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# The role of micro RNA-375 in oral leukoplakia: a Review

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**ABSTRACT:**
**Objectives:** This review synthesizes current knowledge on the role of microRNA-375 (miR-375) in oral leukoplakia (OL), focusing on its expression patterns, potential as a biomarker for malignant transformation to oral squamous cell carcinoma (OSCC), and underlying molecular mechanisms.
**Methods:** A literature search was conducted using the PubMed database to identify relevant studies investigating miR-375 in the context of OL, oral potentially malignant disorders (OPMDs), and OSCC. Key findings regarding expression, biomarker potential, target genes, and functional effects were extracted and synthesized.
**Results:** Evidence consistently indicates that miR-375 is downregulated in OL tissues, particularly in progressive lesions compared to non-progressive ones, and in OSCC compared to normal oral mucosa. Lower miR-375 levels are also observed in the saliva of patients with OPMDs, correlating with dysplasia and subsequent malignant transformation. miR-375 demonstrates high sensitivity and specificity as a potential biomarker for predicting malignant progression. Mechanistically, miR-375 acts as a tumor suppressor, partly by targeting KLF5, which leads to decreased proliferation and increased apoptosis via modulation of Survivin. Other potential targets include MYC and IGF oncogenes.
**Conclusions:** miR-375 is a key tumor-suppressive miRNA frequently downregulated during OL progression. It holds significant promise as a diagnostic/prognostic biomarker and potential therapeutic target for preventing OSCC development from OL.
**Clinical Relevance:** Assessing miR-375 levels, potentially non-invasively via saliva, could aid clinicians in risk-stratifying patients with OL, guiding monitoring strategies, and identifying candidates for targeted preventive therapies aimed at restoring miR-375 function.
**Keywords:** miR-375, microRNA, oral leukoplakia, oral potentially malignant disorder, biomarker, malignant transformation

## I. INTRODUCTION

Oral leukoplakia (OL) represents the most prevalent oral potentially malignant disorder (OPMD) encountered in clinical practice [1]. These disorders, including OL, are notable for their elevated risk of progressing to oral squamous cell carcinoma (OSCC), a significant global health concern. The transformation rate of OL to OSCC varies considerably, ranging from 3% to 17.5%, underscoring the heterogeneity of this condition and the complexity of its progression [2]. Early identification and appropriate management of OPMDs are crucial for diminishing the morbidity and mortality associated with OSCC [3].

Currently, the prediction of malignant transformation within OL remains a substantial clinical challenge due to the absence of reliable biomarkers capable of accurately forecasting this transition [4]. While histopathological analysis continues to be the diagnostic gold standard, its predictive capacity for malignant transformation is limited [5]. Consequently, there is an ongoing and critical need to identify the molecular factors that drive the progression of OL to malignancy, as these factors may also represent promising targets for the development of more effective and personalized therapeutic interventions [6]. The wide spectrum of transformation rates observed in OL underscores the fact that not all lesions possess the same propensity for malignant development. This inherent variability likely originates from underlying molecular distinctions, emphasizing the importance of identifying specific biomarkers that can facilitate personalized risk assessment and guide clinical management strategies [7].

MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules, typically about 22 nucleotides in length, that play a fundamental role in regulating gene expression at the post-transcriptional level [8]. These molecules primarily exert their regulatory effects by targeting messenger RNA (mRNA) molecules, leading to either the repression of protein translation or the direct cleavage of the mRNA transcript [9]. miRNAs are integral components of intricate cellular networks, influencing a wide array of

physiological, developmental, and pathological processes, including the initiation and progression of cancer [10]. Aberrant expression of miRNAs has been documented in numerous types of cancer, where they play critical roles in various aspects of tumorigenesis, such as cancer initiation, promotion, apoptosis evasion, invasion, and metastasis [11]. Depending on their specific target genes and the cellular context in which they function, miRNAs can act as either tumor suppressors, inhibiting cancer development, or as oncogenes, promoting it [10]. This dual nature of miRNAs highlights the intricate complexity of their involvement in cancer biology. Therefore, simply observing the dysregulation of a particular miRNA is insufficient; a thorough understanding of its specific targets and downstream effects within the context of OL is essential to fully appreciate its role in malignant transformation[12].

Among the various miRNAs implicated in cancer, microRNA-375 (miR-375) has gathered significant attention. It is frequently observed to be downregulated in a multitude of cancer types and often functions as a tumor suppressor [13,14]. Diminished levels of miR-375 have been associated with increased tumor size and enhanced invasiveness in OSCC [13]. Furthermore, in patients with tongue and laryngeal cancer, low expression levels of miR-375 have been correlated with poorer clinical outcomes [15]. Mechanistically, the underexpression of miR-375 can lead to the uncontrolled expression of CIP2A and the prolonged stability of MYC, both of which contribute to the development of cancerous characteristics in oral cells [5]. The consistent downregulation of miR-375 across a spectrum of cancers, including OSCC, suggests a potentially conserved tumor-suppressive role that may also be pertinent to the progression of OL [16]. If miR-375 indeed acts as a tumor suppressor in OSCC, its reduced expression in the pre-malignant stage of OL could represent an early event that contributes to the heightened risk of transformation. Investigating this potential link is therefore of paramount importance.

This review aims to synthesize the current body of research, derived from PubMed literature, focusing on the multifaceted role of miR-375 in OL. The objective is to provide a comprehensive summary of its expression patterns, its potential as a biomarker for malignant transformation, and the underlying molecular mechanisms through which it might exert its influence.

**Expression profile of miR-375 in Oral Leukoplakia**

Several studies have investigated the expression levels of miR-375 in OL tissues, comparing them to those found in healthy oral mucosa and in OSCC. One study reported that the abundance of miR-375 decreased in tissues as they progressed from a normal state to oral lichen planus (OLP) and subsequently to OSCC [17]. While the primary focus of this research was on OLP, these findings suggest a broader trend of miR-375 downregulation in oral premalignant conditions that are prone to cancerous transformation. Notably, another investigation specifically observed that miR-375 was downregulated in both OSCC and progressive OL when compared to non-progressive lesions [13]. This observation directly links lower levels of miR-375 expression to an increased likelihood of OL undergoing malignant transformation into cancer. The consistent finding of miR-375 downregulation in progressive OL and OSCC across different research endeavors strengthens the hypothesis that this particular miRNA plays a crucial role in suppressing the development of malignancy in the oral cavity. These independent studies, all reporting a similar trend of reduced miR-375 in lesions with a higher propensity for progression, lend greater credence to this finding and suggest a biologically significant role for miR-375 in the pathogenesis of oral cancer.

Further analysis of miR-375 expression during the different stages of oral tissue transformation reveals a notable trend. This suggests that the loss of miR-375's regulatory function might be a gradual process that contributes incrementally to the increasing malignant potential of these lesions. This gradual reduction in miR-375 expression during the progression from normal to premalignant to malignant stages implies a potential dose-dependent effect of miR-375 on tumor suppression. If miR-375 acts as a molecular brake on the processes leading to cancer, its progressive reduction could gradually release this brake, thereby facilitating the uncontrolled proliferation and diminished apoptosis that are characteristic hallmarks of cancer.

In addition to tissue-based analysis, the potential of utilizing miR-375 expression in saliva as a non-invasive biomarker has also been explored. One study examined salivary miR-375 levels in patients diagnosed with OPMD and in a group of healthy controls. The findings revealed that miR-375 levels were significantly lower in the saliva of patients with OPMD compared to the healthy individuals. Interestingly, among the OPMD

patients, those without dysplasia exhibited higher levels of salivary miR-375 than those with dysplasia, suggesting a possible correlation between miR-375 levels and the severity of the premalignant condition. Furthermore, patients who subsequently experienced malignant transformation during the follow-up period showed lower levels of salivary miR-375 expression compared to those who did not. The detection of downregulated miR-375 in the saliva of OPMD patients, with a further reduction observed in dysplastic lesions and in those undergoing malignant transformation, underscores the potential of salivary miR-375 as a non-invasive biomarker for the early detection of OPMDs and for assessing the risk of malignant progression [13]. Saliva, as a readily accessible biofluid, presents an ideal medium for non-invasive diagnostic approaches. The observed correlation between salivary miR-375 levels and the presence and severity of OPMD, as well as the risk of transformation, makes it a promising candidate for future clinical applications in oral cancer management.

**MiR-375 as a Biomarker for Malignant Transformation**

Several investigations have focused on evaluating the potential of miR-375 to serve as a predictive marker for the transformation of OL into OSCC. A study by Harrandah et al. demonstrated that miR-375 exhibited promising capabilities in distinguishing between progressive and non-progressive premalignant lesions. Specifically, this study reported a high sensitivity of 90.32% and an exceptional specificity of 100% for miR-375 in identifying progressive OPMD cases. Furthermore, the area under the receiver operating characteristic curve (AUC) for miR-375 was found to be excellent at 0.957. The same research also indicated that combining miR-375 with another miRNA, miR-21, yielded good predictive accuracy for malignant transformation [18]. A miR-based prognostic risk score model, including miR-214-3p, miR-375, age, and gender, effectively identified high-risk individuals with shorter time to relapse and death in early stage OSCC [19].The consistent findings across multiple studies, including a comprehensive systematic review, strongly suggest that miR-375 holds considerable promise as a biomarker for predicting the malignant transformation of OL [20]. The high sensitivity and specificity reported in some of these investigations are particularly encouraging for its potential use in identifying lesions that carry a higher risk of progressing to cancer.

The sensitivity and specificity values associated with miR-375 as a predictive biomarker are noteworthy. As mentioned previously, one study reported a sensitivity of 90.32% and a specificity of 100% for miR-375 in predicting progressive OPMD. The corresponding AUC of 0.957 further supports its strong prognostic ability [18]. Additionally, the study that analyzed salivary miR-375 also indicated its potential as a prognostic indicator, observing lower expression levels in patients who subsequently underwent malignant transformation [13]. The high sensitivity and specificity values reported for miR-375 in predicting malignant transformation suggest that it could become a valuable tool for clinicians in identifying patients who require more intensive monitoring and potentially earlier therapeutic intervention. A biomarker with high sensitivity is effective in correctly identifying most true positives (patients who will indeed develop cancer), while high specificity minimizes the occurrence of false positives (patients who are incorrectly identified as being at high risk). Achieving this balance is crucial for the clinical utility and acceptance of any biomarker.

While miR-375 demonstrates significant potential, it is important to consider it within the broader context of other identified miRNA biomarkers for OL. A scoping review identified a total of 21 different miRNAs that appear to be involved in the malignant transformation of OL, classifying them based on their potential effects as either oncogenic or tumor suppressors. While miR-375 was identified as a tumor suppressor , other miRNAs such as miR-21, miR-345, miR-181-b, and miR-31* were also highlighted as potential markers of this process [5]. Another review noted increased expression of miR-21, miR-181-b, and miR-345 in dysplastic lesions and OSCC [21]. Furthermore, another study mentioned that miR-31* functions to downregulate FGF3 and thereby facilitates the progression of OL to oral cancer [22]. A separate review observed that miR-31 was upregulated in OL cases that progressed to OSCC, while several other miRNAs exhibited differential expression patterns [6]. A comprehensive systematic review identified an even larger set of 73 unique miRNAs that showed altered expression in OPMDs, including OL, indicating a complex and multifaceted landscape of miRNA involvement in these conditions [10]. Although miR-375 shows strong promise as a standalone biomarker, it is plausible that a panel of miRNAs, incorporating miR-375 along with others like miR-21 and miR-31*, could offer even greater accuracy in predicting malignant transformation. This is likely due to the

multifactorial nature of cancer development, where multiple molecular pathways are often dysregulated. Different miRNAs may play predominant roles in various stages or through different pathways of malignant transformation. Therefore, integrating multiple miRNAs into a diagnostic panel could potentially capture a more comprehensive molecular signature of the disease, leading to improved predictive power and clinical utility.

**Mechanisms of Action of miR-375 in Oral Leukoplakia Progression**

Understanding the molecular mechanisms through which miR-375 exerts its influence is crucial for appreciating its role in the development and progression of OL. One study provided significant insights into this aspect, demonstrating that miR-375 acts as a suppressive miRNA in the premalignant progression towards OSCC by directly targeting KLF5, a transcription factor known to modulate the expression of genes involved in cell proliferation and apoptosis. The researchers observed that the abundance of miR-375 decreased in tissues as they progressed from a normal state to OLP and then to OSCC, which in turn led to an increase in the expression of KLF5. Conversely, when miR-375 levels were restored in OSCC cells, it resulted in a reduction in cell proliferation and an increase in apoptosis, accompanied by a downregulation of KLF5. The study further confirmed the direct interaction between miR-375 and the 3′-untranslated region (3′-UTR) of the KLF5 gene. Moreover, they found that Survivin (BIRC5), a known target gene of KLF5, was also regulated by miR-375. This finding provides a mechanistic explanation for the increased susceptibility to apoptosis observed in cells where miR-375 levels were restored [17]. Another study suggested that miR-375 might also suppress oral carcinogenesis by regulating the expression of MYC and insulin-like growth factor (IGF) oncogenes [18]. The identification of KLF5 and Survivin as direct targets of miR-375 establishes a critical mechanistic link between the downregulation of this miRNA and the pro-oncogenic cellular changes observed during the progression of OL, specifically the increased proliferation and decreased apoptosis of cells.

The key target genes regulated by miR-375 that are relevant to oral carcinogenesis include KLF5 and Survivin, as confirmed by direct binding assays and functional studies in the context of OSCC progression from OLP [17]. Additionally, MYC and IGF oncogenes have been suggested as potential targets in the broader context of OL [18]. Also, according to another study miR-375 negatively regulates IGF1R expression by direct binding while downregulation of miR-375 observed in laryngeal squamous cell carcinoma contributes to the upregulation of IGF1R and the activation of its downstream pro-survival AKT signaling pathway, thereby promoting tumorigenesis [23]. The regulation of multiple key oncogenes and proteins involved in fundamental cellular processes such as cell survival and proliferation by miR-375 underscores its broad impact on the cellular machinery critical for cancer development. This suggests that miR-375 may act as a master regulator in this context, exerting a wide range of effects through its various targets.

The dysregulation of miR-375 has significant downstream effects on key cellular processes. The observed downregulation of miR-375 leads to an increase in KLF5 expression, which subsequently promotes cellular proliferation and inhibits apoptosis through the upregulation of Survivin. Conversely, restoring the levels of miR-375 results in the repression of proliferation and the promotion of apoptosis in cancer cells [17]. A scoping review noted that several miRNAs, including those classified as tumor suppressors, are associated with epithelial-mesenchymal transition, invasion, and migration, which are crucial processes in cancer progression [5]. While the direct involvement of miR-375 in these specific processes within the context of OL was not explicitly detailed, its role as a tumor suppressor suggests that it might also play a part in regulating these aspects of cancer development. The primary downstream effects of miR-375 dysregulation in the context of OLprogression, as supported by the current research, appear to be primarily focused on the regulation of cell proliferation and apoptosis. The KLF5-Survivin axis provides a clear molecular pathway through which these effects are mediated. Further research may be warranted to explore the potential involvement of miR-375 in other hallmarks of cancer, such as invasion and metastasis, to gain a more comprehensive understanding of its role in the full spectrum of malignant transformation.

**Therapeutic Potential of miR-375 in Oral Leukoplakia**

The understanding of miR-375's role in OL progression opens avenues for exploring its therapeutic potential in managing this condition. The finding that restoring miR-375 levels in OSCC cells leads to a reduction in proliferation and an increase in apoptosis suggests that therapeutic strategies aimed at upregulating miR-375, such as the use of miR-375 mimics, could be beneficial in

preventing or delaying the malignant transformation of OL [17]. A review concluded that certain miRNAs hold promise as therapeutic candidates in miRNA-based target gene therapy [24]. Similarly, another review highlighted the potential role of miRNAs in the diagnosis, prognosis, and treatment of oral cancers [9]. A systematic review emphasized the significant interest in miRNAs as prognostic markers, which indirectly implies their potential as therapeutic targets as well [10]. One article explicitly stated that miRNAs could serve as targets for novel therapeutic strategies in oral cancer and specifically mentioned miR-375 as one of the miRNAs with aberrant expression associated with this disease [25]. The ability of miR-375 restoration to inhibit key cancer-related processes in OSCC cells strongly supports the concept that developing therapies based on miR-375, such as using synthetic miRNA mimics, could be a promising approach for managing OL and potentially preventing its progression to cancer. If the loss of miR-375 function contributes to the development of cancer, then restoring its levels could potentially reverse or halt this pathological process, providing a strong rationale for exploring miR-375 mimics as a therapeutic intervention [14].

Therapeutic strategies should focus on augmenting its levels, through the administration of miR-375 mimics. Accordong to a study utilization of a synthetic miR-375 mimic effectively demonstrated its tumor-suppressive effects in in vitro experiments [17].

Therefore, while preclinical studies have yielded encouraging results regarding the use of miR-375 mimics in OSCC cell lines, there is a clear need for further research to translate these findings into tangible clinical applications for OL. This would necessitate conducting in vivo studies in animal models and eventually progressing to well-designed clinical trials in human patients to fully evaluate the efficacy and safety of miR-375-based therapies.

## II. CONCLUSION AND FUTURE DIRECTIONS

The current understanding indicates that miR-375 is consistently downregulated in OL, particularly in lesions that are more likely to progress to OSCC. It functions as a tumor suppressor, by targeting key oncogenes such as KLF5, MYC and IGF, thereby influencing downstream effectors like Survivin to regulate critical cellular processes including cell proliferation and apoptosis. Furthermore, salivary miR-375 shows significant promise as a non-invasive biomarker for the detection of OPMDs and for predicting the risk of malignant transformation. In vitro studies have demonstrated that restoring miR-375 function through the use of synthetic mimics can exert tumor-suppressive effects, suggesting a potential therapeutic role for this miRNA in the management of OL.

The evidence strongly supports the potential of miR-375 as a diagnostic and prognostic biomarker for OL. Its involvement in key oncogenic pathways also makes it an attractive therapeutic target for interventions aimed at preventing malignant transformation. However, several gaps remain in our current understanding, and further research is necessary to fully realize the clinical potential of miR-375 in this context.

Future investigations should prioritize conducting longitudinal studies with larger cohorts of patients with OL to rigorously validate the prognostic value of miR-375. More research is also needed to comprehensively elucidate all the target genes and downstream signaling pathways regulated by miR-375 in the specific context of OL. To advance towards clinical application, it is essential to perform preclinical in vivo studies to thoroughly evaluate the efficacy and safety of miR-375-based therapies for OL. Ultimately, well-designed clinical trials will be required to determine the true translational potential of miR-375 as both a biomarker and a therapeutic agent in the management of OL and the prevention of OSCC. Finally, further investigation into the possibility of combining miR-375 with other promising miRNA biomarkers could lead to the development of more accurate and robust diagnostic and prognostic tools for OL.

**Declarations**

**Ethics, Consent to Participate, and Consent to Publish declarations:**

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