Pathway

OPMDs and OSCC commonly exhibit activation of the PI3K/AKT/mTOR pathway. This route inhibits apoptosis while promoting angiogenesis, cell survival, and proliferation. Genetic alterations, such as PIK3CA mutations and PTEN loss, contribute to its dysregulation. Targeting the PI3K/AKT/mTOR pathway with specific inhibitors holds promise for treating OPMDs and preventing their malignant transformation.

ii. EGFR Signaling

EGFR signalling is frequently dysregulated in OPMDs. Higher cell survival and proliferation are caused by overexpression of EGFR & its associated ligands, including TGF-α and EGF. EGFR inhibitors, such cetuximab, have demonstrated effectiveness in managing OSCC and may hold promise in the treatment of OPMDs characterised by dysregulated EGFR signalling.

iii.Wnt/β-catenin Pathway

The Wnt/β-catenin pathway contributes to the migration, differentiation, and proliferation of cells. OPMDs are characterised by aberrant stimulation of this system, which is caused by mutations in components including APC and CTNNB1. The initiation and advancement of these lesions are attributed to the dysregulation of Wnt/β-catenin signalling. One possible treatment strategy is to use monoclonal antibodies or small molecule inhibitors to target this route.

iv. NF-κB Pathway

An essential regulator of immunological responses and inflammation is the NF-κB pathway. One established risk factor for OSCC and OPMDs is chronic inflammation. By inhibiting apoptosis and promoting cell survival and proliferation, the NF-κB pathway is activated through genetic changes or inflammatory signals. Targeting NF-κB signaling with specific inhibitors or anti-inflammatory agents may help manage OPMDs and reduce their malignant potential.

V. Notch Signaling

Cell differentiation and destiny determination are influenced by notch signalling. OPMDs are associated with dysregulation of Notch signalling caused by alterations in Notch receptor or ligands. Depending on the context, Notch signaling can act as an oncogene or tumor suppressor. Modulating Notch signaling with specific inhibitors or activators could provide therapeutic benefits in OPMDs.

CLINICAL IMPLICATIONS

The genetic and molecular profiling of OPMDs has significant clinical implications for diagnosis, prognosis, and treatment. Identifying specific genetic alterations and molecular pathways involved in OPMDs can aid in the early detection of lesions with a higher risk of malignant transformation. Molecular biomarkers, such as TP53 mutations, p16 expression, and miRNA signatures, can serve as diagnostic and prognostic indicators.

i. Early Detection and Diagnosis

Genetic and molecular profiling can enhance the early detection and diagnosis of OPMDs. Liquid biopsy approaches, such as exosomal miRNAs and circulating tumour DNA (ctDNA), provide non-invasive means for detecting genetic and molecular abnormalities associated with OPMDs.
These techniques can complement traditional biopsy and histopathological examination, providing a more comprehensive assessment of lesion risk [3]

ii. Prognostic Markers

Molecular markers can provide valuable prognostic information for patients with OPMDs. For instance, a lower prognosis and an increased likelihood of malignant transformation are linked to TP53 mutations and reduction of p16 expression. These markers can help stratify patients based on risk and guide clinical management decisions [18]

iii. Targeted Therapies

Understanding the genetic and molecular landscape of OPMDs opens new avenues for targeted therapies. Agents targeting specific pathways, such as PI3K/AKT/mTOR inhibitors, EGFR inhibitors, and Wnt/β-catenin modulators, hold promise for treating OPMDs and preventing their progression to OSCC. Based on individual genetic and molecular profiles, personalized medicine approaches can optimize treatment efficacy and minimize adverse effects.

iv. Prevention Strategies

Genetic and molecular profiling can inform prevention strategies for individuals at high risk of developing OPMDs. Identifying genetic predispositions and molecular alterations associated with OPMDs allows for implementing personalized prevention plans. Enhanced monitoring and early intervention strategies may prove advantageous for those with a familial history of OPMDs or genetic alterations that are known [11]

FUTURE DIRECTIONS

The genetic and molecular profiling of OPMDs is rapidly evolving, with ongoing research to uncover novel biomarkers and therapeutic targets. Advances in next-generation sequencing, single-cell analysis, and multi-omics approaches are expected to further elucidate the complex molecular landscape of OPMDs.

i.Next-Generation Sequencing

OPMDs can now be thoroughly analyzed for genetic and molecular changes thanks to next-generation sequencing (NGS) methods. Whole-exome sequencing, RNA sequencing, and epigenomic profiling provide detailed insights into the genetic and epigenetic alterations driving OPMDs. Integrating NGS data with clinical and pathological information can improve risk stratification and guide personalized treatment approaches. [4,5]

ii. Single-Cell Analysis

Single-cell analysis techniques allow for examining genetic and molecular heterogeneity within OPMDs. The clonal development and progression of OPMDs can be revealed by identifying subpopulations of cells with unique molecular profiles using single-cell sequencing of RNA (scRNA-seq) & single-cell DNA sequencing (scDNA-seq). Understanding this heterogeneity is crucial for developing targeted therapies and overcoming treatment resistance.

iii. Multi-Omics Approaches

A thorough understanding of the molecular changes in OPMDs is provided by multi-omics techniques that integrate data from proteomics, metabolomics, transcriptomics, and genomes. These approaches can uncover novel biomarkers and therapeutic targets, providing a holistic understanding of the disease. Advanced bioinformatics and computational tools are essential for analyzing and interpreting multi-omics data, facilitating the translation of these findings into clinical practice [7]

CONCLUSION

Genetic and molecular profiling of oral potentially malignant disorders is a rapidly advancing field with significant implications for early detection, prognosis, and treatment. Understanding the genetic alterations, epigenetic modifications, and dysregulated molecular pathways in OPMDs provides valuable insights into their pathogenesis and malignant potential. This knowledge paves the way for personalized medicine approaches, targeted therapies, and prevention strategies to improve clinical outcomes and reduce the burden of oral cancer. Continued research and technological advancements will further enhance our ability to diagnose, monitor, and treat OPMDs, ultimately contributing to better patient care and oral health.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICTS OF INTEREST

There are no conflicts of interest

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