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ROLE OF CIRCULATING miR-21 EXPRESSION PROFILES AND THEIR EMERGENCE AS POTENTIAL BIOMARKERS IN ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Among the widest range of prevalent forms of cancer is oral carcinoma, which can develop anywhere in the mouth or even on the lips. Although there have been many advances in cancer treatment, the expected lifespan for OSCCs have indeed increased marginally. The load of OSCC is anticipated to increase in the near future, yet there is no sign of relief in view. Tumorigenesis is just one of the many physiological processes that can be controlled by microRNAs, a class noncoding endogenous RNAs. Several fibrosis disorders have been linked to miR-21, and it has been utilised to distinguish oral and tongue cancer from healthy individuals. Studies empirically highlighted the significance of these transcripts as a predictor for prediction and diagnosis in OSCCs. Therefore, the present review summarizes the expression levels of miRNAs in OSCCs and evaluates their functioning in the progression or suppression of cancer. miR-21 can be considered as a prospective candidate for their translational use in OSCCs for early diagnosis prognosis surveillance and tailored treatment which should undergo further validation.

KEYWORDS: Oral Cancer, microRNA, Biomarkers, Carcinoma Cells, Oral Squamous Carcinoma Cell..

INTRODUCTION

One of the world's most prevalent malignancies throughout the globe is oral squamous cell carcinoma (OSCC) which is ranked at the sixth position for incidence out of all malignant tumours. Additionally, the ongoing SARS-CoV-2 pandemic had a negative impact on cancer detection and therapy in 2020. According to the statistics predicted by the American Cancer Society it has been predicted to be 1,918,030 fresh cancer instances and 609,360 casualties in 2022, with oral cancer as one of the causes of mortalities aggravated for about 11,230 of those annually. Despite profound recent advances in the research and treatment of oral cancer, the disease still has a high morbidity rate (1). Studies reveal that incipient identification is essential considering stage I and stage II of OSCC patients which have an overall survival rate (OS) of more than 80%, compared to stage III and stage IV patients who have an OS of just about 60% (2). There are several confounding variables, such as eating habits and lifestyle choices, that are contributing to the rise in oral cancer incidence and fatality rates. The two factors that are most widely acknowledged to increase the risk of OSCC are smoking and liquor intake. Considering all the considerable attempts made to discover novel and more effective therapies, malignant diseases still have a high mortality rate, which presents exciting difficulties for the research community.

Carcinoma as a group of diseases which is linked to changed levels of gene expression and function driven upon by genetic and epigenetic changes, as well as to high levels of malignant transformation. Such abnormalities can potentially result in the emergence of a malignant phenotype, uncontrolled cell growth, and metastasis. Furthermore, proto-oncogenes are stimulated whereas tumor-suppressor genes are suppressed. The ability of neoplastic cells to replicate is one of the key factors in tumour progression and is regarded as a critical prognostic marker (3, 4).

Since it was discovered that microRNAs (also known as miRNAs) influence target genes and downstream signalling cascades in malignant tumours, their importance has skyrocketed. Cellular apoptosis, migration, spreading, the epithelial to mesenchymal transition (EMT), resistance to chemotherapy and radiotherapy as well as cell growth inhibition are all linked to miRNAs in oral cancer. Oral leukoplakia (OL) and oral lichen planus (OLP) are two prevalent potentially malignant illnesses and premalignant

conditions that have been linked to abnormal miRNA expression in earlier studies, but the exact mechanism by which miRNA transforms into malignant tissue is yet uncertain (5,6). Interestingly, a slew of recent research found a link between oral cancer and the abnormal expression of several miRNAs, including miR-195-5p, miR-375, miR-143, miR-26b, miR-155-5p, and miR-483-5p (7-12).

As an illustrative example, a study conducted a miRNA microarray analysis of primary OSCCs histopathological samples, highlighting a collection of miRNAs (let-7a, let-7d, let-7f, miR-16, miR-29b, miR-142-3p, miR-144, miR-203, miR-223 and miR-1275) possibly associated with the development and attenuation of oral carcinoma (13). Additionally, miR-497-5p, miR-4417, miR-21, miR-31, miR-338, miR-125b, hsa-miR-133a, miR-133b, and miR-139 have recently been linked to the occurrence of OSCC as suggested by studies (14-15).

BIOLOGICAL ROLE OF miR-21

Certain miRNAs have had their biological roles widely studied, and miR-21 has recently evolved in a way that makes it present in a variety of vertebrate species. Investigational evidence demonstrates that miR-21 inhibits programmed cell death and promote cellular survival in a wide range of cells (16, 17). Elevated miR-21 expression induces tumor cells and act as a frequent symptom of abnormal cell proliferation or cell stress. In addition, it has recently been demonstrated that miR-21 expression are found to be increased in an animal model of myocardial injury and the development of artery neointimal hyperplastic (18, 19). The attention on miRNA-21 levels has grown significantly in recent years, particularly with regard to cardiovascular and cancer illnesses, as a result of its pervasive participation in numerous biological processes. There are currently a number of significant reports outlining the significance of miR-21 in above mentioned conditions. However, the present review instead focuses more on miR-21 modulation and its involvement in genesis, immunology, and EMT.

ROLE OF miR-21 IN OSCC

A family of miRNAs controls a wide range of pathophysiological functions by affecting their cellular expression. Whenever these processes are dysregulated, the tumour cell acquires malignant properties such as increased cell proliferation signaling while preventing cellular processes, inhibit apoptosis, promote invasion, and metastasize to neighbouring cells inducing angiogenic characters (20). Upon extrapolating the data from the study predicted the therapeutic potential of miR-21. Most recent experiments, certainly indicate that miR-21 has an oncogenic effect. In humans, the miR-21 situated in the 17q23.2 locus of the chromosome, close to the fragile domain FRA17B, that HPV integration loci, indicating miR-21 as an anti-apoptotic marker.

It has been observed that miR-21 is typically shown to be overexpressed in malignant lesions, and its inhibition results in tumour shrinkage. It is also noted to help the tumours become more resistant to chemotherapy (21). Additionally, it helps regulate genes like Phosphatase and tensin homolog (PTEN), Transforming Growth Factor (TGF) and human programmed cell death 4 (PDCD4) that are employed in the early stages of cancer (22). It has been hypothesized that miR-21 has immense potential to prevent apoptosis and has role in carcinogenesis. For further validation, the miR-21 deficient mice developed papillomas at a considerably reduced rate, indicating a preventive effect against chemically induced skin carcinogenesis (23).

Research showed that miR-21 expression was linked to smoking (unpublished data), and more current research has shown that miR-21 translation is elevated in alcoholics and tobacco consumers (24, 25). However, Zhang et al. showed that nicotine increases miR-21 *via* EMT and TGF-β pathway (26). The clinical and predictive merit of miR-21 translation has been previously proven in OSCC patients. Karimi et al. eventually revealed that miR-21, miR-24, and miR-29a blood levels could be utilized as potential biomarkers in order to recognize cancer and, consequently, also possibly employed to design novel pharmacological approaches (27, 28). In OSCC tissues, we found that 17 miRNAs were down-regulated and 45 miRNAs had significant up-regulation. Considering that there is little known about miR-21-3p's biological functioning in OSCC, their expression levels were assessed in 95 OSCC specimens using RT-PCR analysis. The findings suggest miR-21-3p expression to be noticeably up-regulated in OSCC samples *versus* the equivalent nearby healthy regions specimens (29).

Increased translation of the miR-21-5p guide strand in human malignancies, has been extensively researched in the majority of malignant tissues and had shown to aid as a carcinogenic agent in controlling the manifestation of tumor, cell growth, metastasis, and drug resistance (30-34). MiR-21-5p malfunction has been linked across several studies to oral cancer cell proliferation, metastasis, and treatment resistance (35). In tongue squamous cell carcinoma (TSCC), miR-21 translation was found to be up-regulated relative to that of the surrounding,

and it could control TSCC development by preventing TSCC cell death in aspect through tropomyosin α-1 chain silencing (36). On the other hand, patients with OSCC who had miR-21 overexpression had significantly poorer prognoses and perineural migration (37).

THERAPEUTIC POTENTIAL OF miR-21

Restoration of a single or few anomalies, despite the massive disruptions in gene expression that occur during the genesis of malignancy, was observed in multiple investigations in order to markedly slow down the growth of cancer cells and enhance the patient survival rate. Numerous studies demonstrate the translation of too many miRNAs was found to be dysfunctional in neoplastic tissues leading to the discovery of a crucial function for miRNAs in carcinogenesis regulation. MiR-21 is essential and plays a significant role at all levels of carcinogenesis and its expression is a key biomarker of a bleak diagnosis in human cancers, according to expanding reports. Their key function in the restricting the spread of tumor which communicate with specific target mRNAs to either promote or repress tumorigenesis. It has been observed that miR-21 was found to be associated with increased prognostic capabilities (38). Furthermore, Hsu et al., who were the first researchers to glance into miR-21's involvement in blood plasma, examined in HNSCC *versus* the healthy subjects. They found that miR-21 had a sensitivity of 83.3%, indicating its employment as a prognostic marker in the HNSCC subjects (39).

A study involved in assessing the quantitative translation of miR-21, miR-181-b and miR 345 in OL and OSCC cases displayed miR-21 overexpression due to higher nuclear/cytoplasmic ratio (40). It has also been observed that the immunohistochemistry expression of Dickkopf-2 (Dkk-2) and ß-catenin exhibited an inverse correlation with miR-21 overexpression. In the region where miR-21 was found to be overexpressed, Dkk-2 expression was found to be decreased. Therefore, it has been hypothesized that in OSCCs, miR-21 suppresses DKK-2, which in turn induces the Wnt/ß-catenin signalling framework and stimulates tumour metastasis. Additionally, a miR-21 downregulation reduced the invasive ability of OSCCs while upregulating Dkk-2. Whereas, miR-21 is thought to regulate the expression of Tropomysin-1 and PTEN, that promote cell growth and prevent apoptosis (41). A study evaluated miR-21 function in stromal (fibroblastic) and endothelial cells found in oral malignancies. The investigators discovered a strong correlation between alpha-smooth muscle actin and miR-21 and it was found to play significant role within the tumor's core rather than at the invasive front (42). Also, miR-21 has been shown to serve as a chemosensitive miRNA (43).

DISCUSSION

Roughly more than hundred publications have looked into the expression of miR-21 in HNSCC patients so far. According to several studies, miR-21 is found to be among the key miRNAs connected to OSCC. However, overexpression of miR-21 in a number of malignancies is associated with breast, colon, lung, pancreas, thyroid and ovary.

Numerous pathological ailments have been linked to the dysregulation of miRNAs. Due to their stability, miRNAs found in saliva would somehow be employed in the diagnosis of mouth cancer (44). Although miR-21 expression rises with tumour progression in oral cancer, it is inversely connected with survival outcomes. Another recent study found that mir-21 could perhaps forecast poor prognosis in OSCCs, and anecdotal evidence suggests that amplification of miR-21 is linked with reduced survival in individuals with TSCC. Additionally, patients with leukoplakia and severe dysplasia were shown to have elevated levels of miRNA-21 activity, based on the previous study. Upregulation of miRNA-21 has been linked to oral premalignant lesions as a precursor to cancer in past research (45). Increased by almost 20-fold in malignant tissue relative to normal neighbouring tissue, miRNA-31 causes oncogenesis in mouth cancer by reducing the activity of a protein that promotes the survival of cancer cells in low oxygen environments (46). A study reports utilizing miR-21 as a biomarker from the saliva and tissue specimen from subjects with OSCCs has shown great diagnostic performance for the evaluation of cervical lymph node metastases, thereby may be utilized as a potential substitute for this purpose prior to surgery (47).

Moreover, through regulating the translation of tumour silencing genes such PDCD4, DKK2, TIMP-3, and PTEN, the carcinogenic miR-21-5p enhances OSCC cell proliferation, migratory, infiltration, drug resistance and cell death (48, 49). It is well established that melanoma patients who develop resistance to standard treatments such as chemotherapy and radiation have a far poorer prognosis. Patients with elevated miR-21 translation have a lower response to chemotherapy and radiation, and miR-21 deregulation confers chemoresistance to cisplatin *via* acting on the PTEN and PDCD4 expression levels (50). Therefore, targeting and inhibiting miR-21 as a treatment strategy to improve outcomes for patients with OSCC is a potential area of research.

CONCLUSION

It has been concluded that miR-21 functioning as an oncogenic marker can benefit as a prophylactic and therapeutic biomarker in cancer prevention. Several sources of evidences suggest the function of miR-21 in aggravating the aggressiveness of OSCC, ultimately resulting in a poor prognosis of the disease.

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