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MicroRNA-375 as a biomarker for malignant transformation in oral lesions

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Research Problem & Hypothesis: Malignant transformation of oral premalignant lesions is the key process in the progression to Oral Squamous Cell Carcinoma (OSCC). Although many clinical and histologic predictors have been used, the risk of malignant transformation in oral premalignant lesions is still difficult to assess. Our hypothesis is that oncogenic and tumor suppressor microRNAs play a role in the carcinogenesis of premalignant lesions and they may be useful molecular biomarkers to detect early malignant changes in these lesions.

Background: Oral squamous cell carcinomas (OSCCs) are the most common oral cancers that affect the oral epithelium. Up to 60% of OSCCs are derived from premalignant lesions. The risk of malignant transformation in premalignant lesions is difficult to assess. MicroRNAs are small non-coding RNAs associated with the control of cancer initiation and progression. Previously, we identified miR-7 and miR-21 as candidate oncogenes and miR-375 and miR-494 as candidate tumor suppressors in OSCC. In this study we aim to evaluate these microRNAs as biomarkers of malignant transformation in oral premalignant lesion.

Aims: Our aim is to evaluate microRNAs as biomarkers of malignant transformation in oral premalignant lesions.

Methods: Formalin-fixed, paraffin-embedded samples from progressive premalignant lesions and paired sequential OSCC tumors at the same site were obtained from same patients (n = 31). Controls were identified as cases with a premalignant lesion that was followed clinically for at least 5 years without report of a later OSCC (n = 6. Total RNA was extracted, reverse transcribed and analyzed for microRNA levels using real-time PCR. Mann–Whitney U nonparametric and Wilcoxon matched-pairs signed rank test were used for statistical analysis. Receiver-operating characteristic (ROC) curve analysis was used to assess the prognostic value of microRNAs in predicting malignant transformation in oral premalignant lesions

Results: Our data show that lower expression of miR-494 and higher expression of miR-21 were associated with the progression from premalignant lesions to OSCC. However, there was no statistically significant difference in their expression between progressive and non-progressive premalignant lesions. This indicates that none of these microRNAs has a prognostic potential in detecting malignant transformation in oral premalignant lesions. On the other hand, miR-375 expression in progressive lesions was clearly lower than in non-progressive control lesions (average 8-fold difference, $p=0.0004$). Furthermore, the expression of miR-375 decreased significantly after the progression from premalignant lesion to OSCC ($p<0.0001$). ROC curve analysis revealed that miR-375 was able to differentiate between progressive and non-progressive premalignant lesions ($p<0.0001$).

Conclusions: We conclude that miR-375 down-regulation in oral premalignant lesions is associated with a higher risk of malignant transformation.

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