Innovations

Role of microrna-510 in various malignancies-A Systematic Review

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Abstract: ***Background:*** *MicroRNA (miRNAs) discovery was first published in 1993.They are a group of small single-stranded noncoding RNA with 18 to 25 nucleotides. These miRNAs regulate cellular processes such as differentiation, proliferation and apoptosis and are widely involved in tumorigenesis, tumour progression and metastasis. miRNAs are important post-transcriptional regulators of gene expression in many types of diseases. Biomarker is a term that defines different types of objective indicators of health or disease. Throughout history, and according to human technological advancements, these indicators have turned increasingly more precise and reliable. miRNAs have first been established as biomarkers for cancer in 2008, when Lawrie et al. utilized them for the examination of diffuse large B-cell lymphoma in the serum of patients, and ever since, their potential use as biomarkers has been mentioned in literature for numerous diseases and malignancies.miR-510 belongs to the miR-506/514 gene cluster. Recent discoveries have shed light on the involvement of miRNA 510 in malignancies.* ***Aim:*** *This paper aims to systematically review current findings on expression of MicroRNA-510 as a diagnostic tool in various malignancies.* ***Methods:*** *A search was done using MeSH terms and keyword search in the electronic databases namely PubMed, Google Scholar, Cochrane, Science Direct ,Lilacs and addition searches were carried out through cross checking the bibliographies of selected articles. Then based on the inclusion and exclusion criteria and availability of the full texts, a total of 9 articles were included in this systematic review.* ***Result:*** *The search yielded a total of 439 articles out of which 9 articles were included based on the eligibility criteria. Quality assessment based on the Quality Assessment of Diagnostic Accuracy Studies 2 tool was used to obtain a risk of bias chart using Revman 5.4 software and it was proved that from the 9 included studies, six had low risk of bias and other three had intermediate risk of bias.* ***Conclusion:*** *Literature based evidence states that microRNA510 has aberrant expression, biological role and precise mechanism in various malignancies .This systematic review aimed at improving the current understanding of microRNA 510 and their applicability in malignancies. Further, this may alleyway for further analysis of the target gene pathways of miR-510 which may help in diagnosis and treatment of various malignancies.*

Keywords: *1.Malignancies, 2.Cancer, 3.microRNA 510, 4.Therapeutic target, 5.Diagnostic Biomarker, 6.Diagnosis, 7.Prognosis*

Structured question

What is the potential role of microrna 510 in malignancies?

Introduction:

miRNAs have first been established as a biomarker for cancer in 2008,when Lawerie et al utilized them for the examination of diffuse large B-cell lymphoma in the serum of patients and ever since, their potential use as a biomarker has been mentioned in literature for numerous diseases

Cancer has become the primary cause of mortality in most countries and regions, and the incidence of human malignancies has increased substantially [1] . There are more than 120 types of Cancers and among them the most common are Bladder Cancer, Breast cancer, Colorectal Cancer, Kidney cancer, Lung cancer, Lymphoma, Melanoma ,Oral and Oropharngeal Cancer, Pancreatic cancer, Prostrate cancer, Thyroid cancer and Uterine cancer.The projected national cancer incidence burden in 2020 will be 98.7 per 100,000 population(1,392,197 patients) as a conservative estimate[24]

In recent years miRNAs have emerged as an important molecules in the complex networks of gene regulation. These naturally occurring small non-coding RNA molecules that regulate the expression of protein coding genes at post-transcriptional level have been implicated in a variety of human disorders, such as infectious diseases, metabolic disease and malignancy[15]. miRNA plays an important role in cellular growth, differentiation, apoptosis, and immune response. During development of malignancy, some miRNAs are upregulated and some are downregulated, so any change in the expression of miRNAs can cause tumor suppression. Apart from functioning as tumor suppressors, miRNAs can also promote tumor development (oncogenes) depending on the tumor types and their specific target protein[18,14]. The main role of microRNA in human body is gene regulation[10]

miR-510 belongs to the miR-506/514 gene cluster, which contains seven distinct miRNAs (miR-506, -507, -508, -509, -510, -513, and -514), and has been previously reported to be abnormally expressed in many types of diseases. It has been suggested to be involved in hypertension[20], Diabetes[21], Diarrhea, Preeclampsia[22] and bowel syndrome[23]. The expression, biological role and precise mechanism of microRNA510 has been previously studied in a number of malignancies such as lung Cancer[11,14], gastric cancer[19], thyroid cancer[13],colon cancer[12], breast cancer[16], ovarian cancer[18], prostate cancer[17] and renal cell carcinoma[15]. In this systematic review, various studies done on microRNA510 in malignancies were included. This study focuses on identifying the gaps in the existing studies to suggest areas for future research on microrna 510 as a potential target in detection of head and neck malignancies.

Aims and objectives:

- To assess upregulation and downregulation of miRNA510 in malignancies
- To explore the potential role of miRNA510 as a potent therapeutic strategy or diagnostic marker in malignancies

Materials and methods:

Study design & search methodology

For this study, we followed the guidelines given by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA).

The studies included in this systematic review were identified by a comprehensive search from the following search engines using the keywords.

- PubMed Advanced search using MeSH terms

- Google scholar Articles
- Cochrane
- Science Direct
- Latin American and Caribbean Health Sciences Literature (LILACS) upto
- Hand searching of relevant articles was done until February 2021
  [Figure 01]

Search strategy

When searching these databases a combination of 'MESH terms' and 'free text words' were pooled through Boolean operators ('AND', 'OR')

Mesh terms used for search strategy:

(MiR-510 OR micro RNA510 OR microRNA-510 OR microRNA-510 OR miR-510-5p OR microRNA-510-5p OR micro RNA 510 OR Micro RNA 510 OR MicroRNA-510 OR MicroRNA 510) AND (Tumor OR Tumour OR Cancer OR Carcinoma OR Neoplasm OR Malignancies OR Carcinogenesis)

Eligibility criteria

Inclusion criteria

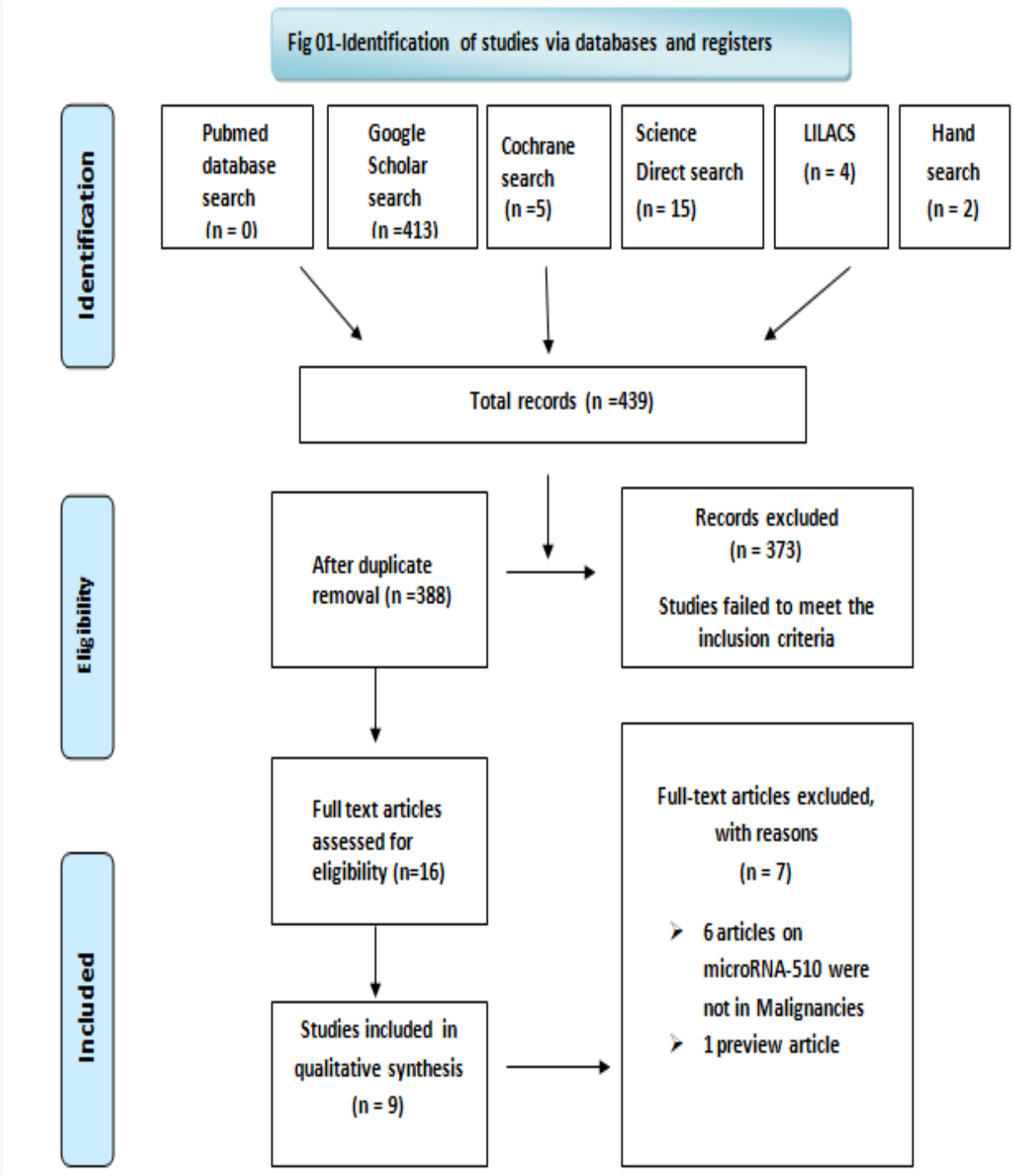
1. Studies on expression of miRNA510 with malignancies (lung cancer, breast cancer, ovarian cancer, prostate cancer, renal cell carcinoma, Colon cancer and leukemia)
2. Histopathologically diagnosed malignancies
3. Studies done and published on tissue and cell lines were only included
4. Full-text articles
5. Studies in English language

Exclusion criteria

1.Studies on expression of miRNA510 other than malignancies(Hypertension, Diabetes, Diarrhoea, Preeclampsia, Bowel Syndrome and other such conditions)
2.Animal studies
3. Systematic review/ Meta-analysis studies excluded
4. Non-english articles
5. Abstract only

Selection process

Two investigators independently evaluated articles retrieved from the databases. First round of evaluation was performed by reading only the title and abstracts of the studies. At the end of first round all studies considered eligible were included for full-text evaluation. A direct search of bibliographies of articles in full-text was carried out, to find out further articles to include. After full-text reading, only studies considered eligible by both authors were included.



Data extraction

Data extraction of the characteristics of included studies and the variables of outcome are given in (Table 01)

Table 01- data extraction and characteristics of the Included studies

S.no	Author, Year	Samples		Study period	Method	Statistical analysis	Result
		Tissue	Cell lines				
1	Wenchen g Yu *et al.*,2019	40 pairs of tumor and adjacent normal tissues were collected from NSCLC patients.	The human lung epithelial cell BEAS-2B, and lung cancer cell lines NCI-H441,PC-9,NCI-H1650,A549	Jan, 2015 to Feb, 2017	RT-qPCR	**Spearman Correlation and multivariate cox regression analysis** confirmed the level of LINC00702 was negatively correlated with tumor size, lymph node metastasis and distant metastasis in patients with NSCLC**.** LINC00702 expression was negatively associated with the survival rate of patients with NSCLC P<0.05.	LINC00702 modulated the expression of PTEN gene by acting as a ceRNA for miR-510 in NSCLC.
2	Fang-Ling Tu *et al.,* 2020	30 pairs of colon cancer tissues and non-tumour normal tissue	Colon cancer cell lines (SW620, HCT116, SW480, HT-29, LoVo) and normal colon epithelial cell line (NCM4600	2011 to 2018	RT-qPCR	**Pearson test** Performed to determine the relationship between circ-0001313 expression and AKT2. A prominent correlation between the expression levels of circ-0001313 and AKT2 was observed. r= 0.7288,p<0.0001	Circ-0001313 competitively bound to miRNA-510-5p, thus upregulating its target gene AKT2.
3	Yongcun Liu *et al.,*2018	50 pairs of thyroid cancer tissue samples and adjacent normal tissue samples	4 human thyroid cell lines (TPC1, FTC133, BCPAP and 8505C) and a normal thyroid cell line.	Not given	RT-qPCR	**Pearson correlation analysis** Compared miR-510-5p expression in different clinicopathologic characteristics of thyroid cancer patients and observed that thyroid cancer tissue samples with advanced clinical stage (III-IV) exhibited higher levels of miR-510-5p in comparison with thyroid cancer tissue samples with early clinical stage (I-II) (P < 0.001). Moreover, high miR-510-5p expression was also observed in thyroid cancer tissue samples with lymph node metastasis compared with thyroid cancer tissue samples without lymph node metastasis (P < 0.001)	miR-510-5p expression is overexpressed in thyroid cancer tissues and cells, and correlated with advanced clinical stage and lymph node metastasis
4	Wei Wu *et al.*,2019	32 paired NSCLC and adjacent non tumor lung tissues were obtained.	4 NSCLC cell lines (A549, SK-MES-1, H522, H460), normal human lung epithelial cell line BEAS-2B, and human embryonic epithelial HEK293T cell lines)	Novem ber 2011 to May 2015	RT-qPCR	**Student's t-test or ANOVA** The association between miR-510 expression and clinicopathological factors of NSCLC patients was seen. miR-510 expression was correlated with TNM stage (p=0.014) and lymph node metastasis (p=0.039) of NSCLC patients. However, there was no obvious association with sex (p=0.946), age (p=0.169), smoking history (p = 0.784), and tumor size (p = 0.492).	miR-510 acted as an oncogene in the regulation of NSCLC cell proliferation and invasion, to a certain extent, via targeting SRCIN1. MiR-510 may serve as a novel prognostic marker and therapeutic target in NSCLC. miR-510 knockdown may have therapeutic potential in NSCLC

5	DUQUN CHEN *et al.,*2015	Total of 48 paired renal cell carcinoma (RCC) and adjacent normal specimens	Two human RCC cell lines, ACHN and 786-O	Not given	RT-qPCR	**Paired t-test** The different expression of miR-510-5p in RCC and paired normal samples was analyzed by a paired t-test. The results showed the expression of miR-510-5p decreased in 81.25% (39/48) of RCC tissues, compared with paired normal tissues, with an average reduction in expression of 0.4283-fold	Downregulated miR-510-5p functioned as a tumor suppressor by reducing cellular proliferation and migration, and inducing apoptosis in RCC
6	Qi J Guo *et al.,*2013	-	Human breast cancer cell lines (MCF7, CAMA-1, MDAMB-231, MCF10A and BT549)	Not Given	RT-qPCR	**Two sided paired student's t-test** Using three mir-510 independent clones, a two-to four fold increase in migration and four-to- five fold increase in invasion across coated membranes was observed	miR-510 overexpression in non-transformed and breast cancer cells can increase their cell growth, migration, invasion and colony formation in vitro
7	Durairaj Sekar *et al.,*2016	-	Human prostate cancer cell lines (androgen sensitive—LNCaP and VCaP; androgen insensitive—DU145, PC-3 and MDA PCa 2b) and normal prostate epithelium cell line (PNT1A, HPrEC)	2014-2015	RT-qPCR	**One-Way ANOVA** The expression level (Fold Induction) of miR-510 in both the androgen insensitive cell lines (DU145 and MDA PCa2b) was higher than the androgen sensitive prostate cancer cell lines (LNCaP and VCaP) and normal prostate cell lines (PNT1A and HPrEC) P-value< 0.05 was considered statistically significant	miR-510 was up-regulated in metastatic form of prostate cancer cell lines (DU145 and MDA PCa 2b) and in human prostate cancer biopsies but no significant changes were noticed in miR-510 expression in other cell lines (LNCaP, VCaP and PNT1A) as well as in BPH samples.
8	XINCHEN ZHANG *et al.,*2015	42 cases of HGSC and 36 cases of CCC in Ovarian Carcinoma	-	2004-2011	RT-qPCR	**Mann-Whitney or Kruskal-Wallis Analysis** miR-510 expression was significantly associated with the FIGO stage (P<0.01).The expression of miR-510 was not associated with the age of the patient(p>0.05). Downregulation in the expression of miR-510 was associated with poor prognosis	The expression of miR-510 was significantly higher in the HGSC and CCC tissues, compared with the HGSC and normal ovarian tissues. s
9	WEIDONG CHEN *et al.,*2012	33 cases of primary gastric cancer with corresponding normal tissue	Cell lines AGS, SGC7901,GES-1,MKN-28	May 2006 to Dec 2007	RT-qPCR	**One-way ANOVA** Expression of miR-510 in 33 primary gastric cancer tissues demonstrated with/without lymph node metastasis is P=0.204	MiR-510 downregulated in lymph node metastatic sites as compared to primary gastric cancer

MiR-MicroRNA, NSCLC-Non-small cell Lung Cancer, RT-Reverse Transcription, qPCR- Quantitative polymerase chain reaction, HGSC-High grade serous carcinoma, CCC-Clear Cell Carcinoma

Quality assessment of the studies

The quality of these 9 studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool. This tool includes 14 items which assess the risk of bias and sources of variation in diagnostic studies. It is recommended by the Cochrane Collaboration, Agency for Health Care Research and Quality and the UK National Institute of Health and Clinical Excellence to assess the quality of diagnostic studies. QUADAS-2 is an improvised redesigned tool from the Cochrane Collaboration based on feedback from editors of the original QUADAS tool

Risk of bias

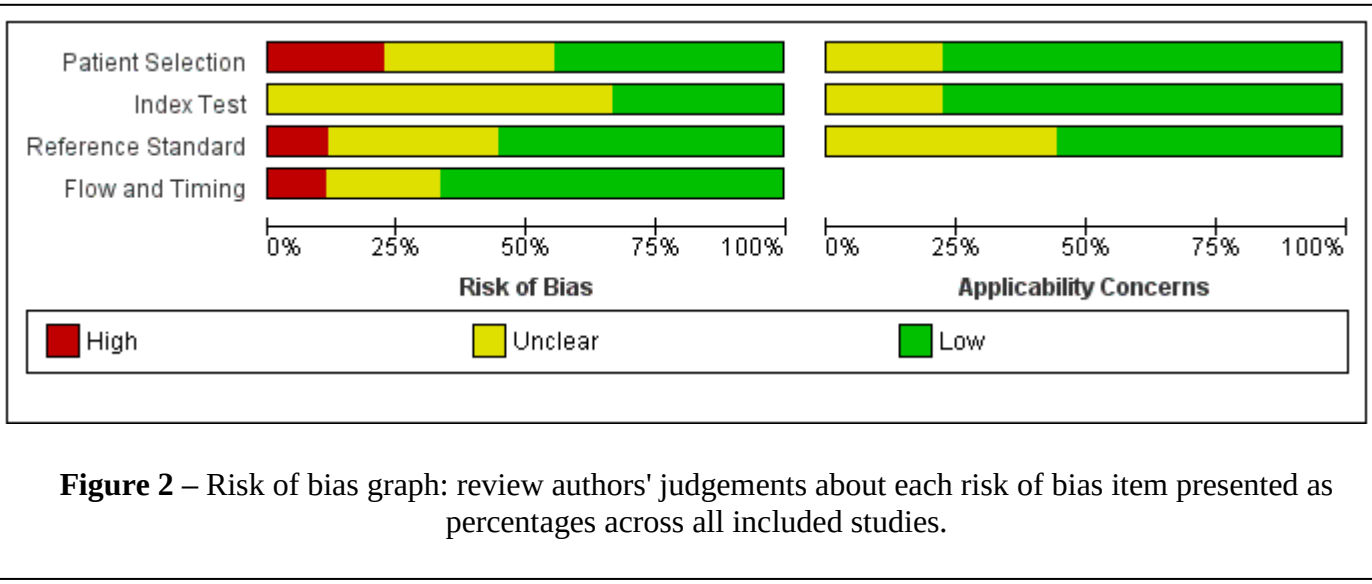


Figure 2 – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

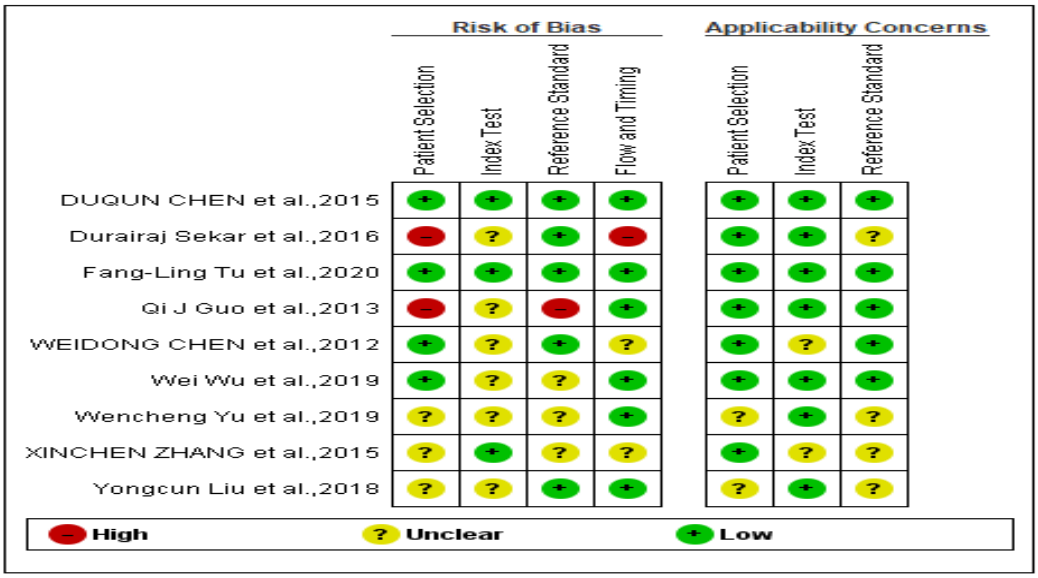


Figure 3 – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

GRAPH 5 – Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Result:

The search yielded a total of 439 articles out of which 9 articles were included based on the eligibility criteria. Statistical analysis carried in these nine studies included One-Way ANOVA, Pearson test ,Spearman Correlation and Mann-Whitney or Kruskal-Wallis Analysis(Table 01)Expression level of microRNA-510 in malignancies are tabulated.(Table 02)

Two of these studies were done only in Culture cell lines. RT-qPCR is used for analysis in all the studies. Quality assessment based on the Quality Assessment of Diagnostic Accuracy Studies 2 tool was used to obtain a risk of bias chart using Revman 5.4 software and it was proved that, six had low risk of bias and other three had intermediate risk of bias.(Figure 2& 3)

Table 02 Expression of microRNA-510 in malignancies

Cancer type	Expression status	References
Prostate Cancer	Elevation in prostate cancer tissue and metastatic form of prostate cell lines	[17]
Renal Cell Carcinoma	Decreased in RCC tissue compared with normal Renal tissue Samples	[15]
Gastric Cancer	No difference in expression seen between Gastric Cancer tissue and adjacent normal tissue	[19]
Thyroid Cancer	Overexpressed in thyroid Cancer tissues and Cells	[13]
Ovarian Cancer	Low expression seen	[18]
NSCLCC	Upregulated in NSLCC cell lines compared with BEAS-2B cell lines	[14]
	LINC00702 was downregulated in patients with NSCLC	[11]
Breast Cancer	Upregulated in cancer tissues compared to non tumor	[16]
Colon Cancer	High expression seen in Colon Cancer tissue	[12]

Moreover, the expression of microRNA was tightly correlated with advanced TNM stage and Lymph node metastasis.

Discussion:

Originally, these studies have demonstrated that expression of microRNAs is associated with the occurrence and development of various types of cancers. The identification of miRNAs and their target genes provides a novel insight into understanding the mechanisms of the tumor formation and progression, and promising therapy for different cancers[5],Wencheng Yu et al established the correlation between miR-510 and PTEN expression levels in lung Cancer by qRT-PCT and suggested that miR-510 could directly target PTEN gene and demonstrated that LINC00702 regulated PTEN pathway via directly interacting with miR-510[11].Fang et al revealed that circ0001313 regulates the pathogenesis of colon cancer by sponging miRNA-510-5p to upregulate AKT2 expression. Circ-0001313 was verified to be negatively associated with miR-510-5p as circ-0001313 over expression pulled down miR-510-5p, whereas circ0001313 reduction decreased miR-510-5p.Furthermore, miR-510-5p exhibited a low expression in colon cancer cells [12] . Guo et al found that miRNA-510 was upregulated in breast cancer and was positively correlated with the invasion, migration and colony formation ability of breast cancer cells[16]

Yongcun Liu et al, provided evidence to support a pivotal role for miR-510-5p in regulating thyroid cancer cell proliferation, migration, and invasion as an overexpressed miR-510-5p expression was observed in tumor tissues with advanced clinical stage or lymph node metastasis[13].Moreover, Sekar et al showed that levels of miR-510 expression were elevated in prostate cancer tissues and metastatic form of prostate cancer cell lines compared with benign prostatic hyperplasia and normal prostate cell lines, respectively[17]. In ovarian cancer, Zhang et al suggested the levels of miR-510 expression in clear cell carcinoma and low-grade serous carcinoma tissues were obviously higher than high-grade serous carcinoma and ovarian surface epithelium tissues and low miR-510 expression has been shown to be associated with advanced FIGO stage and poor

histopathological classification[18]. Chen et al reported that miR-510-5p expression was markedly decreased in renal cell carcinoma tissue samples compared with normal renal tissue samples. In addition, miR-510-5p served as a tumor suppressor to regulate renal cell carcinoma cell proliferation, migration, and apoptosis through targeting AKT2, AKT3, and FAS. [15] Fang et al suggested that miR-510-5p directly binds to circ-0001313 in colon cancer cells[12] In lung Cancer, the levels of LINC00702 was negatively correlated with tumour size, lymph node metastasis and distant metastasis in patients with NSCLC[11].

There was no difference of miR-510 expression between gastric cancer tissues and adjacent normal stomach tissues.[19]Wei Wu et al suggested that miR-510 downregulation of miR-510 mediated suppressed NSCLC proliferation and invasion.Thus,miR-510 knockdown may have therapeutic potential in NSCLC.[15].In breast Cancer,miR-510 is identified as an oncogene. MicroRNA-510 is a therapeutic target in breast cancer patients.

A number of studies have reported that miRNA expression signatures are associated with specific tumor subtypes, clinical outcomes, stages and responses to therapy.

Conclusion:

Extensive studies have demonstrated the aberrant expression, biological role and precise mechanism of miR-510 in various malignancies. Yet, it's role in Oral Carcinoma has not been established. The research of miRNAs as biomarkers is still in its early stages, therefore at the moment, the findings generally lack reproducibility. A standardized protocols must be developed both for the initial stages of the process, like sample collection, transport, and storage, as well as data analyzing for the diversity of technological methods used. Moreover, there is need for more studies to prove the potential role of microRNA510 in head and neck malignancies, especially in countries like India where there is increased prevalence of malignancies. As current techniques evolve, we anticipate that miRNAs will become a routine approach in the development of personalized patient profiles, therefore allowing targeted therapeutic interventions.

Recommendations for future research:

There is an impervious need for faster ways to detect different pathologies, seeing that many types of cancer are discovered in late stage. miRNAs as biomarkers can fulfill this, thus being an impressive research field.

The most important evaluation criteria for circulating miRNAs as diagnostic and prognostic biomarkers are high sensitivity and specificity, to avoid false positive or negative diagnosis. An appropriate biomarker for a specific cancer type should be both significantly differentially expressed and in correlation with the outcome of patients. The contribution of miRNAs in various types of cancers differs. Therefore, it is essential to have a larger sample size to be able to decide between the healthy or diseased status

Further, the identification of miRNAs and their target genes provides a novel insight into understanding the mechanisms of the tumor formation and progression and promising therapy for different cancers. The correlation between miR-510 and PTEN expression levels in lung cancer by analyzed by qRT-PCR, and transfection with miR-510 significantly decreased the mRNA levels of PTEN by 60% and 55% in NCI-H441 and PC-9 cells respectively, thus indicating that miR-510 could directly target PTEN[11].This PTEN gene is a tumor suppressor that is frequently mutated/deleted in cancers after p53 and Rb genes and it is established as a target gene for microRNA510.Moreover , alteration of PTEN is an important molecular event in pathogenesis and carcinogenes of Oral carcinoma[7,8,9].

Since,microRNA-510 could directly target this PTEN gene, in future researches on the potential role of microRNA 510 and its target in Oral cancers paves a way for development of biomarker.

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Conflict of interest
There is no conflicts of interest

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